

The Gynecologic Oncology Group

The Gynecologic Oncology Group: 43 Years of Success

Philip J. DiSaia, MD - Group Chair



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Acknowledgements

A special word of gratitude to Mr. Kevin Schnieder for his editorial efforts in the production of this monograph.

Dedications

This effort is dedicated to current GOG Group Chair and President, Dr. Philip J. DiSaia.

Gynecologic Oncology Group

Mission Statement

The Gynecologic Oncology Group is a non-profit organization with the purpose of promoting excellence in the quality and integrity of clinical and basic scientific research in the field of gynecologic malignancies. The Group is committed to maintaining the highest standards in clinical trials development, execution, and distribution of results. Continuous evaluation of our processes is utilized in order to constantly improve the quality of patient care.

Preface |



Philip J. DiSaia, MD
Chair

Since 1970, the Gynecologic Oncology Group (GOG) has moved progressively into the lead position among clinical trial groups studying gynecologic cancer. The results of multiple GOG study protocols have formed the basis of the standard of care for many malignant gynecologic neoplasms. Additionally, the GOG has contributed greatly to improvements in staging procedures, quality of life analyses, and more recently, prevention knowledge.

This monograph summarizes the highlights of the Group's accomplishments. None of these successes could have been achieved without our multi-disciplinary investigators and their institutions who have carried the burden of excellence in research despite less than recommended funding. The real heroes of our successes are

the members of the Group themselves and the support provided by both the NCI and our industry partners.

We look forward to many more years of productivity and successful research into gynecologic malignant neoplasia as we affiliate with NSABP and RTOG to form the new NRG Oncology.

A handwritten signature in black ink that reads "Philip J. DiSaia". The signature is written in a cursive, flowing style.

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Gynecologic Oncology Group
July 2013

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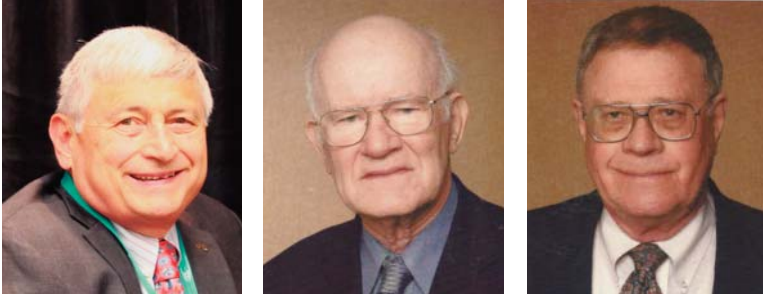
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History of the Gynecologic Oncology Group



Philip J. DiSaia, MD, George C. Lewis, Jr., MD; and Robert C. Park, MD

Introduction

The field of Gynecologic Oncology has its roots in many developments over the past 100 years, but it would be inappropriate to embark upon a description of that history in this text. Suffice it to say that prior to 1960, the performance of clinical trials in female reproductive tract malignancies was a rarity. Most of the investigation was focused on improving surgical techniques, improving surgical support therapy and the evolving field of Gynecologic Radiotherapy.

By 1960, the use of chemotherapy had found its place in the treatment of hematological malignancies, but little had been done in solid tumors. Indeed, the first medical oncologists were hematologists/oncologists. These individuals were the first to form what we would later come to call “cooperative groups.” The activity of cooperative groups was greatly influenced by the push from peer-reviewed journals that each and every clinical study have statistical support information to justify the author’s conclusions. Thus, we had all of the initial ingredients of a cooperative endeavor; those being an interest in cancer treatment, multi-institutional trials and statistical analysis.

Initial Organizational Efforts

The seminal event in the formation of the Gynecologic Oncology Group began with the creation of the Endometrial Cancer Adjuvant Study championed by Dr. George Lewis in 1963, initially of Hahnemann University Hospital and later of Jefferson University Medical School, in which patients with endometrial adenocarcinoma, Stage I, were randomized to receive standard therapy with surgery and, possibly, radiation followed by Depo-Provera versus placebo by intramuscular injection in a double-blind study. The purpose of the study was to see whether the addition of hormone therapy (Depo-Provera) to standard therapy for endometrial adenocarcinoma improved the disease-free interval and survival. A statistician was recruited from Roswell Park/SUNY Buffalo to

review all data and assist in publication of the results. Forms, operative notes, pathology reports with their description of the disease were reviewed/processed by the statistician in consultation with the principal investigator. All patients were followed for disease-free interval and survival, and the final analysis revealed no significant difference between the placebo and the Depo-Provera group. Although this was a negative trial, it was the first time that 20 institutions across the country had agreed to cooperate in a single protocol and more than 500 cases were enrolled. This trial which was executed during the 1960’s definitely set the pace for the formation of the Gynecologic Oncology Group.

Records of the events that came next are still available in the GOG Administrative headquarters. These records demonstrate that the initial steps of evolving a gynecological cooperative group started out with a limited objective that expanded considerably as time passed. Dr. Luther Brady, the Chairman of Radiation Therapy at Hahnemann Medical College and Hospital, initially sent out a series of invitations to participate in a presentation on the topic of “Carcinoma of the Ovary” before the Radiological Society of North America, on Sunday November 1, 1968. The conference was held at the Palmer House in Chicago, IL. There was to be a two hour, panel format, discussion starting at 3:00 pm. Also included in the letter about the panel discussion was an invitation to join Dr. Brady at brunch at the Palmer House in Chicago before the panel discussion. Panel Members at that brunch were Luther Brady MD, Chair of Radiation Therapy at Hahnemann; Fredrick Kraus, MD, Pathologist, Washington University; J. Edward Hall, MD, Professor of Gynecology, Down State Medical Center; Gerald Hanks, MD, Assistant Professor of Radiology at Stanford University; Paul Calabresi, MD, Professor of Medicine, Brown University, and George Lewis, Jr. MD, Professor and Chair of the Department of Obstetrics and Gynecology at Hahnemann, also the Chair of the Endometrial Cancer Adjuvant Study as outlined above. Dr. Brady’s planning session was diverted to the topic of a

cooperative effort identical to the Endometrial Cancer Adjuvant Trial but labeled "Ovarian Cancer," and not one protocol, but a series of protocols to be developed.

It was decided that the NCI should be approached by Drs. Lewis and Brady. Then the group would become involved in preparation of protocols and the Ovarian Cancer Group formation paperwork. Dr. Lewis was given the job of setting up collaboration through the NCI. It was also noted at that meeting that the statistician for the Endometrial Adjuvant study who was recruited from Roswell Park/SUNY Buffalo would be available if an ovarian cancer study group was to be formed. It was announced that a cooperative group operating out of Buffalo, the Cancer and Leukemia Group B (CALGB), was about to move out of Buffalo. Several of the statistical personnel who had worked with CALGB would be staying in Buffalo and might be available to run a statistical operation for this gynecologic proposal. Dr. Brady reporting in a later letter to other members present at that initial meeting explained that Dr. Lewis had talked to a Dr. Larry Foye at the NCI and that the NCI was interested. Dr. Foye had agreed to meet with the Group in Bethesda, November 13, 1969. Those present were Drs. Foye, Brady, Lewis, Hanks, and a Dr. Kaplan representing Dr. Calabresi. A rough draft of an Ovarian Cancer Cooperative effort was presented to Dr. Foye. He told everyone that the NCI was not approving single site oriented protocols and that the NCI was only interested in research organized to deal with a body system. As an example he suggested that our thoughts should be directed toward formation of a system type group and Dr. Foye also suggested it be designated as a Cooperative Gynecologic Oncology Study Group. Dr. Foye urged recruiting of investigators, designing a series of objectives to be listed as protocols and organize standard operating procedures. Dr. Foye went through the concept of such a cooperative group, strong and weak points, membership types and programs for support including indirect costs. Dr. Foye also noted that several other investigators had already approached him just as this set of doctors had and they had also been turned down. He gave us instructions on how to contact them and investigate possible collaboration.

Using Dr. Foye's list of interested parties, 17 additional individuals throughout the United States, were approached for recruitment. His comments meant that we would seek a few more names for participation, names such as Drs. Wilbanks, Linton, Malkasian and Sall. The situation was publicized at meetings of the Radiologic Society of North America and meetings of the American College of Obstetrics & Gynecology. Recruitment efforts went on through 1969. Dr. Sall in New York offered to have a preliminary meeting at the Hospital of the New York Medical College. It was decided the new Group would be called the Cooperative GOG (Gynecologic Oncology Group).

Dr. Sall's proposal for an administrative meeting in New York City was endorsed. It was decided that Dr. Lewis would get in touch

with Dr. Myron Hreshchyshyn in Buffalo as a potential first chairperson of the Group as he was familiar with the grant submission process, knew about the activities of the CALGB that had worked in his area for years, and he was familiar with the SUNY/Buffalo Statistical Center that had served the CALGB. A letter was sent to Dr. Hreshchyshyn covering the history to that point in time. In the letter, Dr. Hreshchyshyn was asked to consider favorably the chairmanship of the Group. Dr. Hreshchyshyn expressed willingness to accept the chairmanship if it was offered.

The next event was a meeting of interested persons at the New York Medical Center. After Dr. Sall welcomed the Group to New York, Dr. George Lewis introduced Dr. Hreshchyshyn. The date of the meeting hosted by Dr. Sall was February 20, 1970. The attendees at that meeting were recorded by Dr. Hreshchyshyn as: Dr. Luther Brady, Dr. George Lewis, Dr. George Wilbanks, Dr. John Lewis, Dr. Sanford Sall, Dr. Kaplan, Dr. Mostaf Estatata, Philip Di Saia, Dr. Myron Hreshchyshyn, Dr. Gerald Hanks, Dr. Robert Rogers and Dr. Alfred Sherman. There were 15 institutions represented who saw about 2,000 new cancer patients per year. They accepted the concept of a "system" type of cooperative group. It named Dr. Hreshchyshyn as preliminary chairperson. It decided types of membership and it voted to make this a truly multi-disciplinary activity. Many other characteristics were set up and it was realized that several aspects of this activity would be unusual, but characteristic of gynecologic cancer research. About five preliminary proposals for protocols were suggested. Institutions were to be the members. Investigators would be representatives from the member institution and a preliminary organizational structure was decided. Types of institutional membership were discussed and the requirements of protocols and eligibility were reviewed. The concept of multi-discipline representation from each member institution was discussed and it was agreed that the Group would require that at least three different oncology related specialties would be named as institutional representatives: Gynecology, Radiation Therapy and Medical Oncology. It was agreed that "the function of the group was to accelerate progress made in gynecologic oncology during the recent years and it was felt that using the potential of the group, many of the problems related to current employed therapy modalities could be quickly resolved and at minimal cost."

Applications for institutional group membership would have to name individual representatives in these three required and other optional specialties when applying for membership in the GOG. It was anticipated that institutions might have additional members to serve on active committees such as nurses, pathologists, etc. Dr. Hreshchyshyn was elected Chairman. He stated he would send in an application for recognition and funding. An Executive Committee was elected at that time to advise and work with the Chairman. The members at that meeting tentatively agreed with five concepts for protocols. After the meeting, Dr. Hreshchyshyn carried out more recruiting and meetings were held in conjunction

with ACOG. He discussed the formation of the GOG with other gynecologists and representatives of medically oriented groups, representatives of NCI and HEW. After consultation with the NCI, a second organizational meeting was held in New York City in April 1970. This explored a further relationship with the NCI which obviously had to do with funding. At that time, the NCI offered to coordinate the development of protocols and grant applications. The NCI suggested that about 10 institutions rather than 20 would be more appropriate initially and would have a better chance of funding. Interestingly, 18 institutions were represented at this meeting. The seven proposed protocols were discussed of which five were eventually approved. It was at this meeting that the group changed its name from the "Cooperative Gynecologic Oncology Group" to the Gynecologic Oncology Group (GOG). The NCI offered to host a group meeting in June 1970. Dr. Hreshchyshyn found more support expressed by Dr. Carmel Cohen, Dr. Robert Park and Dr. Hugh Shingleton. At the 25th anniversary of the GOG, Dr. Hreshchyshyn, in a speech to recognize the occasion, noted that during the April 1970 meeting the name of the Group was decided as GOG dropping the term cooperative. Dr. Hreshchyshyn submitted a grant request. The NCI stated this type of money was not available until May of 1971, but he did get the NCI to partially fund a meeting of the new Group's membership with the NCI representatives in Bethesda, June 25-26, 1970. At the June 1970 meeting at the NCI, there were representatives from 14 institutions present. A constitution and bylaws were adopted. An executive committee was formed. Protocols were discussed and five were finalized. Two additional representatives attended, Drs. William Creasman and Charles Boyce. Dr. Charles Hammond from Duke University joined in on discussing the future direction for the GOG. The June 1970, two day gathering was the first official meeting of the organized GOG. Representatives from the NCI urged further pursuit of organization and investigation, but again stressed no funds were available until May of 1971. At the June meeting, the Executive Committee was elected. Nelson Slack, PhD was named as the Group Statistician and a Group Executive Officer, H. James Wallace MD, was named. Both individuals were located in Buffalo.

It was decided at this meeting that the original participating institutions would be the University of Alabama Hospital, Duke University Medical Center, George Washington University Medical Center, Hahnemann Medical Center, Hahnemann Medical College and Hospital, New York Medical College, University of Rochester-Strong Memorial Hospital, Roger Williams General Hospital, Rush Medical College-Presbyterian St. Lukes Hospital, Walter Reed Hospital, Wayne State University-Hutzel Hospital. University of Southern California.

During the early 1970's organizational structure was established and original flow diagrams are noted. There was a decision to have site specific committees and modality come and specific protocol

concepts and, later, fully developed protocols were to be discussed and approved in these committees. Then the committees were to give their reports before a general meeting involving everyone at the meeting. This worked out well when the GOG was small and could fit a committee meeting into a motel bedroom and use an empty dining room or small meeting room in a motel for the general business discussions. Meetings were held twice yearly with rotation in site so as to extend knowledge of the concept of this new Group throughout the USA.

The initial year was devoted to Group organizational procedures, committee organization, especially discussions of objectives and areas that might benefit from additional research or areas ripe for clear new objectives that were suggested at meetings. The administrators, the investigators and the Statistical Office collaborated in the design and production of data sheets applicable to gynecologic cancer, radiation therapy and chemotherapy. Statistical considerations were established before a protocol was initiated. Protocols were sent to NCI's CTEP for comment and approval. As protocols of Phase III type were being designed and activated medical oncologists in the group were extremely valuable in getting CTEP and the FDA to provide the lines of communication, under the LOI process, to start Phase II evaluations. In fact, a group of institutions were identified who were familiar with the Phase I process of testing and they were selected for this activity at the initiation of the group and through the guidance of participating medical oncologists. Initially, the process was that of evaluating a drug or two with the process being relatively slow and not as efficient as it might have been. The process was just beginning to work well by the mid 70's. A final organizational meeting was held at Roswell Park Cancer Center in the Spring of 1971; additional attendees were Dr. Julian Smith, Dr. Philip DiSaia, and Dr. Steven Piver.

Member Institutions were funded by grants based on review through CTEP mechanisms. This was the standard procedure at that time. By 1975, the GOG grew from 10 to 34 institutions which provided about 4,000 new invasive cancers a year and 23 protocols had been activated. When affiliates were joined in as participants the total number of institutions expanded to over 100. Years of limited funding hampered the choice of meeting sites and the extent of protocol development. It has to be remembered that funding started in the fall of 1971 for this new Gynecologic Oncology Group and CTEP. During its contacts with Group leaders the shortage of research support was always stressed. In 1974, several of the gynecologic leaders in the Group heard that a grant renewal review had been unfavorable. It was claimed by the CTEP that the Chairman had been sent the "pink" sheets. The Chairman claimed he had not been sent any notice. Most vigorous was the NCI claim that the Group had not yet published a single paper. On the other hand, it was reported that officials in the NCI could not locate the "pink" sheets alleged to have been sent. Outstanding leaders in the Group then asked for an election process for a new Chairman who

would take office starting in 1975. This election was carried out in July, 1974. Dr. George Lewis was elected as the new Chair to take over in 1975. The new Chair spent the year visiting CALGB and a new Group, RTOG, to determine what changes in GOG performance were needed. The NCI while reducing its planned funding did award enough money to continue existence on a yearly basis. The whole year of 1974 used for evaluating GOG performance led to decisions to identify and tighten up SOP (Standard Operating Procedures).

With the election of a new Chairman of the Group, the Statistical Section at SUNY /Buffalo replaced the prior Group statistician with a new Director of the Statistical Office, Dr. John Blessing. The activity of protocol processing was altered by creating a "Protocol Committee" that was made up by Chairmen of Site and Modality Committees and later, their Co-chairs were to be added as voting members. Other cooperative groups were also invited to send member representatives, but with no voting privileges. A Medical Oncologist, Dr. Tate Thigpen, was selected by the new Chairman of the Group as Chairman of the Protocol Committee. That individual and the new Chairman then reviewed the Phase II Processing so that it could process a large number of drugs in a shorter period of time. In fact, after that process was initiated, CTEP complimented the Group as the most productive group in Phase II processing. While that was going on, several of the Medical Oncologist representatives reorganized the Phase I-II procedures in the GOG under the Guidance of the Protocol Committee Chairman. Especially for Phase I evaluations institutions were designated for the GOG tasks as most likely to succeed based on their past experience with Phase I evaluations. A Phase I Working Committee was set up to conduct and monitor performance of participant institutions.

Membership requirements were tightened with a point system to be awarded to each member for each patient entered into GOG protocols. These points and other factors were used to determine the membership status of each institution. Each protocol was rated by perceived value to the Group and the amount of work involved by the PI and staff at the institution. That number was to be reviewed by the Protocol Committee Chairman and the Chairman of the Group based on financial incentives to investigators and the complexity of given protocols. As part of this process of tightening up the validity of information coming in from member institutions it was decided by the new Protocol Committee that each Modality Committee would prepare a manual of specifications defining what were standard procedures for the Group members to follow with the object of obtaining effective therapy that was uniform, proper and fitting. Those published definitions while originally used to check old records from the first four years were to be used by future designers in the process of developing new protocols. Quality control was introduced for and defined by the Modality Committees.

Protocols during this period of change over from the mid-70's to the mid-80's remained stable and there was a trend toward Surgical Operative/Surgical Pathology research to define the characteristics of cervical, endometrial and ovarian cancers. About that time, endometrial cancer staging was thoroughly evaluated based on surgical pathology findings and the subsequent outcome of the clinical course for each patient in a pilot study, and a subsequent major

full protocol initiated through efforts of outstanding representatives/investigators in the GOG. Basically these studies: endometrial staging, ovarian staging and cervical cancer staging were conducted to better define the natural history of these malignancies. In brief, the information gained from large scale staging studies such as the endometrial staging approach was intended to provide a dependable basis for classifying patients relative to their risk for recurrence. That meant as the GOG went on in its studies of different programs and went into translational research, patients involved in such studies could be most appropriately selected for study because the staging studies established the basic risk patterns of their disease. In short, patients entered into the Endometrial Surgical Pathology protocol were meant to later help separate patients to be enrolled in future protocols by defining dependable categories of risk so that comparative studies (Phase III type) would be defined by meaningful selection of patients. It has to be remembered that before this Group came into being the information everyone depended on was very empiric as it was based upon testimonial type publications over many years. The Group was the first body to really examine the patho-physiology of malignant challenges posed by each patient as far as their planned therapies were concerned. These studies led to major changes in staging for endometrial and vulvar cancers. FIGO, based on these studies now have adopted surgical staging compared to previous clinical staging. The first clinical publication of the GOG was 1976, the preliminary results of Pilot 1, surgical staging of endometrial cancer. By the end of the decade a total of 40 manuscripts had been published.

The first three to four years of GOG existence were devoted to tooling up the organization and testing effectiveness of treatments used for years under the cover of observational evidence, but the testing was now in Phase III trials of agents claimed to be the indicated therapy. The evidence was analyzed with statistical methods and nothing was found to be superior. The next 10 years were devoted to tightening protocol specifications to achieve within a given protocol evidence that was thoroughly monitored as an ongoing process and therefore reliable. Those same years were also ones in which the GOG devoted a lot of its effort to the conduct of Phase II studies. After all, if past programs had not proven very successful where does one go from there? The question became: what was in line to be the next potential most effective treatment. The GOG tooling up to conduct Phase II studies. Result: It was commended for its demonstrated ability to screen a large number of agents to seek the few that might move onto Phase III testing.

The successful screening of a large number of agents was in large measure due to the active contributions of the Medical Oncology representatives in the GOG.

But in the 1980's, not surprisingly, there were a lot of administrative financial pressures to be borne by the GOG and other cooperative cancer related groups. The cooperative groups were informed by the HEW that government financed research support costs had to be kept stable for some of the groups. Some others were to be entirely eliminated. Money normally directed toward cancer research was being diverted into other research related to a plague-like illness (AIDS) that could be related to cancer (that's what the GOG was told) and findings from this new research potentially would prove, in the long run, useful and effective in understanding, treating and possibly curing cancer. This trimming back on the cooperative group members and the diversion of funds led to a virtual feeding frenzy, just as one might apply the terms to sharks in their natural habitat! The cooperative group membership number was cut again and again; the remaining members looked forward to sharing some of the spin off money available from cancelled groups. Successful maneuvering of the GOG and the intervention of at least two women's support groups helped keep the GOG from being food for one well recognized shark. The national attitude toward medical funding efforts tightened up a lot. Federal support for cancer related research got skimpy toward the latter years of the 70's and during the 80's. Several research cooperative groups were not funded and ceased to exist.

As the 80's transpired, the stream of Phase II studies was beginning to pay off with some winners. Actually, in the mid-70's it had paid off royally with the evaluation of platinum-based chemotherapy. The Group felt it was in a position to attract more participants and to enroll more patients. As the decade was ending, the GOG administrative office began to seek ways of attracting entrees from a wide range of medical institutions. The public and the press were noting that there were a lot of patients out there who could not get into cooperative group studies because the structure of the cooperative groups did not allow inclusion of entries from institutions that encountered less than ten candidates per year. With such low enrollment these institutions would not be eligible to be members. The GOG had already a system for enrolling institutions who had affiliates and who had a system in place for reviewing and controlling the entries.

One of the PI's in the GOG, Dr. Clarence Ehrlich used his notebook computer to design a program to operate a system for expanding patient enrollment through a reimbursement system that related to the already existing point system for membership. Computer programming was initiated by Dr. Clarence Ehrlich sending questionnaires to a lot of PI's and their staff members asking them to provide an idea of their costs of doing clinical research. With answers from participants, Dr. Ehrlich was able to provide meaningful, by case, estimates of the cost of research. After that was

approved by CTEP, payment to the institution of the PI throughout the USA was based on Dr. Ehrlich's calculation of costs. If the patient met requirements for eligibility and evaluability payments would now go per patient registered based on Dr. Ehrlich's point system. Awards to institutions as part of a grant system have been dropped. This approach dramatically increased registrations for the GOG.

As the 1980s came to an end, Dr. George Lewis stepped down as the Group Chairman and Dr. Robert Park was elected as the new Chairman; also the GOG and other cooperative groups were advised to modify protocols by adding to as many protocols as appropriate translational. research projects. The costs of these modifications of research were not covered by any funding proposal in advance. The GOG set up a modality committee to deal with this new challenge of translational research. This twist to clinical research has begun to integrate basic science investigators into the arena of clinical investigation. Results are now being analyzed in the GOG's earliest programs of translational research. The GOG is looking into integrated targeted therapies that may improve the outcome of treatment as never before. The GOG prospered with Dr. Park as Chairman and enrollment went up considerably. In 2001, Dr. Park announced that he would not be a candidate for re-election after 12 years of service and Dr. Philip J. DiSaia was elected as his successor in 2002.

Beginning in 2001-2002 the Group grew rapidly. Such that by 2010 the Gynecologic Oncology Group involved close to 200 institutions across the country. Patients were accrued from intuitions either as member institutions or as affiliated institutions working alongside a member institution. Protocols requiring as many as 5000 patients were successfully completed. The Developmental Therapeutics Committee became very active in Phase I and Phase II trials. The Committee on Experimental Medicine attached translational science protocols to most of the Phase III and some of the Phase II studies. Attendance at biannual meetings approached 1000 individuals in most cases. The Group was very dynamic and successful when it was told that it needed to merge with two other groups. This merger was to take place in the Spring of 2014 and the two Groups with whom the merger would be accomplished were the Radiation Therapy Oncology Group (RTOG) and the National Surgical Adjuvant Breast-Colon Project (NSABP). The three Groups will merge into what has been entitled NRG. The first funding of this new entity will begin March 1 of 2014 and the mechanisms necessary for this new entity to be successful has been under study for two years. In the interim all the activities of the Gynecologic Oncology Group as it was known from 1970-2014 continued uninterrupted.

A Proud History and Productive Future

The Gynecologic Oncology Group, over 43 years, has come a longway from its early struggles of just learning how to function as a Cooperative Group. The popular expression to describe the

progress of the GOG is to say that it has "matured." It has along with other cooperative groups learned to survive and maintain, (despite interval stresses), well organized and high quality scientific research. It has progressed dramatically from checking earlier reported therapeutic outcomes to developing means of rapid and dependable processing of studies, especially, in the field of translational research. In summary, it has been very successful in

adjusting to the changing presentations of scientific progress in oncology research. Not stressed enough is the fact that from the beginning this Group has essentially been the first and only Group to strongly emphasize the role of various specialties working together to care for patients who have or may develop a cancer of the female reproductive track. The Group functions as a multi-disciplinary group.



GOG Finance and Development Office staff - *Crofton, MD*



GOG Administrative Office staff - *Philadelphia, PA*

The Gynecologic Oncology Group Scientific Process: A Unique Approach to Cooperative Clinical Trials



J. Tate Thigpen, MD, and John A. Blessing, PhD

Until the advent of the twentieth century, options for treating patients with cancer focused on the early identification and surgical removal of malignant masses. For patients with disease no longer amenable to surgical resection, various potions of natural remedies produced the occasional shrinkage and disappearance of clinically identifiable masses without any evident prolongation of life. As medical science began to identify approaches such as radiation or chemicals with apparently greater and more predictable ability to shrink tumor masses, the need to evaluate the relative merits of these various approaches became evident. The randomized clinical trial evolved as the vehicle for such evaluations, and the science of biostatistics blossomed as the means for sophisticated analyses of data generated by these clinical trials.

It soon became apparent that no single physician or medical institution saw sufficient patients with a particular diagnosis to conduct these comparative trials in a timely fashion. So it was, in the decade of the 1950s, that the cooperative clinical trials group was born. Such a group consisted of an agreement among a number of medical investigators and institutions to develop a common clinical protocol to evaluate the relative merits of one or more new therapies as compared to a standard control regimen which was generally accepted as the standard of care at the time. The combined efforts of these multiple investigators and institutions permitted the accrual of sufficient patients with a particular cancer to allow a more rapid evaluation of new therapies for that diagnosis.

The focus of this discussion is on the character of such groups, the challenges that face participants in the cooperative process, and the contribution of a unique approach to cooperative clinical trials by the Gynecologic Oncology Group, one of the National Cancer Institute funded cooperative cancer clinical trials groups.

General Characteristics of Cooperative Groups

The early cooperative groups evolved usually as the result of the

efforts of one or a small number of individuals highly interested in a particular disease process. Leadership was vested, in most instances, in an individual who was designated as the Group Chairman. This individual and a few of his close associates usually determined the trials to be performed, recruited the institutions and investigators who participated in the trials, developed the support system for the collection and analysis of the data, and oversaw the process of publication of the results.

That these early cooperative groups succeeded in making major contributions to our knowledge of disease processes and our management of specific patient problems is remarkable when one considers that much about the cooperative group process ran contrary to the interests of the individual investigators. Most participants were in the academic arena and were participating in a process which did not provide them with academic or publication credit. The objectives of the trials often were contrary to the biases of at least some of the participants. From the investigator's perspective, recruiting patients required more time to explain the trial as well as a willingness to admit that the best approach to treatment was in fact not known. Funding provided by the National Cancer Institute in the form of an institutional grant was often the only glue that held the cooperative group together and encouraged the entry of patients onto study; but the independence between grant funding and level of participation often resulted in slow accrual to studies which asked questions often not of the greatest interest to all investigators.

These and other problems in fact plagued the early years of the Gynecologic Oncology Group (GOG). The early attempts at group-wide studies reflected these problems. Members insisted on a final vote by all participants; hence, the last issues in protocol design were debated in a general forum of all members. Protocols tended to reflect the bias of individual vocal institutions rather than a comprehensive strategy for the improvement of management of

gynecologic cancers. As a result, many institutions did not participate in the studies; and accrual lagged. By the fourth year of group activity, prominent members of the GOG realized that a change in approach was needed. The process of change started with the election of a new group chair who promised substantial changes in the way the group worked.

Evolution of the GOG Process: 1976-2003

With the election of a new group chair (Dr. George Lewis) came the appointment of a new statistician (Dr. John Blessing) for the GOG. These two individuals led the way in initiating a new and very different approach to the development and execution of group studies. Several considerations were paramount in determining the nature of that approach. Firstly, oversight of the scientific process had to be designed to develop an overall strategy, to insure that studies were consistent with that strategic direction, and to apportion GOG resources to the various studies effectively and efficiently. Secondly, all members of the GOG needed to have the opportunity to submit study proposals and to feel that each was a part of the process of study development so that a sense of ownership would encourage participation. Thirdly, the process had to foster interdisciplinary collaboration so that well-designed multidisciplinary trials resulted. Finally, the process needed to produce studies and publications in a timely fashion so that “down time” between studies was minimized so as not to waste patient resources and results were disseminated rapidly to those responsible for patient care. Additionally, the process had to include a forum which permitted interaction with other groups with which the GOG collaborated.

Scientific Oversight

The first step in the evolution of a new approach to the scientific activity of the GOG was to instigate an oversight mechanism which could develop an overall strategy, insure that studies were consistent with that strategy, and assign resources to studies effectively and efficiently. At the time that this process was being considered, the GOG had a committee structure which included disease-oriented committees (Endometrial Cancer, Ovarian Cancer, Cervix Cancer, Uterine Sarcoma, Trophoblastic Disease) and modality committees (Gynecology, Radiotherapy, Chemotherapy, Pathology). In addition, the structure included a Protocol Committee which focused solely on reading through the final version of a protocol for errors before it was submitted to the National Cancer Institute.

The first major decision was to change the composition, scope, and role of the Protocol Committee. This committee was designated as the oversight committee for all of the scientific activities of the GOG. For the committee to perform its new role, its composition had to be altered significantly. Since all other scientific committees would be reporting to the Protocol Committee, the leadership of the Protocol Committee needed to be multidisciplinary;

and the composition of the committee had to include the leadership of each of the other scientific committees that would report to the Protocol Committee. The GOG Group Chair appointed a gynecologic oncologist and a medical oncologist as the co-chairs of the Protocol Committee and changed the committee membership to consist of the chairs of the other scientific committees, representatives of the GOG Statistical and Data Center and the GOG Administrative Office, the Group Chair and Group Vice-Chair, and representatives of the National Cancer Institute and of other groups with which the GOG collaborated.

The members of this new oversight committee met in Buffalo, New York, at the GOG Statistical and Data Center to flesh out the details of the new process and to develop a manual outlining these policies. This meeting produced the first GOG Protocol Procedures Manual that, with minor modifications to accommodate the expanded activities of the GOG, still governs the scientific effort today. This manual set out the process by which new ideas were to be received, priorities were to be set, protocols were to take form from adopted concepts, studies were to be monitored during the execution phase, and publication of results was to occur.

In brief, each scientific committee, through its chair, would bring its recommendations to the Protocol Committee, which had to approve or reject each recommendation. The Protocol Committee would then oversee the process of developing approved concepts into protocols, activating and running those protocols to conclusion, and publishing the results. The Protocol Committee was also responsible for assuring that the appropriate scientific committee began development of study replacements in a timely fashion.

From the inception of the Protocol Committee, several principles characterized the committee’s activities. Firstly, decisions were based on a majority vote of the committee. Secondly, the committee operated strictly under parliamentary procedure to protect the rights of the minority positions to be heard. Thirdly, meetings of the Protocol Committee occurred not only at the semi-annual business meetings of the GOG but also at two interim meetings that were held at the midpoint between business meetings. These operational principles of a defined and fair decision-making process and frequent meetings better enabled the committee to fulfill its role as the scientific leader of the GOG.

Empowerment of Members

The second important aspect of the GOG approach to protocol development focused on the role of the individual member of the GOG. The leadership recognized that the ultimate success of the GOG depended on the active participation of each member in group studies. Without adequate patient accrual, the greatest scientific ideas and study designs for clinical trials mean very little; hence, the process had to provide an opportunity for meaningful input from those who would provide the patients for the trial.

Providing for meaningful input from GOG members required first that appropriate forums for receiving that input be put into place. This in turn required that the committee structure answering to the Protocol Committee be modified. Multidisciplinary forums for the development of phase III trials were appointed and, over time, evolved into three major multidisciplinary committees: Committee on Cancers of the Ovary, Committee on Cancers of the Cervix and Vulva, and Committee on Cancers of the Uterine Corpus. Specialty forums to focus on specific areas of interest were added to the structure and included: Developmental Therapeutics Committee (new agent and new approach testing), Committee on Experimental Medicine (basic and translational research), Quality of Life Committee, and Committee on Cancer Prevention and Control. Each of these seven committees provided a forum in which any GOG member could introduce a concept for a new GOG study. Determination as to what concepts would be approved for further development was to be decided by a majority vote of the committee after each concept proposer had an opportunity to present and defend his or her concept. Modality forums focusing on quality control and the role of that particular discipline were expanded to permit the discussion of modality-specific concerns and included: Gynecologic Oncology Committee, Radiation Oncology Committee, Medical Oncology Committee, Pathology Committee, and Nursing Committee.

Each of the various forums would then bring the approved concepts forward for consideration by the Protocol Committee which would take such issues as availability of necessary resources, overall scientific direction of the GOG, and the merit of the individual concept into account. The Protocol Committee would then decide by majority vote which concepts would proceed to full protocol development and ultimately a GOG study.

Within this system, each individual GOG member would have an opportunity to have meaningful input in regard to the proposal of new study ideas and voting on proposals. This in turn provided a sense of ownership to members regarding the studies of the GOG. This sense of ownership became a powerful incentive for active participation in studies by the accrual of patients.

Multidisciplinary Collaboration

The third critical aspect of designing phase III cooperative group trials was to insure that the studies were multidisciplinary. The evolving GOG process was geared to foster multidisciplinary interactions. The committees assigned the primary responsibility for developing phase III trials were multidisciplinary committees. By design, each of these committees including the Protocol Committee had a chair and co-chair from different disciplines and a planned multidisciplinary composition. In addition, each protocol involving a particular discipline had to be reviewed by the modality committee representing that particular discipline. This process assured proper review by members who practiced that particular discipline and also assured that concepts were considered by a

forum which included representatives of all the disciplines involved.

Timely Publication

The fourth concern in the evolution of the scientific process within GOG was the timely reporting of study results. To address this concern, the leadership of the Protocol Committee appointed a subcommittee with multidisciplinary membership to oversee publication of completed studies. When the Statistical and Data Center determined that data were sufficiently mature to permit the generation of a publication, the subcommittee, in consultation with the Statistical and Data Center, applied the publication policy to determine who would serve as the co-authors for the trial. The study chair, who was the first author, generated the manuscript which, in turn, was reviewed by the co-authors and the Publications Subcommittee. The subcommittee set deadlines for each step of this process and reported progress to the Protocol Committee until the publication was in press.

Intergroup Collaboration

The fifth concern in the evolution of the scientific process was to provide a forum in which intergroup collaboration could be fostered and hence more rapid accrual to studies could be achieved. This was addressed by the GOG by providing for Protocol Committee membership for a representative from each group with which the GOG worked. This mechanism was subsequently replaced in the 1990s by the Gynecologic Cancer Intergroup (GCIG) which includes representatives of 25 cooperative groups worldwide. Collaborative studies are now developed through the GCIG.

Evolution of the GOG Process: 2003-2013

Dr. Phil DiSaia, upon election as Group Chair in 2003, initiated a process of internal reassessment that has led to two significant changes in the GOG approach to trial design and execution: the division of the Protocol Committee into two committees with a resultant reorganization of responsibilities and the establishment of a separate mechanism for the development of studies outside the jurisdiction of the Cancer Therapy Evaluation Program of the National Cancer Institute.

Reorganization of the Protocol Committee

The increasing complexity of studies and the study design process had by 2003 created tremendous pressure on the leadership of the Protocol Committee to oversee both protocol development and execution. Based on the deliberations of a task force appointed the Group Chair, Dr. Phil DiSaia, the Protocol Committee was replaced by two committees, the Protocol Development Committee and the Operations Committee.

Protocol Development Committee (PDC). The PDC accepted responsibility for the development of studies from concept to activation of the trial. Seven protocol-generating committees report to the PDC: the Committee on Ovarian Cancer, the Committee on

Cancer of the Cervix and Vulva, the Committee on Cancers of the Uterine Corpus, the Development Therapeutics Committee, the Committee on Experimental Medicine, the Committee on Health Related Outcomes, and the Committee on Cancer Prevention and Control. The membership of the PDC includes the chair and co-chair of each of the seven reporting committees to insure accurate reporting and factual advocacy for the proposed studies.

Operations Committee (OC). The OC was charged with overseeing the conduct of the studies from activation to results reporting. The seven protocol-generating committees listed above reported on the progress of each study to the OC at each semi-annual business meeting. The modality committees (Gynecologic Oncology, Radiation Oncology, Medical Oncology, Pathology, and Nursing) provided oversight for quality control and assurance. Finally, the Publications Subcommittee monitored the publications process to insure timely reporting of study results.

Critique of the New Structure. The new structure provided the GOG several advantages while retaining the GOG principles of study design and execution that have already been described. First, the PDC was able to focus entirely on interrelating with the NCI-based protocol review process. This process has become exceedingly complex and includes the Gynecologic Cancer Steering Committee (GCSC), task forces of the GCSC for each major disease site (ovary, cervix, endometrium, etc), the Central IRB, and multiple teleconferences. The impact on the time required to activate a phase III trial has been investigated and well documented in a study commissioned by the NCI and averaged 600 days from concept to activation for all cooperative groups. The benefits derived from the new structure and the concentration of effort on study development in a committee whose only function was study development was reflected in the fact that the GOG had the shortest time from concept to activation of any group at 409 days.

At the same time, the new structure provided better focus on issues related to the conduct of trials. In particular, the OC has provided intensive oversight to accrual rates on each trial and has been able to identify and address problems before they become fatal flaws for the trial. In addition, the GOG has been able to eliminate delays in results reporting by defining each step in the publications process and developing oversight for each of the steps.

These enhanced functions derived from the new structure have allowed the GOG to maintain a very robust menu of phase I, II, and III trials as well as translational research and studies of patient-centered outcomes in gynecologic cancers. Most importantly, the structure has made possible the retention of the principles delineated in the first 35 years of the GOG, particularly that of retaining an open forum that allows every investigator an opportunity for meaningful input.

Establishment of a CTEP-Independent Initiative

By 2010, the NCI had announced its intention to restructure the cooperative group system into the National Clinical Trials Network (NCTN). The decision was based on a study commissioned by the NCI and conducted by the Institute of Medicine (IOM). The study recommended that the number of adult cooperative groups be reduced to eliminate duplication. What resulted was the decision to reduce the number to four with the retention of the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), the Alliance (formerly three groups including Cancer and Leukemia Group B, the North Central Clinical Trials Group, and the American College of Surgeons Oncology Group), and a fourth group to result from a merger among the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group and the GOG. The total funding was to be capped at a level lower than the current funding for the groups, and accrual was to be capped at less than the then current accrual of the nine groups. This plan will come to fruition in March 2014.

It became apparent to the leadership of the GOG that the specifications of the NCTN would not permit the GOG to retain its robust research agenda. Following a retreat in April 2010, the decision was made to establish GOG Partners, a separate entity that would foster collaboration between the GOG and industry in the development of trials of new approaches and agents independently of the CTEP process. GOG Partners oversees study development and execution through the PDC and the OC so that the decision to conduct a trial is based on the scientific merit of study concepts and the financial feasibility of the trial through industry funding rather than funding from government sources. To date, in the first three years, three trials have been activated: two phase III studies and one phase II study. At least six other studies are under consideration.

GOG Partners provides the GOG with several significant advantages. First, it allows the GOG to continue its extensive investigation of new agents and approaches through phase I and II trials without the encumbrance and complexity of the CTEP mechanism. Secondly, it provides the funding that allows the GOG to maintain the extensive and very valuable support resources at the GOG Statistical and Data Center and the GOG Administrative Office. Thirdly, the GOG has provided the Gynecologic Oncology community of physicians an important resource for the education of fellows about clinical trials. GOG Partners will make it possible for the GOG to continue to exist as an important entity for promoting and teaching about cancer clinical trials studying the management of gynecologic cancers.

Unique Features of the GOG Process

The GOG process for protocol development exhibits unique features which have served the GOG well and which have retained their uniqueness and importance even as the GOG adapts to the changing world of cancer clinical trials. Firstly, the process is an

entirely open process. Any GOG member can submit a concept for a study. The success or failure of that concept depends entirely on the scientific merit of the proposal and the ability of the submitter to defend the proposal's merit. Even proposals from such other entities as the National Cancer Institute are subjected to the same rigorous debate and review for scientific and clinical merit. This aspect of the process insures that the ideas under consideration for GOG clinical trials provide a wide range of options. This open process creates a milieu which draws ideas from a broad range of sources, a range reflected in the diversity of group membership, and provides a forum for open debate to enable the selection of the best possible ideas for ultimate trial design.

Secondly, the adoption of strict parliamentary procedure for the meetings of the scientific steering committees, the Protocol Committee first and then later PDC and the OC, guaranteed the right of any minority position to be heard. While this may not seem like a major step, this right is not always protected in traditional cooperative group structures. This protection seeks to empower members to feel that their viewpoint received a fair hearing. In turn, this actually encourages participation in the ultimate study that is adopted. As the meetings of the Protocol Committee served as an example of what could be accomplished with a strict application of parliamentary procedure, other committees within the GOG adopted similar procedures with similar salutary effect.

Thirdly, the process encourages multidisciplinary input by treating all disciplines as equal. Any member, regardless of discipline, can submit a concept for consideration. The primary committees to consider concepts for phase III trials are multidisciplinary in both leadership and composition. Once a concept is adopted, the study chair and co-chairs are appointed to insure multidisciplinary representation. Perhaps the best indicator that all disciplines are treated as equals within the GOG process is the fact that the Protocol Committee was chaired by a medical oncologist from its inception to the change of the structure in 2003.

Fourthly, the process is sufficiently flexible to adapt to the changing environment in the scientific community. This process has successfully integrated a number of new areas of endeavor into the GOG scientific process; these areas have included, among others, translational research, assessment of quality of life, cancer prevention and control studies, and multi-institutional phase I studies. This has been handled by the addition of new forums for discussion and debate of ideas within the category previously described as Special Studies Committees. The increasingly frequent need to respond quickly to new initiatives was met by the creation of a subset of Protocol Committee members, the Chairman's Working Group, under the direction of the Group Chair. This entity, which continues under the new structure to act as a scientific executive subcommittee, was able to respond to urgent requests for proposals from the National Cancer Institute as well as industry and also to assist the Group Chair, the Protocol Committee, and later the PDC

and OC with difficult issues related to the GOG's interface with other groups and with the National Cancer Institute.

Finally, the GOG process has married finances to study participation by the GOG's becoming the first group to forego a system of institutional grants and support accrual to clinical trials entirely through a per capita reimbursement system for patient accrual. This resulted in a tripling of the annual accrual of patients to studies and an even greater increase in the number of participating institutions from 40-50 to now a number that approaches 300+. The result has been the ability to answer questions that could not previously be addressed because of the lack of patient accrual.

The GOG Process in Perspective

The GOG process for protocol development and execution finds its strength in the open nature of the process. This permits maximum input from the largest number of members possible, input limited only by the willingness of members to work to develop concepts and defend them in scientific forums. This in turn encourages members to feel a sense of ownership of the science of the GOG since that science ultimately evolves from their ideas, their work, and their participation. At the same time, the concept of a central scientific committee or, under the new structure, committees into which the entire process feeds has allowed for a measure of control to insure that major scientific goals are met and resources apportioned appropriately; and the marriage of finances to patient accrual has stimulated accrual to levels that permit questions to be addressed.

An open process, however, is by its nature at times a messy process. The greatest strength can at times become the greatest weakness and can result in an unfocused effort. The major criticism that has been leveled at the GOG over the years has been the contention that good science cannot result from an open protocol development process. The purveyors of this opinion in general favor a "top down" system in which the leadership dictates the studies that will be run and the individuals who will chair those studies. Such systems allow far less opportunity for member input. Furthermore, who can say that a particular individual's ideas are superior to others without proper debate and input?

The value of the GOG process, at least for the GOG, is clearly shown by the results achieved. GOG studies have methodically and logically moved the therapy for ovarian carcinoma from single agent melphalan to the current standard of paclitaxel plus carboplatin, demonstrated the activity of systemic therapy including a targeted agent (bevacizumab) for recurrent cervix carcinoma as well as the efficacy of concurrent chemoradiation for locally advanced disease, and changed the paradigm for the management of endometrial carcinoma by demonstrating the value of chemotherapy not only in disseminated or recurrent disease but also in earlier stage (stages III-IVA) disease. These achievements have taken place despite the fact that gynecologic malignancies are far less

common than such cancers as breast cancer, lung cancer, and gastrointestinal cancers. The track record speaks for itself.

In short, the GOG process combines an open system which provides maximum access to input by the group members with sufficient controls from a steering committee (the Protocol Committee and, under the new structure, the PDC and OC) and strict parliamentary procedure to insure a fair hearing for all ideas and a focused effort through well-designed clinical trials. The process

links finances directly with patient accrual to study and thus encourages study participation. The result is that the GOG has been able to establish and improve the standard of care for gynecologic cancer patients through the last three decades. The process is flexible enough that the group has been able to adapt to the changing scientific environment successfully and to introduce new initiatives without a major overhaul of the system. The return from the process has been well worth the challenges associated with any open process.

Gynecologic Oncology Group Trials in Ovarian Cancer



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Introduction

The Gynecologic Oncology Group (GOG) has an extensive history of research in ovarian cancer, with the results of many of its clinical trials establishing the standard of care for treatment of this disease both in the United States and abroad. These trials have addressed the role of staging, surgery and treatment in ovarian cancer. Treatment trials have been distributed by stage, amount of residual disease and cell type. More recently, ovarian cancer clinical trials have evolved to adapt to greater insight into the molecular mechanisms of certain cell types and the prevalence of newer targeted strategies. The purpose of this chapter is to review the ovarian cancer trials of the GOG from the beginning to the present day. In order to demonstrate the progression of the GOG experience in an orderly fashion, we have divided the GOG experience into early stage epithelial ovarian cancer, optimally debulked advanced epithelial ovarian cancer, suboptimally debulked advanced epithelial ovarian cancer, malignant germ cell tumors of the ovary, malignant stromal tumors of the ovary, and other trials in ovarian cancer.

Early Stage Ovarian Cancer

Protocol #1 was activated in 1971 and closed to patient entry in 1978. (1) Eligible patients with stage I epithelial ovarian cancer following surgical therapy were randomized to one of three groups: 1) no further therapy; 2) pelvic irradiation (5000 cGy over five to six weeks); or 3) melphalan chemotherapy (oral dosage of 0.2 mg per kg daily for five days every four weeks for 18 months). Patients with tumors of low malignant potential and patients with ascites were excluded. One hundred sixty-eight patients were enrolled and 86 were evaluable. Recurrence of cancer by type of therapy was 17% for the no further therapy arm; 30% for the irradiation arm; and 6% for the chemotherapy arm. Recurrence was also related to grade (grade 1: 11%, grade 2: 22%, grade 3: 27%) and to substage (IA1 – 10%, IB2 – 50%). The authors concluded that with the exception of IA1 tumors, patients with stage I cancers

of the ovary are best managed by melphalan chemotherapy. They further concluded the patients could only be classified as stage IA1 if they underwent a full surgical staging operation.¹

However, the use of an alkylating agent was not without adverse sequelae. In 1982, the National Cancer Institute (NCI) Epidemiology Branch published a follow-up report on the patients treated in this study as well as patients treated with alkylating agent chemotherapy at M.D. Anderson Hospital and Princess Margaret Hospital. Nine hundred and ninety-eight patients treated with alkylating agent chemotherapy, twelve cases of acute nonlymphocytic leukemia occurred in these patients compared to an expected number of 0.11.²

In 1976, two collaborative clinical trials were begun to further evaluate the therapy of early ovarian cancer. These trials began as studies of the Ovarian Cancer Study Group (composed of physicians from the Mayo Clinic, the M. D. Anderson Hospital and Tumor Institute, the National Cancer Institute and the Roswell Park Memorial Institute) and in 1978 were joined by the GOG. GOG #7601 (number assigned when the GOG joined the study) studied stage IA 1 and stage IB 1 (well and moderately differentiated) epithelial ovarian cancer randomizing patients to no further therapy versus melphalan chemotherapy (0.2 mg/kg orally days one to five on a 28 day cycle for 12 courses or 18 months). GOG protocol #7602 randomized patients with stage IC and II A, B, C, and selected stage IA 2 and IB 2 to either melphalan chemotherapy (as above) or intraperitoneal P32 (chromic phosphate) at a dose of 15 mCi. The findings from these trials were published as a single paper in April 1990.⁽³⁾ In protocol #7601, with median follow-up of more than six years and most surviving patients followed for more than three years, there was no significant difference in either disease-free survival ($P=0.41$) or overall survival ($P=0.43$). The five-year survival rate was 94% for the no treatment arm and 98% for the melphalan arm. For protocol #7602, after

follow-up of more than six years in surviving patients with 86 % followed over three years, there was no difference in disease-free survival ($P=0.48$) and overall survival ($P=0.87$). The five-year survival for the melphalan arm was 81% and, for 32P, it was 78%. The authors concluded that patients with stage IA 1 and IB 1 well or moderately differentiated tumors that are well staged surgically do not benefit from additional treatment. For other early stage patients treatment is indicated, but there is no clear difference in benefit for either melphalan or intraperitoneal 32P.³

Building on the results of GOG #7602, the GOG opened protocol #95 in 1986 as a prospective randomized trial of intraperitoneal P32 compared with cyclophosphamide/cisplatin combination chemotherapy in women with early-stage ovarian cancer at high risk for recurrence.⁴ These included surgically-staged patients with stage IA grade 3, IB grade 3, stage IC, or completely resected stage II ovarian cancers. A total of 251 patients were randomized to a treatment of intraperitoneal P32 versus cisplatin/cyclophosphamide (CP) chemotherapy using a standard phase III study design between the years 1986 and 1994. The cumulative incidence of recurrence at 10 years was 35% for patients receiving intraperitoneal P32 and 28% for those receiving CP ($p=0.15$). The death rate for patients treated with CP was 17% lower than for patients treated with intraperitoneal P32. The authors concluded that although there were no statistically significant differences in survival, the lower cumulative recurrence seen with CP and the increased toxicity of intraperitoneal P32 administration made the platinum-based combinations the preferred adjuvant therapy for early ovarian cancer patients.⁴ This trial was important in introducing cisplatin based chemotherapy to the treatment of ovarian cancer.

Building upon the demonstrated efficacy of paclitaxel in more advanced stage clinical trials, the next trial in early stage disease incorporated both paclitaxel and a platinum based agent in the form of carboplatin. GOG #157 compared carboplatin (AUC 7.5) and paclitaxel (175 mg/m²) for three cycles as the control arm versus six cycles of the same drugs as the experimental arm using the same high-risk criteria of surgically-staged patients in an effort to define the optimal duration of therapy. Between 1995 and 1998, 457 eligible patients were enrolled in this study and the results were reported after a median duration of follow-up of 6.8 years. The recurrence rate was 24% lower with six versus three cycles ($p=0.18$). The overall death rate was similar for these two regimens with a hazard ratio of 1.02. Of note, the patients who had the six cycle regimen experienced 11% grade 3 or 4 neurotoxicity versus 2% in the three cycle regimen. The authors concluded that compared to three cycles, six cycles of carboplatin/paclitaxel did not significantly alter the recurrence rate in high-risk, early-stage epithelial ovarian cancer, but are associated with more toxicity (Figure 1).⁵ The interpretation and application of this study has been the source of controversy and editorials.^{6,7}

Further analysis of the high-risk, early-stage ovarian cancer

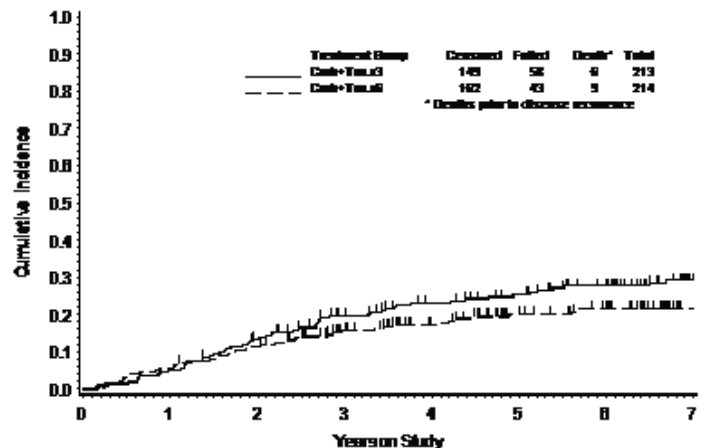


Figure 1. GOG-157 Cumulative incidence of recurrence by randomized treatment.

patients in GOG #95 and #157 indicated that a disproportionately large percentage of recurrences were coming from the stage II group. Indeed, GOG #95 reported that the 10-year accumulative incidence of recurrence for stage I patients was 27%; however, this increased to 44% for stage II patients ($p=0.01$). Similar data was seen for GOG #157. Based on this compelling data, the GOG opted to remove stage II patients from future protocols analyzing early-stage, high-risk disease and, instead, incorporate these patients into trials with advanced-stage patients.⁵

The most recent trial for high-risk, early-stage ovarian cancer was GOG #175. Based on the theory that low dose therapy with paclitaxel has anti-angiogenic properties, this trial randomly assigned patients to three cycles of paclitaxel (175 mg/meter squared) and carboplatin (AUC 6) chemotherapy with or without 24 weekly doses of paclitaxel (40 mg/meter squared) maintenance chemotherapy. This trial enrolled 571 patients of which 542 were evaluable for the study endpoints from 1998 to 2006. There was no additional benefit in the risk of recurrence and overall survival at 5 years with the addition of maintenance paclitaxel (Figures 2 and 3).⁸ There were higher rates of peripheral neuropathy, infection/fever and dermatologic events with the addition of maintenance paclitaxel.

GOG 175 represents the most recent trial for treatment of women with high risk, early stage ovarian cancer. At the time of this publication, there are no active treatment trials in this patient population.

Optimally Debulked Advanced Epithelial Ovarian Cancer

Historically, the GOG separated patients with advanced stage ovarian cancer into optimally debulked or suboptimally debulked clinical trial populations after GOG trial #2. This was based on many publications demonstrating an increase in PFS and OS based on

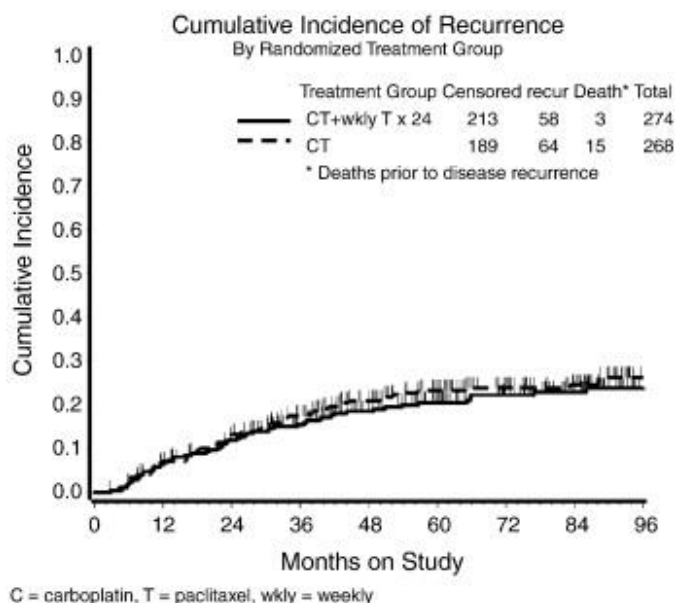


Figure 2. GOG 175 Risk of Recurrence

the amount of residual disease at the time of surgical cytoreduction. The strict definition of optimal debulking changed over time as demonstrated in the inclusion criteria of the following studies, with a stricter definition of smaller residuals as optimally debulked over time. Ultimately, changes in strategy towards cell type driven treatment and the advent of targeted therapy, has led to inclusion of both optimally and suboptimally debulked patients together in GOG advanced stage ovarian cancer clinical trials.

GOG #2 opened in 1970 and closed in 1976. Eligible patients were stage III ovarian cancer patients (low malignant potential excluded) and they were stratified into optimal residual disease (3 cm or less) and suboptimal residual disease (greater than 3 cm).⁹ Randomization was to one of four treatment arms: 1) whole abdominal irradiation alone (2000 to 2500 cGy over 3 to 4 weeks); 2) whole abdominal irradiation (as above) followed by melphalan chemotherapy (0.2mg/kg daily for five days every 4 weeks for 18 months); 3) melphalan chemotherapy alone (dosed as above); and 4) melphalan chemotherapy (as above) followed by whole abdominal irradiation (as above). Progression-free and overall survival for the optimal group of patients was 11.8 months and 28.5 months; for the suboptimal group of patient’s progression-free survival was 7.3 months; overall survival was 15.7 months. Survival by treatment is shown in Table I. The authors concluded that progression-free survival appeared better with combined modality therapy but due to small numbers it was not statistically significant. Overall survival was not different.⁹

GOG #25 was one of two studies of immunotherapy to be performed in ovarian cancer¹⁰ opened in 1977 and closed in 1981, and randomized stage III optimally debulked epithelial ovarian cancer

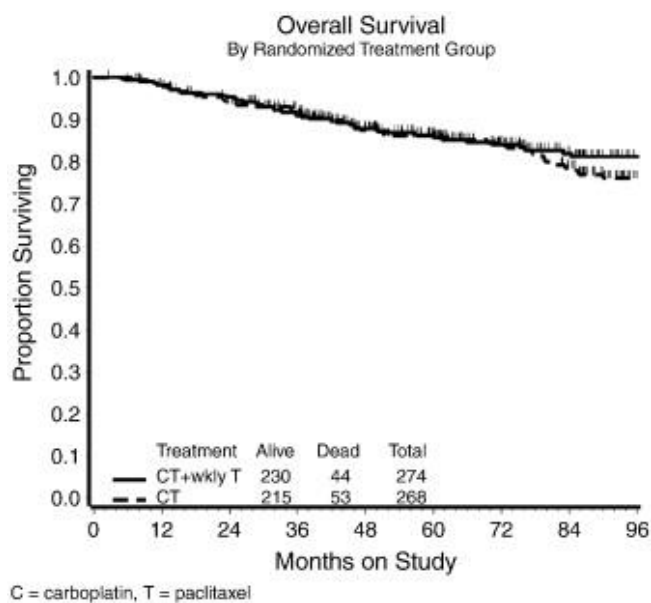


Figure 3. GOG 175 Overall Survival

patients to melphalan alone or melphalan plus corynebacterium parvum. Optimal disease was defined as residual disease of 3 cm or less. Melphalan was given at a dose of 7mg/m² daily 1–5 orally on a 28 day cycle and the C parvum was infused intravenously at a dose of 4.0mg/m² in 100cc of normal saline over one hour on day seven. Treatment in both regimens was for 10 courses or 18 months, whichever came first. Progression-free and overall survival for the C parvum plus melphalan arm was 15.4 months and 33.7 months, respectively, and for the melphalan alone arm was 15.5 months and 32.9 months (no difference), respectively. Patients on the C parvum plus melphalan had significantly more chills, fever and gastrointestinal side effects.¹⁰ In a separate publication Creasman et al,¹¹ reported on the 84 patients in protocol #25 who underwent second look surgical reassessment. Patients with a negative second look reassessment had an 82% 4-year survival compared to 41% for patients with a positive second look reassessment. Only 27% of patients with a negative second look recurred at 13 to 77 months following surgery.¹¹

Evaluation of cisplatin in optimally debulked advanced stage ovar-

Table I: Survival for GOG # 2 by treatment.

Treatment Regimen	Progression-free Survival	Overall Survival
RT Alone	6.8 Mo	18.8 Mo
RT/Melphalan	10.5 Mo	18.1 Mo
Melphalan Alone	6.0 Mo	16.7 Mo
Melphalan/RT	12.5 Mo	20.0 Mo

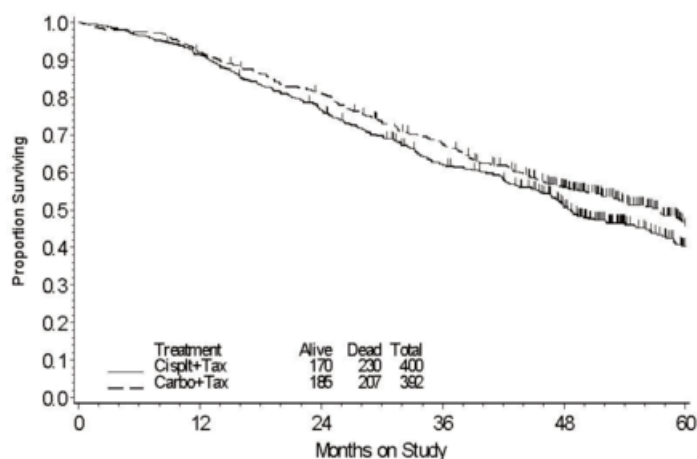
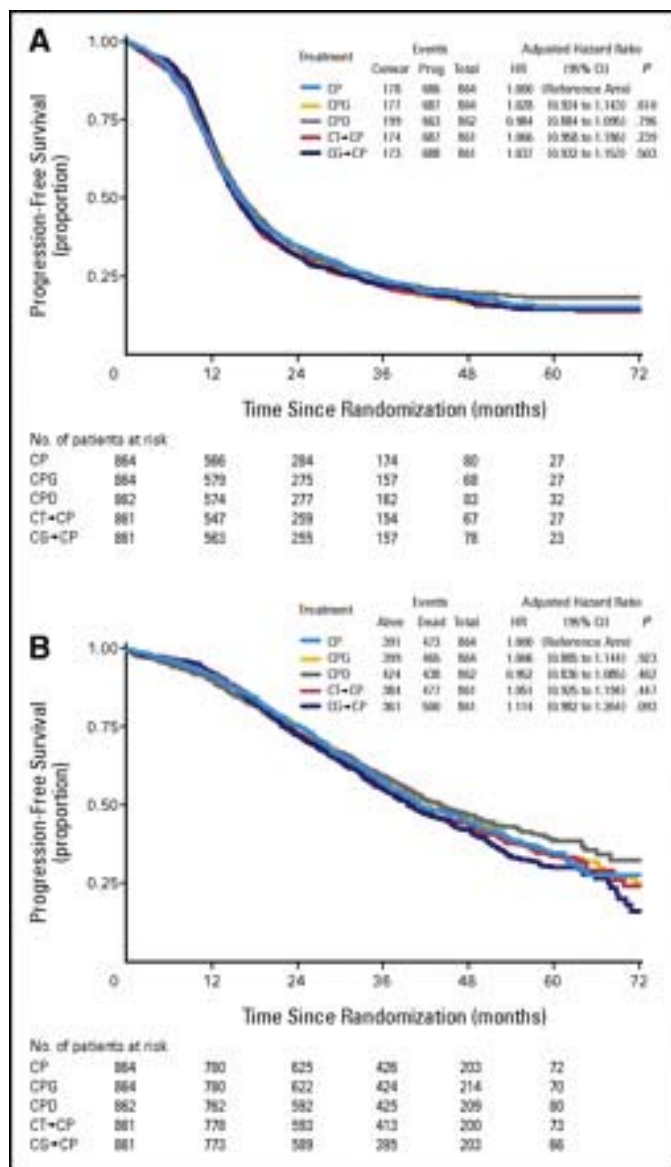


Figure 4. GOG-158: Overall survival by randomized treatment group

ian cancer began with GOG #52. GOG #52 compared cyclophosphamide plus cisplatin with or without doxorubicin (CP vs CAP) in front line therapy.¹² This protocol used what was to become the GOG standard for classifying patients as optimal disease for all future trials, i.e., residual disease with a maximum diameter of one cm or less. The protocol opened in 1981 and accrued 349 evaluable patients before closing to patient entry in 1985.¹² Progression-free interval was approximately 23 months with no significant difference between the two arms ($P=0.50$). Likewise, there was no significant difference in overall survival ($P=0.24$). Despite a multivariate analysis looking at multiple prognostic factors, there was no difference in survival between the two arms of the study. The authors were able to show statistically significant differences in survival between patients with no gross residual versus those with gross residual up to 1 cm and grade 1 tumors versus those with grade 2 or 3.¹² Other factors found to be important in risk of recurrence were more than 30 years of age (RR of 1.4 to 2.4), and clear cell carcinoma (RR of 2.4). The authors concluded that the addition of doxorubicin using dose schedules with equal hematological toxicity in optimal residual stage III has no significant advantage.¹²

Of note, there were three additional papers published using protocol #52 data either alone or in combination with other protocols.¹³⁻¹⁵ Sutton et al in 1990¹³ reported on 32 cases found to have tumors of low malignant potential, concluding that they could not demonstrate a role for adjuvant chemotherapy as only one of the patients died after a median of 31.7 months and the one patient, who died, had no cancer at autopsy. In 1991, the Ovarian Cancer Meta-Analysis Project used the data from GOG protocol #52, along with data from five other large trials, to accrue a total of 1194 patients for analysis of the potential benefit of adding doxorubicin to cyclophosphamide and cisplatin.¹⁴ Using a meta-analysis, they were able to show a 5% to 7% survival benefit from year two to year six ($P=0.02$). They concluded that it was not possible to determine



Figures 5 and 6. GOG 182 Progression Free and Overall Survival.

if this benefit was due to the doxorubicin or to the increased dose density of doxorubicin-containing arms.¹³ In 1992 Hoskins et al¹⁵ re-evaluated data from protocol #52 to attempt to address the question of benefit of surgical cytoreduction versus biology. They concluded that patients with less than 1 centimeter of disease at the time of surgery had an improved survival relative to patients with greater than 1 cm of abdominal disease at the beginning of surgery who were cytoreduced to 1 centimeter residual or less. They also reported age greater than 30 years, grade 2 or 3 tumors, and greater than 15 tumor nodules to have a greater relative risk of recurrence. They concluded that while the success of cytoreductive surgery was important as a prognostic factor, it was not the only important factor and that biology of the tumor ap-

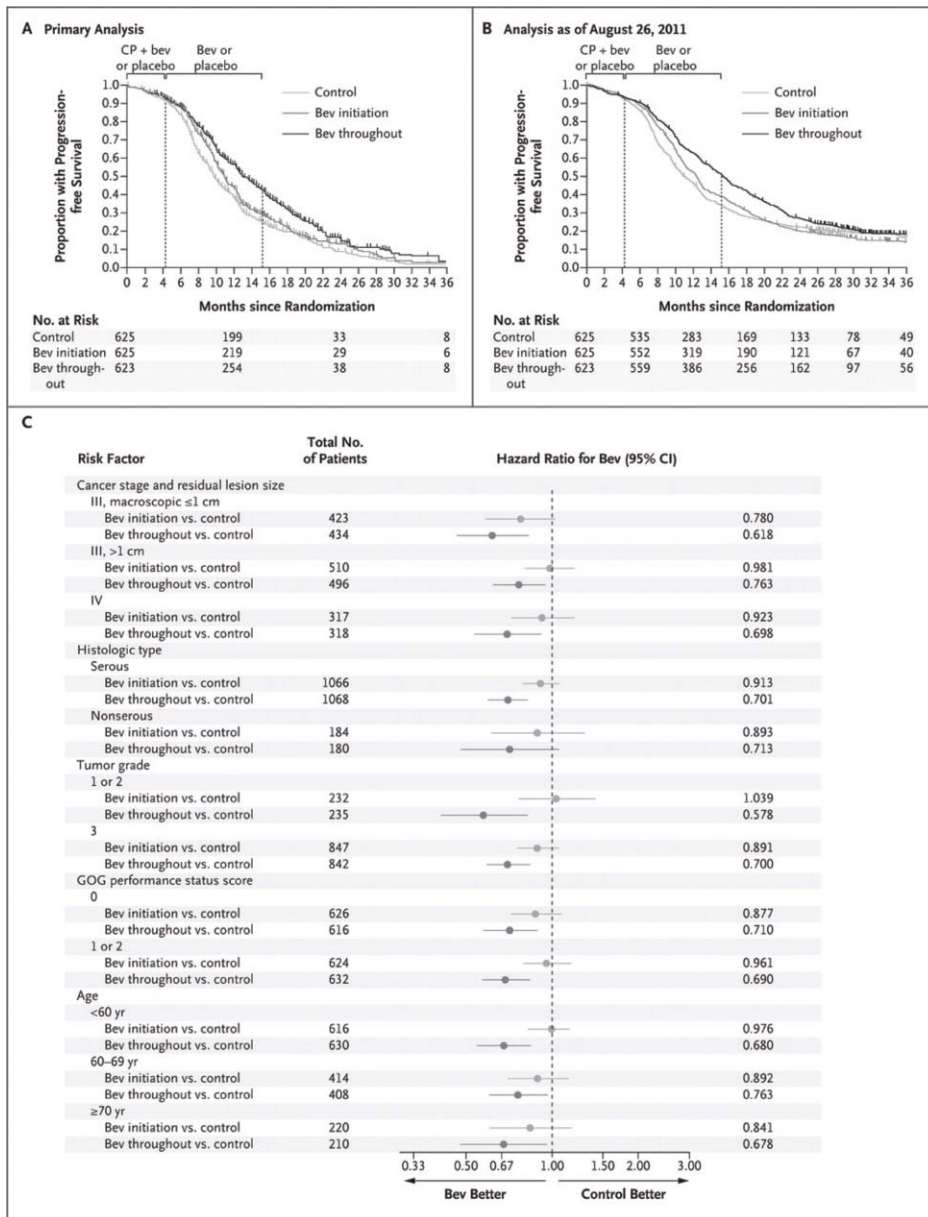


Figure 7. GOG 218 Progression Free Survival

peared to play a role in outcome.¹⁵

Following the success of GOG #111, which demonstrated the superiority of paclitaxel combined with cisplatin in ovarian cancer patients with suboptimally debulked advanced disease, the GOG opened protocol #158 comparing carboplatin (AUC 7.5) and paclitaxel (175 mg/m²) over three hours versus cisplatin (75 mg/m²) and a 24-hour infusion of paclitaxel (135 mg/m²).¹⁶ These patients had advanced ovarian cancer with no residual mass greater than 1 cm after surgery. This was designed as a non-inferiority trial. A total of 792 eligible patients were accrued from 1995 to 1998. The

authors found that gastrointestinal, renal and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in the cisplatin/paclitaxel arm.¹⁶ In addition, the relative risk of progression for the carboplatin plus paclitaxel group was 0.88 with a 95% confidence interval of 0.75 to 1.03; the relative risk of death was 0.84 with a 95% confidence interval of 0.72 to 1.02. The authors concluded that for patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior when compared with cisplatin plus paclitaxel (Figure 4).¹⁶

The next phase III trial (GOG #182) built upon the combination of carboplatin and paclitaxel chemotherapy to assess new active agents in front-line therapy in regimens incorporating sequential doublet and triplet treatment strategies. The additional agents included pegylated liposomal doxorubicin, gemcitabine and topotecan. In this study, optimally and suboptimally debulked disease were combined in one protocol.¹⁷ This study, designed as a Gynecologic Cancer InterGroup trial, enrolled 4312 women from 2001 to 2004. The patients were randomized to one of five separate regimens. The addition of a third cytotoxic agent provided no benefit in progression-free or overall survival (Figures 5 and 6).¹⁸ A unique strategy employed in this study was the statistical design of pairwise comparison to the reference arm, allowing for future evaluation of multiple experimental regimens against a single reference arm.

GOG #218 was the first prospective, randomized clinical trial in advanced ovarian carcinoma of the GOG to utilize a targeted agent. Based upon the evidence that vascular endothelial growth factor (VEGF) and angiogenesis are important promoters of ovarian-cancer progression, the design of this study was to evaluate the addition of bevacizumab, a VEGF inhibitor, to standard front line therapy. This trial randomized patients to paclitaxel (175 mg/meter squared) and carboplatin (AUC 6) chemotherapy for 6 cycles plus one of the following three targeted agent schedules for a total of 22 cycles: placebo for cycles 2-22 (control), bevacizumab for cycles 2-6 followed by placebo for cycles 7-22 (bevacizumab initiation) and bevacizumab for cycles 2-22 (bevacizumab throughout). The median progression free survival for the arms were 10.3, 11.2 and 14.1 months respectively with the bevacizumab throughout demonstrating a statistically significant improvement in progression free sur-

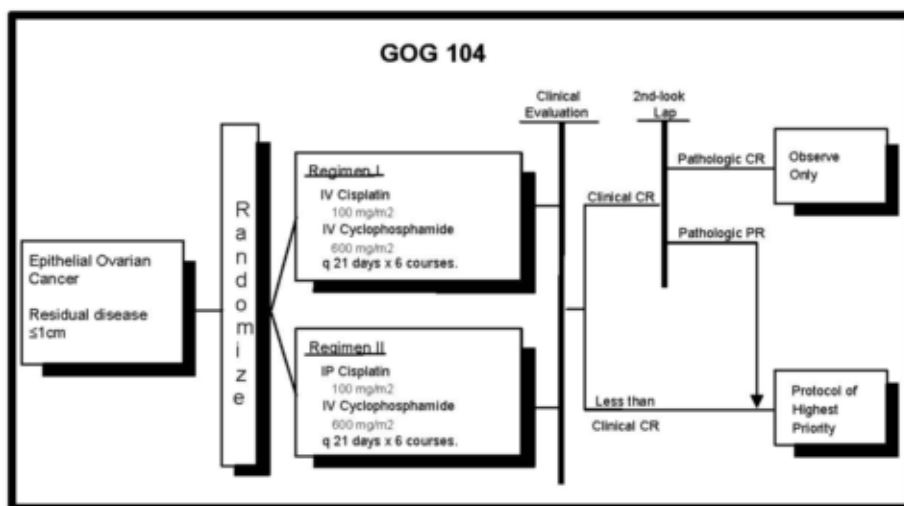


Figure 8. GOG 104 Study Schema

vival compared to the control arm (Figure 7).¹⁹ Median overall survival had not been reached at the time of manuscript publication.

Based on data from the Japanese Gynecologic Oncology Group²⁰ demonstrating a statistically significant improvement in progression free survival with the use of dose dense paclitaxel in front line ovarian cancer, GOG #262 further evaluated this strategy. This trial randomized patients with initially suboptimally debulked ovarian cancer but ultimately opened to include patients with both optimally and suboptimally debulked ovarian cancer after the closure of GOG #252 to carboplatin (AUC 6) plus either weekly paclitaxel (80 mg/meter squared) or every three week paclitaxel (175 mg/meter squared). This trial design also allowed for the use of bevacizumab (15 mg/kg every three weeks until progression) at the patient and investigator's discretion, selected before randomization. A unique amendment in this trial's design ultimately permitted the use of a neoadjuvant treatment strategy with interval cytoreductive surgery. This trial enrolled 692 patients from 2010 to 2012. Survival data is under evaluation with planned first analysis in late 2013.

Optimally Debulked, Advanced Stage, Intraperitoneal Chemotherapy

The GOG has been a leader in the development and evaluation of intraperitoneal chemotherapy in ovarian cancer. The first phase III study demonstrating the superiority of intraperitoneal (IP) chemotherapy for advanced, optimally debulked ovarian cancer was a cooperative intergroup study initiated by the Southwestern Oncology Group (SWOG) in 1985 (SWOG #8501). This study compared intravenous (IV) cisplatin and cyclophosphamide to intraperitoneal cisplatin and intravenous cyclophosphamide. Due to slow accrual, SWOG asked the GOG to join the trial in 1988, and

this trial was opened within the GOG as GOG#104 (Figure 8). Eligibility to this trial included all patients with stage III ovarian cancer with no residual lesion measuring greater than 2 cm diameter.²¹

The IP arm was associated with statistically significant prolongation of survival. The median overall survival of the IP arm was 49 months compared to 41 months for the IV arm, with a hazard ratio of 0.77 (Figure 9). The IP arm had fewer incidences of clinical hearing loss, tinnitus, granulocytopenia, leukopenia and thrombocytopenia. The IV arm had fewer incidences of abdominal pain and cramping.²¹

The study had potential weaknesses with respect to contemporary treatment. Paclitaxel, one of the front line drugs in the current standard of care, was not utilized; thus, raising the question as to whether the addition of paclitaxel would potentially neutralize the apparent advantage of the IP administration. Since the control arm did not contain paclitaxel, it has been suggested that the study lacked relevance to contemporaneous treatment planning.

With GOG #104 demonstrating an improvement in median overall survival for the intraperitoneal (IP) arm of the study, the GOG opted to do a follow-up trial.

GOG #114 compared IV cisplatin (75mg/m²) with IV paclitaxel (135 mg/m²) over 24 hours versus carboplatin (AUC 9) IV every 28 days times two followed by cisplatin (100 mg/m²) IP and paclitaxel (135 mg/m²) over 24 hours IV.²² The study was limited to patients who had stage III disease with less than or equal to 1 cm of residual tumor following surgery. Between 1992 and 1995, the

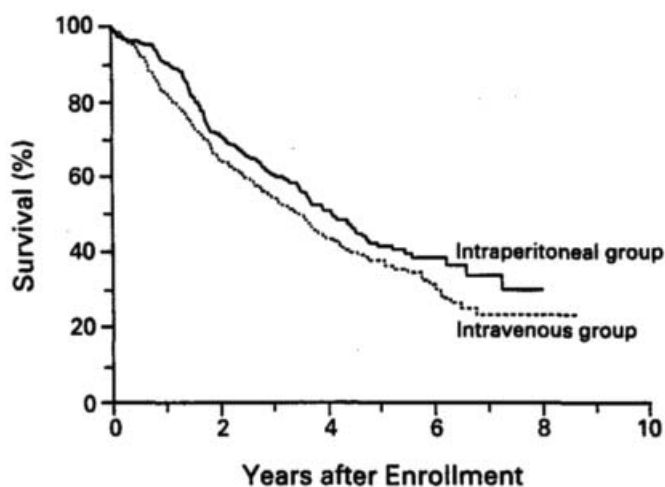


Figure 9. GOG-104: Survival by randomized treatment.

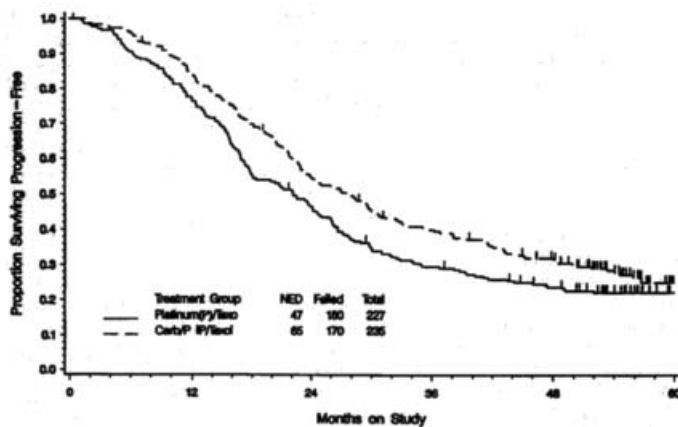


Figure 10. GOG-114 Progression-Free survival by randomized treatment group.

GOG enrolled 462 patients on this protocol. The median duration of survival for the experimental regimen containing IP cisplatin was 67 months versus 51 months for the IV arm. The treatment hazard ratio for progression-free survival in the IP group was 0.78 (Figures 10 and 11). Though the study was statistically significant from a progression-free survival standpoint, questions were raised regarding which component of therapy was most important in the improvement in survival. The patients in the experimental arm did receive two cycles of high-dose carboplatin, and an AUC of nine, in addition to the IP cisplatin.²²

Further evaluation of intraperitoneal chemotherapy was undertaken in GOG #172, comparing IV paclitaxel (135 mg/m²) over 24 hours with IV cisplatin (75 mg/m²) on day two versus IV paclitaxel (135 mg/m²) over 24 hours followed by cisplatin (100mg/m²) IP on day two and paclitaxel (60mg/m²) IP on day eight. (23) Treatment on both arms was administered every three weeks for a total of six courses and quality of life was assessed at four time points. As in GOG #114, the patients had optimally surgically resected ovarian or primary peritoneal carcinoma with residual disease less than or equal to 1 cm after initial surgery. Between 1998 and 2001, a total of 415 eligible patients were entered. Both progression-free and overall survival was significantly improved in the IP arm (Figures 12 and 13).²³

The median overall survival for the IV and the IP arms was 49.5 and 66.9 months, respectively. The relative risk of death was 0.71 with a 95% confidence interval of 0.54 to 0.94 for the IP group with a p=0.0076. In spite of this impressive improvement in survival, concern was raised regarding the tolerability of the experimental regimen. Grade 3 and 4 hematologic, metabolic and GI toxicities, as well as fatigue, infection and pain, were significantly more common (p<0.001) on the IP arm. Indeed, only 42% of the patients were able to complete all six cycles of the IP therapy. The authors concluded that compared with standard IV paclitaxel plus

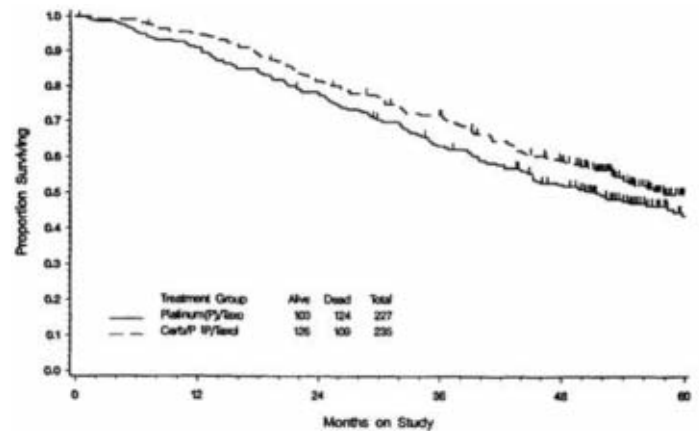


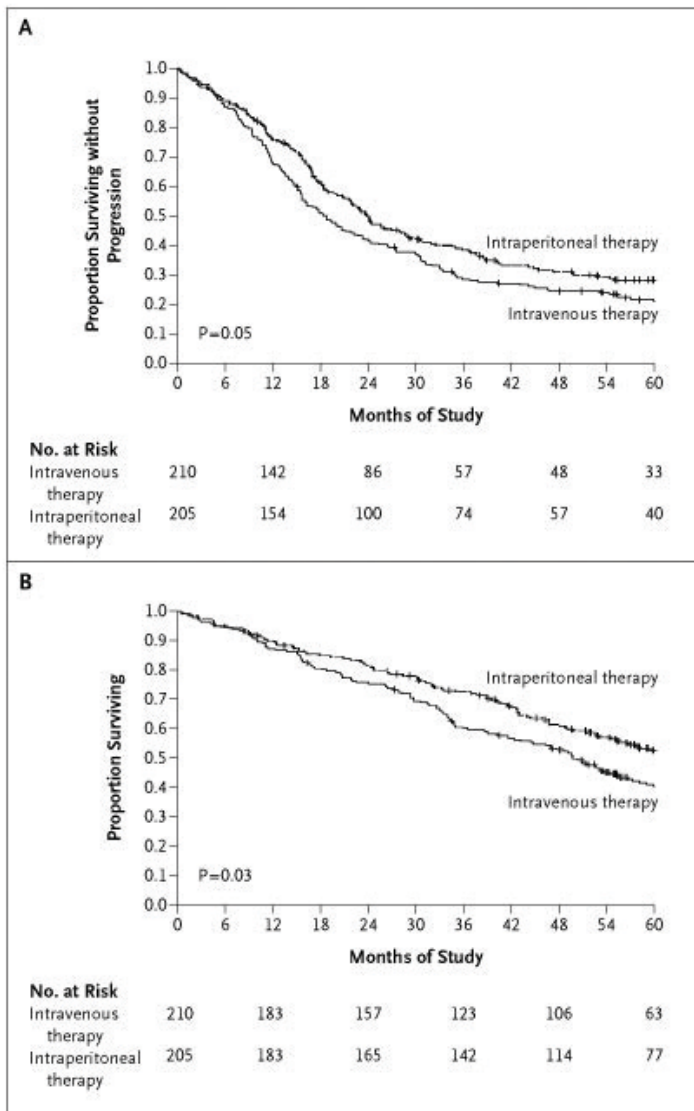
Figure 11. GOG-114: Survival by randomized treatment group.

cisplatin, an intensive regimen of IV paclitaxel plus sequential IP cisplatin and paclitaxel significantly improved progression-free and overall survival in patients with optimally-debulked stage III ovarian cancer.²³ However, the IP regimen used in GOG #172 had substantial toxicity that compromised treatment delivery. With GOG #172, a quality of life tool was utilized to compare the treatment arms. The IP group reported significantly worse quality of life prior to cycle four, as well as three to six weeks post-treatment; however, there were no significant differences in quality of life between the IP/IV arms one year post-treatment.²³

In an effort to improve the tolerability of IP chemotherapy and to further investigate the role of IP chemotherapy relative to dose dense IV chemotherapy, GOG #252 was initiated. The trial enrolled 1560 patients from 2009 to 2011 with optimally debulked ovarian cancer although was open for the inclusion of suboptimally debulked patients for a portion of the enrollment period. This trial randomized patients to three arms. The first arm was a modification of the IP arm in GOG #172, reducing the IP cisplatin to a dose of 75 mg/meter squared on day 2 for 6 cycles. The other two arms utilized weekly paclitaxel (80 mg/meter squared) IV with either IV or IP carboplatin (AUC 6) for 6 cycles. All arms included bevacizumab (15 mg/kg) IV every three weeks for 21 cycles (cycles 2-22) The statistical rationale of this trial allowed for two comparisons. The first is comparing an IP carboplatin based regimen to the modified GOG #172 IP regimen in the hopes of reducing toxicity with the other a comparison of IP to IV carboplatin in addition to dose dense weekly paclitaxel. Survival data are not mature at the time of this manuscript with planned initial analysis in 2014.

Suboptimally Debulked Advanced Epithelial Ovarian Cancer

GOG protocol #3 evaluated stage IV primary ovarian cancer and recurrent ovarian cancer equivalent to stage III or IV.(24) The pa-



Figures 12 and 13. GOG 172 Progression Free and Overall Survival

Table II: Response of measurable disease in patients by treatment.

Response	Treatment		
	Melphalan	Melphalan + Cyclophosphamide	Hexamethylmaeamine
Complete Response	20.3%	27.8%	31.9%
Partial Response	17.2%	23.8%	16.7%
Total Response	37.5%	51.6%	48.6%

tients were randomized to one of three groups: 1) melphalan alone; 2) melphalan plus 5 FU; 3) melphalan, 5FU and dactinomycin; and 4) cytoxan, 5 FU and dactinomycin. There was no significant difference in either progression-free or overall survival between any of the treatment arms. Toxicity was greatest in the three drug regimens. The authors concluded that single agent melphalan was as efficacious as any of the combination regimens in advanced/recurrent epithelial ovarian cancer.²⁴

GOG protocol #22 opened in 1976 and closed in 1979. (25) This protocol was carried out in suboptimally debulked (residual tumor diameter of 3 cm or larger) stage III, stage IV and recurrent ovarian adenocarcinoma, and randomized patients to melphalan versus melphalan plus hexamethylmelamine versus adriamycin plus cyclophosphamide. During the study period, 432 patients were randomized into this trial. After two and one half years, an interim analysis²⁵ indicated melphalan alone was significantly inferior in achieving clinical complete responses and the GOG elected to close that arm to patient entry (Table II).

Although there was a trend towards improved complete and overall response in the combination chemotherapy arms, this was not statistically significant in the patients with measurable disease. Also progression-free survival was not significantly different (M = 7.7 months, M+H = 6.0 months and A+C = 9.5 months). Overall survival was also similar (M = 12.3 months, M+H = 13.5 months and A+C = 14.2 months). Review of the toxicities by treatment arm revealed more hematologic and gastrointestinal toxicity in the combination chemotherapy arms. The authors concluded that results in measurable disease patients indicated some progress (in the combination chemotherapy arms) in improving complete response rates, but that the overall benefit in terms of survival were disappointing. At the end of the article, they mention promising results in pilot studies with cisplatin and comment on its possible role in future trials.²⁵

In 1979, the GOG opened its first phase III trial of cisplatin in advanced epithelial ovarian cancer. This trial, GOG #47, evaluated cyclophosphamide and doxorubicin with or without cisplatin (CAP vs CA).²⁶ This trial closed in 1982, having accrued 440 evaluable patients with stage III suboptimal (3 cm or greater residual diameter), stage IV and recurrent cancer equivalent to stage III suboptimal or stage IV. For patients with measurable disease, the response rate for CA was 26% (CR) and 48% (CR + PR), while for CAP it was 51% (CR) and 76% (CR + PR). The difference in complete response rate was highly statistically significant (P = <0.0001).²⁶ Table III illustrates median survival numbers for patients on this protocol. The authors concluded that because of the clear improvement in response rate and progression-free survival in all patients and overall survival rate

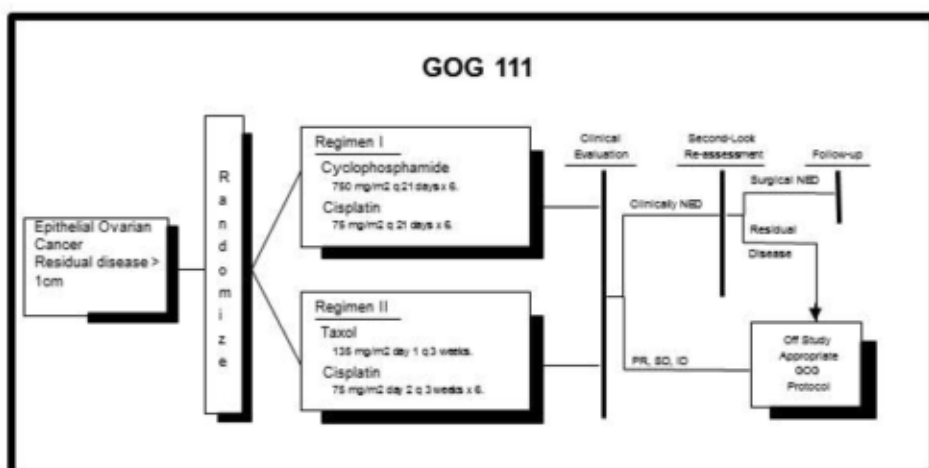


Figure 14. GOG-111 Study Schema.

for patients with measurable disease, cisplatin-based therapy is a “significant step forward” in the therapy of epithelial ovarian cancer. They expressed confusion as to the lack of a statistically significant overall survival in the entire group of patients, indicating the possible reasons being some imbalance in the arms or, more likely, the result of crossover therapy to cisplatin in patients who failed the non-cisplatin arm.²⁶

In 1991, Omura et al²⁷ published the long term follow-up and prognostic factors of patients treated on GOG protocols #22 and #47. There were 319 patients evaluable for protocol #22 and 407 evaluable patients for protocol #47. All patients were suboptimal (3cm or greater) stage III or stage IV. Almost 60% had measurable disease. They found cell type other than clear cell and mucinous, good performance status, cisplatin-based therapy, younger age, lower stage, smaller residual tumor and absence of ascites to be favorable prognostic factors. Second look surgery was more often negative in endometrioid tumors ($P < 0.05$) and of the 30 patients with suboptimal stage III who had a negative second-look, 18 (60%) recurred and 13 (43%) died.²⁷

With the division of the ovarian cancer population into optimally

Table III. Median survival in GOG Protocol 47: Progression-free and overall survival for all patients and overall survival for patients with measurable disease.

	Progression-free Survival (all patients)	Overall Survival All Patients	Measurable Disease Patients
CA	7.7 Mo	16.4 Mo	15.7 Mo
	P = 0.0001	P = NS	P=0.03
CAP	13.1 Mo	19.3 Mo	19.7 Mo

and suboptimally-debulked patients, the GOG initiated a sequence of trials looking at suboptimal stage III (greater than 1 cm residual disease) or stage IV ovarian cancer patients. GOG #97 study evaluated whether dose intensity of standard chemotherapy improved outcomes in patients with suboptimally debulked ovarian cancer. Patients with suboptimally debulked stage III or stage IV ovarian cancer received either eight cycles of cisplatin 50 mg/m² plus cyclophosphamide 500 mg/m² or four cycles of cisplatin and cyclophosphamide at 100 mg/m² and 1000mg/m², respectively. The more dose intense regimen did not provide improved response rates, progression free intervals or survival. However, a greater toxicity profile was reported with the dose intense regimen.²⁸

A secondary analysis of the relationship of the size of the residual disease to outcome revealed that, compared to the group of patients with disease less than 2 cm in diameter, all patients with disease equal or greater than 2 cm—analyzed in 1 cm increases—had a relative risk of dying of between 1.74 and 2.16 with no statistical difference between any of the groups above 2 cm.²⁹ Based on this information, if technically possible, advanced ovarian cancer should be tumor debulked to at least less than 2 cm in diameter at primary surgery.

The GOG was fundamental in the development of paclitaxel as an active agent in the ovarian cancer chemotherapy. The GOG conducted two consecutive randomized phase III trials assessing the potential value of paclitaxel as first line treatment. The first trial, GOG #111, compared cisplatin and paclitaxel versus cisplatin and cyclophosphamide (Figure 14). The study was opened in April 1990 and closed in March 1992. Eligibility for the trial was all stage III and IV ovarian cancer patients with residual disease great than 1 cm in diameter. The combined complete and partial clinical response rate for patients with measurable disease favored the paclitaxel arm 77% to 64%. The risk of progression was 28% lower among those patients treated on the paclitaxel arm. The risk of death was 34% lower among those treated with the paclitaxel regimen (Figure 15).³⁰ The frequency of negative second-look surgery was not statistically different.

However, before the results of that trial were available, the GOG initiated protocol #132 in a similar patient population. This trial was designed to assess whether paclitaxel was more active than cisplatin in the management of ovarian cancer patients.³¹ GOG #132 was designed to compare the activity in terms of progression-free survival and overall survival of single-agent cisplatin or paclitaxel or the combination of cisplatin and paclitaxel. Between

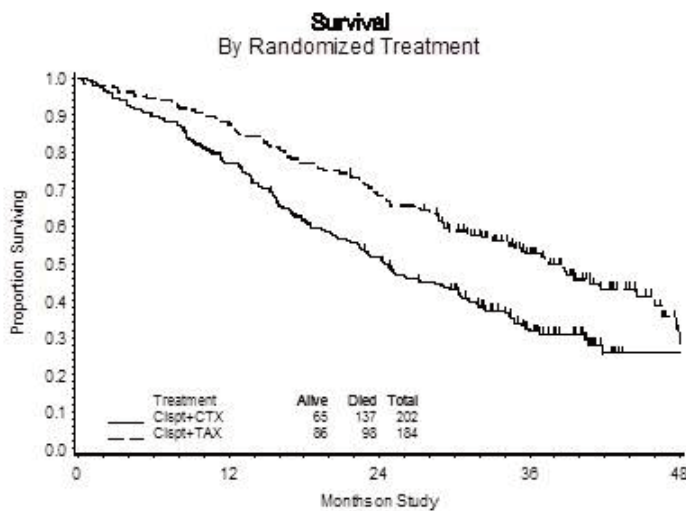


Figure 15. GOG-111: Survival by randomized treatment group.

1992 and 1994, 648 eligible patients were enrolled on the trial. The response rate on paclitaxel monotherapy was significantly lower compared with the cisplatin regimen (42% versus 67%). The relative hazard for progression-free survival was significantly greater than those randomized to paclitaxel (relative hazard = 1.41 with a 95% confidence interval of 1.15 to 1.73). The authors concluded that cisplatin alone or in combination with paclitaxel yielded a superior response rate and progression-free survival relative to paclitaxel.³¹ In addition, the drug dosages used with the combination therapy had a better toxicity profile; therefore, the combination of cisplatin/paclitaxel was deemed to be the preferred initial treatment option.

The GOG also addressed the role of secondary surgical cytoreduction for advanced ovarian carcinoma. GOG #152 concentrated on patients with stage III ovarian carcinoma with residual intraperitoneal tumor exceeding 1 cm in diameter after they had undergone surgery with the goal of removing as much tumor as possible.³² Two weeks after the third cycle of cisplatin/paclitaxel chemotherapy the patients were evaluated for a response by means of physical exam, CT scan and CA-125. Patients whose disease had not progressed and who had residual extraperitoneal of tumor no more than 1 cm in diameter were randomly assigned to receive chemotherapy plus secondary surgical cytoreduction versus chemotherapy alone. From 1994 to 2001, 424 eligible patients were randomized onto this protocol. The likelihood of progression-free survival in the group assigned to secondary surgery plus chemotherapy, as compared with the chemotherapy alone group, was 1.07 with a 95% confidence interval of 0.87 to 1.31 with a $p=0.54$ and the relative risk of death was 0.99 with a 95% confidence interval of 0.79 to 1.24 with a $p=0.92$ (Figure 16).³²

These results were in contrast to an EORTC trial reported in the *New England Journal of Medicine* that showed a significant im-

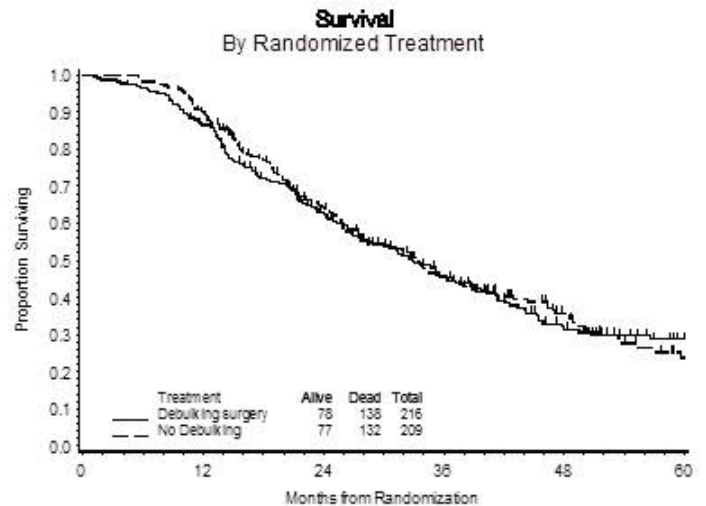


Figure 16. GOG-152: Survival by randomized treatment.

provement in both progression-free and overall survival in patients who underwent suboptimal primary debulking followed by secondary surgery. The authors concluded that the difference in the reports was secondary to the nature of the initial surgical effort.³³ In the GOG trial, the patients had an initial attempt at aggressive tumor debulking; whereas, this was not a requirement for the European trial. The authors concluded that for a patient with advanced ovarian carcinoma in whom primary cytoreductive surgery was considered to be maximal, the addition of a secondary cytoreductive surgery to postoperative chemotherapy with paclitaxel plus cisplatin did not improve progression-free survival or overall survival.³²

GOG trial #162 to evaluate the impact of dose schedule on outcome in suboptimally debulked ovarian cancer. This was a phase III randomized trial of cisplatin and paclitaxel administered by either a 24-hour or 96-hour infusion in patients with suboptimal stage III or stage IV epithelial ovarian cancer. From 1996 to 2000, 293 patients were enrolled. Accrual was terminated due to a scheduled interim futility analysis as the median progression-free survival was 12.4 versus 12.6 months for the 24-hour versus 96-hour arm, respectively. The authors concluded that prolonged paclitaxel infusion did not significantly increase duration of survival over a 24-hour infusion.³⁴

Secondary Surgical Cytoreduction

The use of secondary cytoreductive surgery in patients with recurrent ovarian cancer has been utilized to varying degrees by gynecologic oncologists based on retrospective cohort studies in the literature. Factors predicting the success of this type of operation have been identified as the amount of residual disease at initial surgery, interval of time since completion of initial surgery, presence or absence of ascites and performance status among others.³⁵ There have been no prospective randomized trials to assess the

true impact of this intervention. Based on this, the GOG included a surgical randomization component to GOG 213, a prospective randomized trial evaluating the addition of bevacizumab to paclitaxel and carboplatin chemotherapy in patients with platinum sensitive ovarian cancer defined as detection of recurrence greater than six months since initial therapy. Data are not yet mature for the chemotherapy component of the study. The study remains open for surgical randomization with the plan to continue surgical randomization with ensuing platinum sensitive recurrence studies until a sufficient sample size is obtained.

Treatment of the Elderly

GOG 273 is a prospective trial for women with advanced ovarian cancer. This trial is designed to evaluate the pharmacokinetics of chemotherapy in the elderly (defined as greater than 70 years of age) as well as quality of life impact. This trial will enroll patients treated in 3 cohorts: single agent carboplatin, every three week paclitaxel with carboplatin and weekly paclitaxel with every three week carboplatin. Enrollment is ongoing.

Malignant Germ Cell Tumors of the Ovary

The early experience of the GOG in the treatment of malignant germ cell tumors of the ovary was presented in two publications: a preliminary report in 1978 and a final report in 1985. (36, 37) Protocols #10 and #11 were opened in 1971 to study the effect of multi-agent chemotherapy on malignant germ cell tumors since prior reports had failed to demonstrate success with surgery alone or surgery combined with irradiation or single agent chemotherapy. During the first year, three-drug combinations using dactinomycin, 5-fluorouracil, cytoxan and methotrexate were tried, but from 1972 until the phase II study closed in 1978, the regimen of therapy was vincristine, dactinomycin and cyclophosphamide (VAC). In the 1978 preliminary report, there were 27 patients with endodermal sinus tumor, embryonal carcinoma and mixed tumors. Stages varied from IA through III and four patients had recurrent disease.³⁶ There were 12 patients with immature teratoma stages IA through III with two patients having recurrent disease. For the endodermal sinus tumor group, 16 of 27 patients (58%) who received VAC were alive and well. For those patients with resection of all gross tumors, 11 of 16 patients (69%) were alive and well. Of patients with advanced/recurrent disease, 45% remained disease free. For the immature teratoma patients, all completely resected patients (eight) were living following chemotherapy, although one required a second operation to excise residual grade 1 teratoma. Only one of the four patients with unresected disease was disease-free following chemotherapy and three operations to resect disease.³⁶ The final report in 1985 reported 76 patients with malignant germ cell tumors treated with postoperative VAC. Only 15 of 54 patients (28%) failed following complete resection of disease followed by VAC chemotherapy. VAC chemotherapy, however, was only effective in about 32% of incompletely resected patients and, again, this was true of all cell types.³⁷

These early GOG studies of malignant germ cell tumors demonstrated the importance of complete tumor resection and the value of combination chemotherapy with VAC. They also demonstrated the importance of histology as the overall failure rate for endodermal sinus tumors was 48%, and for mixed germ cell tumors it was 53%, while only 18% of grade 2 and 3 immature teratoma patients failed.^{36, 37}

Between 1978 and 1987, the GOG evaluated adjuvant vincristine, dactinomycin and cyclophosphamide (VAC) in malignant germ cell tumors of the ovary after resection of all gross tumors (phase II) and vinblastine, bleomycin and cis-platinum (BVP) in stage III and IV and recurrent malignant germ cell tumors of the ovary. (38-40) An abstract was presented at the Society of Gynecologic Oncologists annual meeting in February, 1989, described 126 evaluable patients stages I, II, and III with thorough surgical staging and complete tumor resection.³⁸ One hundred patients received six to nine courses of VAC. At the time of presentation, with a median follow-up of four years, 78% of the patients were disease-free. The disease-free rate for endodermal sinus tumors was 73% (35 of 48 patients) and, for grade 2 and 3 immature teratomas, the disease-free rate was 84% (42 of 50 patients). The authors also reported on 26 patients who were treated with three courses of BVP over nine weeks. Twenty-four of 26 of these patients (92%) had a median follow-up of 19.2 months. Nine of 10 patients with mixed germ cell tumors were disease-free; and nine of nine patients with endodermal sinus tumors and six of seven patients with immature teratoma were disease-free as well. They stated that although follow-up was short, they believed the BVP regimen to be superior.³⁸

Also in 1989, investigators from the GOG reported on 97 evaluable patients with stage II through IV and recurrent malignant germ cell tumors treated with BVP.³⁹ Five patients were stage II; 37 were stage III; nine were stage IV; and 38 patients had recurrent disease. Thirty-seven percent of the non-dysgerminoma patients were recurrent after VAC chemotherapy. Table IV provides a summary of the disease-free patients by selected patient characteristics. Based on these results in advanced/recurrent malignant germ cell tumors of the ovary, the authors concluded that cisplatin based therapy is superior to previous regimens. They further stated that cisplatin-based chemotherapy will cure a substantial number of patients with malignant germ cell tumors.³⁹

In 1994, the GOG reported on second-look operations in patients with malignant germ cell tumors of the ovary.⁴⁰ This report included patients from GOG protocol #45 as well as patients from later protocols (GOG #78 and GOG #90). Based on the findings of second look surgical reassessment procedures in 117 patients with malignant germ cell tumors, the following recommendations were made by the GOG authors: 1) patients with completely resected germ cell malignant tumors rarely, if ever, benefit from second-look surgery; 2) patients with advanced incompletely resected malignant germ cell tumors that do not contain immature teratoma elements rarely, if ever, benefit from second look surgery; 3) pa-

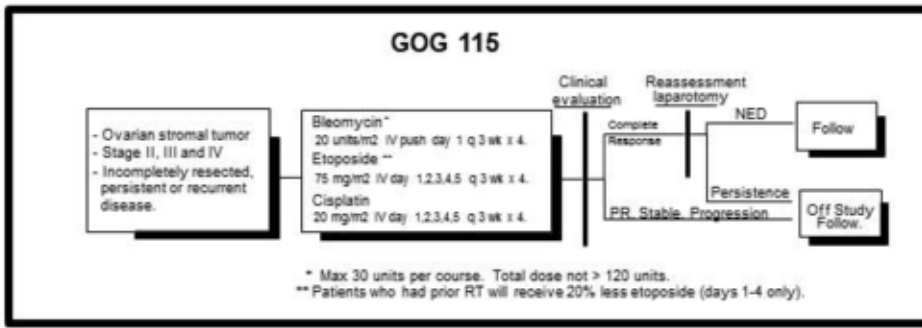


Figure 17. GOG-115 Study Schema.

tients with incompletely resected malignant germ cell tumors containing teratoma elements have a substantial likelihood of benefiting from surgery to include the resection of residual tumor. They further recommended that VAC chemotherapy be considered in these patients with residual disease found at second-look surgical reassessment.⁴⁰

GOG #90 evaluated the effectiveness of induction chemotherapy with cisplatin, etoposide and bleomycin (BEP) followed by con-

Table IV. Advanced and Recurrent Malignant Germ Cell Tumors of the Ovary: Disease-free Survival after treatment with Vinblastine, Bleomycin and Cisplatin (GOG # 45)

Patient Characteristics	Number Disease-free/Total (%)
Cell Type	
Endodermal Sinus Tumor	16/29 (55)
Embryonal	1/4 (25)
Mixed	14/27 (52)
Immature teratoma	14/26 (54)
Choriocarcinoma	2/3 (67)
Stage	
II	5/5 (100)
III	22/37 (60)
IV	5/9 (56)
Recurrent	15/38 (40)
Measurable Disease	
Yes	12/35 (34)
No	35/54 (65)
Prior Therapy	
Yes	14/35 (40)
No	33/54 (61)
Residual Disease	
Optimal	
At initial surgery	10/12 (83)
After debulking surgery	17/29 (59)
Suboptimal	20/48 (42)

solidation with vincristine, actinomycin, and cyclophosphamide (VAC) in previously untreated patients with advanced stage ovarian germ cell tumors. The study also was to evaluate the effect of BEP chemotherapy in patients with recurrent or progressive disease during or after previous non-platinum containing chemotherapy. Publications related to this study were published in the early 1990s.⁴¹ This study population, analyzed with two earlier GOG studies (GOG #45 and #78) demonstrated

that second-look laparotomy was not necessary in patients with completely resected disease initially or in patients with advanced disease that did not contain teratoma. However, the procedure seemed to be of some value in patients with incompletely resected tumors containing elements of teratoma.⁴²

Malignant Stromal Tumors of the Ovary

Between 1971 and 1981, there were two other GOG studies of non-epithelial ovarian tumors. Protocol #13 evaluated VAC chemotherapy and whole abdominal irradiation in ovarian sarcomas and protocol #14 evaluated chemotherapy and irradiation in malignant stromal tumors of the ovary.^{43,44} Of the ovarian sarcoma patients in protocol #13, there was very inconsistent therapy and the main value of the study is as a registry to document the poor survival of these patients. Only three of six early stage I and II patients survived more than three years and only one of 24 patients with stage III and IV survived more than three years.⁴³ Protocol #14 has only been published in abstract form.⁴⁴ Fifty-five patients with malignant stromal tumors were evaluable and were treated following surgery with some combination of irradiation and chemotherapy with dactinomycin, 5 fluorouracil and cyclophosphamide (AcFuCy). Although no therapeutic conclusions were possible due to the heterogeneity of cell types and stages, there were some complete responses with chemotherapy in patients with measurable disease and one complete response in a recurrent pa-

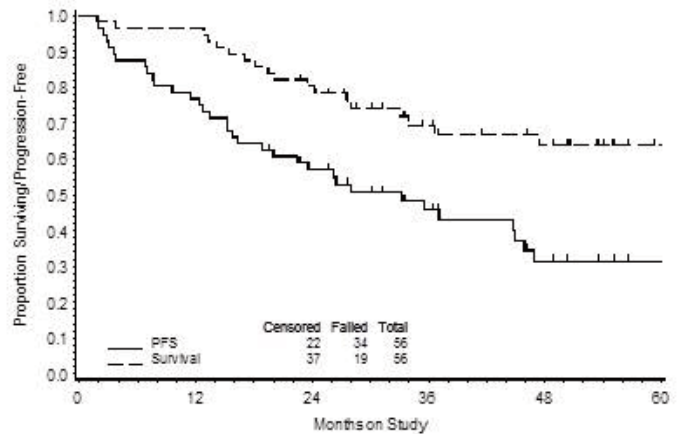


Figure 18. GOG115: Progression-free and overall survival

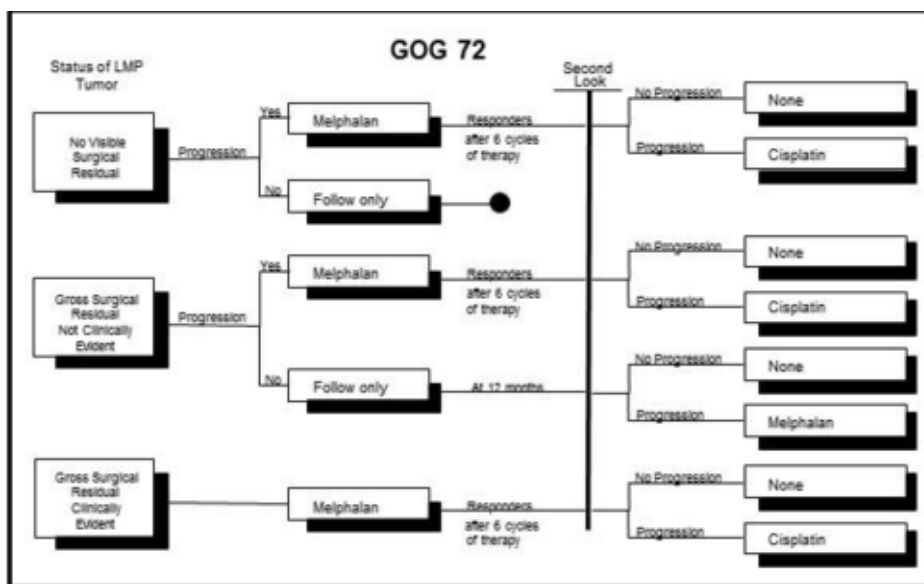


Figure 19. GOG 72 Study Schema.

tient with measurable disease. The authors concluded that chemotherapy appears effective in the disease, but that no conclusions were possible in regards to irradiation.⁴⁴

In addition, GOG #115 evaluated the efficacy of bleomycin, etoposide (VP-16), and cisplatin (BEP) chemotherapy in patients with malignant tumors of the ovarian stroma of the ovary as a first-line regimen for patients with histologically confirmed stage II – IV disease with incompletely resected disease, recurrent, or persistent tumor (Figure 17). The study was opened in April 1991 and closed in April 1997. The combination of BEP appeared active for first-line chemotherapy of malignant ovarian stromal tumors (Figure 11). Of patients with recurrent disease, 21 of 41 (51%) were progression free. Age and measurable disease were identified as risk factors. Seventy-five patients were entered on the study. Two bleomycin-related deaths occurred in 1992 and the study accrual was temporarily suspended until the dose and schedule of bleomycin was changed. Grade 4 myelotoxicity was reported in 61% of patients. Limiting the bleomycin dose to 30 units per treatment course and to less than 120 units total dose avoided serious pulmonary morbidity (Figure 18).⁴⁵

Other Ovarian Cancer Trials

Assessment of Cytologic Techniques

In GOG protocols #6 and #7, investigators attempted to cytologically evaluate peritoneal fluid obtained by serial culdocentesis during and following therapy for epithelial ovarian cancer.⁴⁶ The authors attempted to stratify 72 women by both stage and type of treatment. Although severely limited by small numbers of patients in the various subgroups the investigators did demonstrate that women with persistent malignant cells in the peritoneal cavity following therapy always died of their disease and women with no demonstrable malignant cells usually survived. They also had

anecdotal evidence that the appearance of malignant cells in the peritoneal cavity following treatment of early stage disease often predicted clinical recurrence six months or longer prior to clinical recurrence.⁴⁶

Tumors of Low Malignant Potential

One of the few studies ever conducted in tumors of low malignant potential (LMP) was done so by the GOG. The purpose of GOG #72 was to evaluate the biologic behavior of ovarian tumors of LMP. These tumors are also referred to by other terminology: most commonly, borderline tumors and proliferative tumors. The schema of this trial was anticipating the opportunity to evaluate management options for recurrent disease (Figure 19). The trial was opened in December 1983 and closed in February 1992. With the exception of the pseudomyxoma peritonei syndrome, the recurrence rates were very small, offering no opportunity to evaluate the therapeutic component of the study. Stage I ovarian tumors of low malignant potential rarely occur. The long term data for patients with advanced disease continues to mature.⁴⁷

Stage I ovarian tumors of low malignant potential rarely occur. The long term data for patients with advanced disease continues to mature.⁴⁷

Surgical Staging

From 1979 to 1987, GOG investigators evaluated surgical staging of ovarian cancer (GOG protocol #41).⁴⁸ All cell types were eligible and 187 of 264 patients had epithelial ovarian cancer. The operative procedure was prescribed and 57 of the eligible patients required re-exploration in a GOG institution because the initial operation was performed at a local hospital and the patient did not have all of the prescribed elements. Of those patients with epithelial ovarian cancer, 97 patients were stage I; 43 were stage II; and 47 were stage III optimal (3 cm or less residual disease diameter).⁴⁸

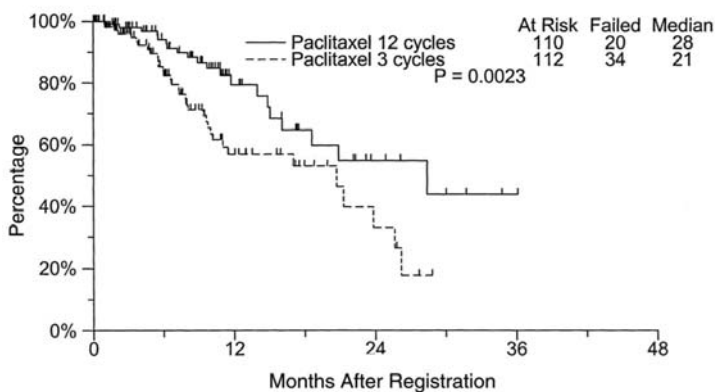


Figure 20. GOG 178 Progression Free Survival.

Table V. Up/down staging as a result of a comprehensive surgical staging procedure in 187 epithelial ovarian cancer patients. GOG #41.

Surgical Stage	Number	Up/down staged		
		I	II	III
I	97	88	2	7
II	43	7	21	15
III	47	10	0	37
Total	187			

Table V demonstrates the degree of up/down staging that occurred as a result of comprehensive surgical staging.

Pelvic lymph nodes were positive in 0.0% of stage I patients, 19.5% of stage II patients, and 11.5% of stage III patients. Para aortic nodes were positive in 4.2% of stage I patients, 19.5% of stage II patients and 15.2% of stage III patients. Twelve of 55 (22%) of grossly negative omental specimens were positive and more than one-half of the positive diaphragmatic biopsies were not clinically evident. The authors conclude that there is poor correlation between clinical assessment by inspection and palpation versus a full surgical staging procedure.⁴⁸

Ovarian Sarcomas

GOG #50 opened in 1980 and evaluated adriamycin alone in malignant mixed mesodermal tumors (MMMT) of the ovary.⁴⁹ The protocol closed in 1987 and accrued 31 evaluable patients. The majority of the patients (90.3%) were stage III, IV or recurrent. There were no complete responses and one partial response (total response rate of 10%) in 10 patients with measurable disease. Of the 21 cases with non-measurable disease, 10 were dead of disease three to 34 months from diagnosis (median survival of seven months). The authors concluded that single agent adriamycin was not clinically useful in this disease.⁴⁹ Currently, patients with ovarian MMMT are eligible for GOG #161, a trial designed for MMMT of the uterus, randomizing patients to paclitaxel chemotherapy with either carboplatin or ifosfamide

Maintenance Therapy

GOG #178/SWOG Intergroup Trial was undertaken to evaluate maintenance therapy. The study attempted to determine whether continuing paclitaxel for an extended time period in women with advanced ovarian cancer, who had a clinically-defined complete response to platinum/paclitaxel based chemotherapy, could prolong subsequent progression-free survival and affect ultimate survival.⁵⁰ Patients who were determined to achieve a complete response were assigned to either three or 12 cycles of single-agent paclitaxel administered every 28 days. From 1999 to 2001, 262 eligible patients had entered the trial and an interim analysis was performed. The median progression-free survival was 21 and 28 months in the three cycle and 12-cycle paclitaxel arms, respec-

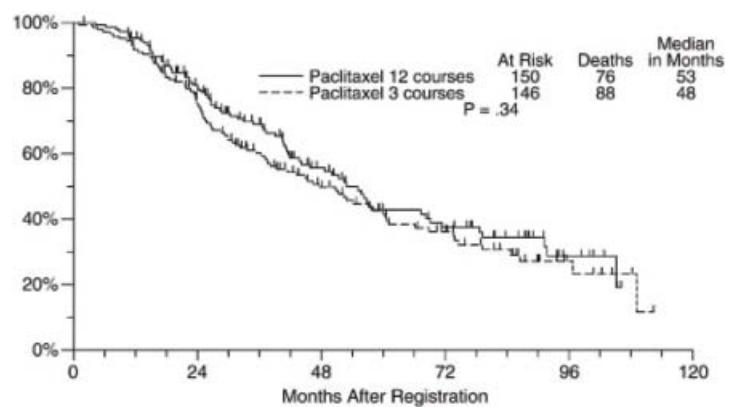


Figure 21. GOG 178 Progression Free Survival.

tively ($p=.0035$).⁵⁰ With a protocol-specified early termination boundary of $p=.005$, these findings led to SWOG's Data Safety Monitoring Committee to discontinue the trial and allowed for crossover of the patients treated on the 3 cycle arm to the 12 cycle arm. At the time of closure, there was no difference in overall survival between the treatment arms. It should be noted, however, that there is a high likelihood of crossover for those patients having only received three cycles of paclitaxel maintenance therapy to receiving additional treatment cycles. The authors' conclusion was that 12 cycles of single-agent paclitaxel administered to women with advanced ovarian cancer who obtained a clinically-defined complete response to initial platinum/paclitaxel-based chemotherapy significantly prolonged the duration of progression-free survival (Figure 20).⁵¹ A followup publication in 2009 evaluated the impact on overall survival. The overall survival for the 12 cycle arm versus the 3 cycle arm was 53 versus 48 months respectively.⁵¹ This difference was not statistically significant (Figure 21). Crossover of patients from the 3 cycle to the 12 cycle arm may have masked a potential difference. In order to further evaluate the overall survival question and respond to criticisms of the lack of a pure control arm, GOG has opened protocol #212 that will randomize a similar population of patients with complete response to observation versus 12 cycles of paclitaxel maintenance therapy versus 12 cycles of a new regulated taxane (Xyotax™). The primary endpoint of this trial will be overall survival in an attempt to determine if timing of prolonged taxane-based maintenance therapy is critical. Enrollment is ongoing.

The Role of Second-Look Laparotomy in Epithelial Ovarian Cancer

In most of its early ovarian cancer trials, the GOG utilized second-look laparotomy for assessment of response. The role of second-look laparotomy was brought into question in the 1990s as a surrogate marker for long-term outcome. Of particular interest was whether or not knowledge of the second-look laparotomy and the presence or absence of disease could alter the treatment strategies that would impact long-term outcomes. GOG initiated trial

#93 in 1987, closed it in 1996 with an attempt to prospectively evaluate the progression-free survival and overall survival of patients with a negative second-look laparotomy assigned to observation versus IP P32.⁵² Two hundred-two eligible patients were randomized during this time frame and long-term follow-up has been achieved. For the IP P32 group, the relative risk of recurrence was 0.9 with a 90% confidence interval of 0.68 to 1.19 and the relative risk of death was 0.85 with a 90% confidence interval of 0.62 to 1.6. The authors concluded that IP P32 did not decrease the risk of relapse from progression-free survival of patients with stage III ovarian cancer after negative second-look laparotomy. In addition, they noted that 61% of the patients with stage III ovarian cancer had tumor recurrence within five years of a negative second-look laparotomy.⁵²

To further determine the importance of second-look laparotomy and patient management, the GOG looked at a non-randomized comparison of protocol #158 for patients who chose whether or not to undergo a second-look laparotomy prior to chemotherapy randomization. In this protocol, 393 eligible patients elected second-look laparotomy and 399 elected no second-look laparotomy. The adjusted relative risk of progression was 0.89 with a 95% confidence interval of 0.75 to 1.07, a difference in median progression-free survival of one month. The survival curves were considered superimposable. The authors concluded that the performance of the second-look laparotomy was not associated with a longer survival.⁵³ Based on the results of these trials, the GOG no longer considers second-look laparotomy as a standard for their protocol.

Summary

The first three decades of the trials of the Gynecologic Oncology Group established it as a leader in the field of cooperative group clinical trials in ovarian cancer. The GOG transformed the specialty of Gynecologic Oncology, resulting in a virtual end of single institution trials and establishing the principles of statistically sound, evidence-based practice. The group established that well-staged, good prognosis (low risk), early stage ovarian cancer does not need additional therapy and set the stage for future trials in high risk, early stage disease. They demonstrated that in the cooperative group setting, early stage ovarian cancer could be studied in a scientifically sound manner.

The group also established the superiority of chemotherapy as compared to radiation therapy for advanced ovarian cancer and introduced the concept of “optimal” and “suboptimal” residual disease. It demonstrated the survival benefit of combination chemotherapy over single agent alkylating agents, and introduced new drugs and drug combinations. Furthermore, it clearly established the roles of cisplatin and paclitaxel in the management of both optimal and suboptimal epithelial ovarian cancer. Later it established that the best current therapy of advanced epithelial ovarian cancer was a combination of carboplatin and paclitaxel, including the survival benefit of intraperitoneal chemotherapy leading to the 2006 National Can-

cer Institute Clinical Alert supporting intraperitoneal chemotherapy as a standard of care for women with advanced ovarian cancer. Current efforts are underway to decrease the side effects associated with intraperitoneal chemotherapy while maintaining the efficacy associated with this approach.

Through a surgical staging protocol, the group established both the technique and value of surgical staging in epithelial ovarian cancer. Using surgical data from a variety of its trials several GOG investigators demonstrated the importance of maximal surgical cytoreduction in the management of epithelial ovarian cancer.

In the field of malignant germ cell tumors of the ovary, the group evaluated VAC chemotherapy and later proved BVP to be a superior regimen to VAC, setting the stage for further refinement of therapy in later decades. Finally, it defined the role for second look surgical reassessment in malignant germ cell tumors.

The future of ovarian cancer research will need to include flexible and innovative trial design to incorporate the rapid development of targeted agents. Due to the heterogeneity of molecular defects in ovarian cancers, development of drugs targeted to these pathways will need to be evaluated individually, in combination, sequentially and with chemotherapy. The GOG, through the continued collaboration of the Committees on Experimental Medicine, Developmental Therapeutics and Ovarian Cancer will be a leader in the development, implementation and completion of these trials in the future. This commitment will maintain the GOG as the leader in defining the standard of care for women with ovarian cancer.

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Establishing a New Paradigm in Uterine Corpus Malignancies



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Endometrial Cancer

Introduction

Until the early 1970's when the GOG was first launching a multicenter, multidisciplinary therapeutic approach for all gynecologic cancers, endometrial cancer therapy had, for decades, been based on institutional experiences rather than randomized trials. For the first time, a large collaborative group made it possible to conduct prospective trials in endometrial cancer well into the future while at the same time accumulating essential statistical data necessary for subsequent trial designs. One of the first concerns was the impact of staging on treatment. At that time, clinical staging was the basis for therapy. It was decided that the nodal status of the patient as well as other histopathologic features should be studied prospectively in large numbers of patients to construct a database for statistical analysis that would be key to creating specific, feasible trials. Findings from previous randomized GOG trials would be used as the basis for design of new trials. Since results of the ongoing or recently closed trials were not always available, the design of a subsequent trial in that patient population was out of necessity based upon best available data. Often recent findings from phase II trials would be incorporated into new trials before data was mature from the immediate prior randomized trial.

Surgical Staging

After a successful feasibility study conducted by Boronow, Creasman, DiSaia, and Morrow, a massive staging study (GOG 033) with entry of nearly 1200 patients with endometrial cancer accrued patients between 1977 and 1983. Seventeen abstracts and publications resulted from this work along with numerous presentations.¹⁻⁶ These findings led to the revision in FIGO surgical staging for endometrial cancer in 1988. The FIGO staging system has since been further modified, but the importance of patient-specific surgico-pathologic data remains.⁷

Between June 20, 1977 and February 5, 1983, the Gynecologic Oncology Group entered 1180 women with clinical stage I or II (occult) endometrial carcinoma into a surgical-pathological staging study.¹⁻³ Eight hundred ninety-five patients with endometrioid or adenosquamous carcinoma were evaluable for this study, which related surgical-pathological parameters and postoperative treatment to recurrence-free interval and recurrence site. Proportional hazards modeling of time to recurrence was performed. For patients without metastasis determined by surgical-pathological staging the greatest determinant of recurrence was grade 3 adenocarcinoma histology, relative risk (RR) = 15; adenosquamous carcinoma grade 3, RR = 8.1; all adenocanthomas, RR = 1.0. Of 48 patients with histologically documented aortic node metastases, 47 had one or more of the following features: (1) grossly positive pelvic nodes, (2) grossly positive adnexal metastasis, and/or (3) outer one-third myometrial invasion. Pelvic radiation was administered to 48% and vaginal brachytherapy alone to 10% of patients postoperatively; 42% received no adjuvant radiation therapy. None of three recurrences in the vaginal implant group were vaginal or pelvic. Of the recurrences in the pelvic radiation therapy group 7% (7 of 95) were vaginal and 17% were pelvic. Of the recurrences in the no adjuvant radiation group 18% (8 of 44) were vaginal and 32% pelvic. Because of the high degree of selection bias, no valid comparisons could be made of recurrence-free intervals in these groups. The five-year recurrence-free interval for patients with negative surgical-pathological risk factors (other than grade and myoinvasion) was 93% (low risk). The five-year recurrence-free interval decreased with involvement of the isthmus/cervix (70%), positive pelvic cytology (56%), vascular space invasion (55%), pelvic node or adnexal metastases (58%) (intermediate-risk), and aortic node metastases or gross laparotomy findings (41%) (high-risk).

It was not clear that cervix invasion, per se, diminished survival, because it was associated with higher tumor grade (35% versus

24%, grade 3) and deep myoinvasion (47 vs 19 %). The relapse rate among cervix-positive and -negative cases with grade 3 lesions and deep myoinvasion was not dramatically different (49% vs 40 %). The proportion of failures that were vaginal/pelvic (35% for the surgery only group compared to 12% of the RT group) appeared to favor the use of adjuvant radiation for patients with more than one-third myoinvasion and grade 2 or 3 tumor. There were 97 patients in the study group with malignant cytology of which 29% had regional/distant failure, compared to 10% of the cytology-negative patients.

By using the data from GOG 033, patients could be grouped as low, intermediate and high risk for recurrence. The low risk patients documented by the staging procedure had an excellent prognosis and were not considered amenable for clinical trials except for trials such as assessment of the risk of estrogen replacement therapy in patients with low risk endometrial cancer (GOG0137). The low risk group accounted for about 70-80% of all patients with endometrial cancer.

On the other hand, intermediate risks patients with deep myoinvasion, lymphovascular invasion, high grade or rare histologies such as clear or serous cancers were candidates for prospective trials combining surgery with other modalities.

The high risks patients with positive nodes or extra-uterine disease, even with non-measurable disease, were identified as a new group of patients where trials were designed to compare modalities, investigate adjuvant chemotherapy, or use combined modalities.

Laparoscopy

Advances in laparoscopic technology emboldened a few surgeons to undertake cancer operations with the improved instrumentation. As is often the case, the technology advanced beyond the evidence to support it. The GOG sought to determine if the technology was indeed an advancement, and Homesley et al. reported the results of GOG #9206 describing the feasibility of laparoscopic staging of endometrial cancer.⁸ Spirito et al. reported on behalf of the GOG that laparoscopic staging could be successfully undertaken in incompletely staged cancers of multiple gynecologic sites.⁹ These studies led to GOG LAP2. Patients with clinical stage I to IIA uterine cancer were randomly assigned to laparoscopy (n = 1,696) or open laparotomy (n = 920), including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. The main study end points were six-week morbidity and mortality, hospital length of stay, conversion from laparoscopy to laparotomy, recurrence-free survival, site of recurrence, and patient-reported quality-of-life outcomes. Initial results were published in 2009.^{9a} About 26% of percent of patients were converted from laparoscopy to laparotomy, primarily because of poor visibility. Laparoscopy had a significantly longer operative time than laparotomy (median, 204 v 130 minutes, respectively; P < .001) but resulted in fewer complications and

shorter hospital stays. In 2012 oncologic outcomes were reported.¹⁰ The patients entered on the trial had a good prognosis. With a median follow-up time of 59 months there were 309 recurrences (210 laparoscopy; 99 laparotomy) and 350 deaths (229 laparoscopy; 121 laparotomy). The estimated hazard ratio for laparoscopy relative to laparotomy was 1.14, which did not meet the protocol-specified definition of noninferiority. The estimated three-year recurrence rate of 11.4% with laparoscopy and 10.2% with laparotomy. The estimated five-year overall survival was almost identical in both arms at 89.8%

Single Modality Adjuvant Therapy: Radiation therapy or Chemotherapy

The role of adjuvant pelvic radiation in “intermediate risk” early stage endometrial cancer was described by Keys et al. GOG #99 compared the results of pelvic irradiation with those of observation following hysterectomy and lymphadenectomy.¹¹ The estimated two-year cumulative incidence of recurrence (CIR) was 12% in the observation arm and 3% in those irradiated (P = 0.007). The treatment difference was particularly evident among a “high intermediate risk” subgroup defined as those with (1) moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above where the CIR in the observed patients was 26% versus 6% in the treated. Overall survival rates at four years did not differ significantly between the two groups, although the patients accrued were strongly weighted a lower risk profile.

Because upper abdominal failures have been reported previously in patients with stage III disease, attention was focused on the potential role of whole-abdominal irradiation (WAI). Although subsets of patients had done well with WAI, it was unclear whether this more aggressive therapy has any benefit over pelvic irradiation. A GOG phase II trial of WAI (GOG #94) demonstrated a three-year, progression-free survival rate of 35%.¹² The GOG then completed a trial of WAI compared with combination doxorubicin and cisplatin (AP) chemotherapy (GOG #122). The patient population included patients with stages III and IV disease (75% and 25%, respectively) with 50% endometrioid histologies. The stage-adjusted death hazard ratio was 0.68, favoring the chemotherapy arm. The five year stage-adjusted survival rate was projected to be 55% for patients receiving AP compared to 42% for WAI patients. Grades 3 and 4 toxicity were higher with chemotherapy, and an increased risk of death as well as cardiac, GI, and hematologic toxicity was observed with chemotherapy treatment. Pelvic and abdominal recurrences were the predominant pattern of recurrence for both treatment arms. Distant recurrences were slightly less frequent for patients treated with chemotherapy.¹³ These results established the role of chemotherapy as a new standard of care in locally advanced endometrial cancer and supported the concepts of testing adjuvant chemotherapy combined with involved-field radiation in subsequent trials.

Combined Modality Adjuvant Therapy with Radiation Therapy and Chemotherapy

Significantly, after the completion of GOG 99, the GOG opened GOG 0249, comparing Vaginal Brachytherapy (VBT) followed by three cycles of paclitaxel/carboplatin with pelvic RT. This trial represented a consensus opinion reached at a State of the Science meeting on endometrial cancer held in Manchester, England in 2006. As a result, this trial incorporated a number of modifications that reflected current practice and thought, and it was the first study to incorporate a combined chemo-RT arm in low stage patients. The patient population included the traditional “intermediate-risk” population eligible for GOG 99. However, higher risk patients were also eligible, including stages I and II clear cell and serous tumors with negative peritoneal cytology, as well as patients with gross cervical involvement. Surgery could be performed via laparotomy or laparoscopy, and nodal sampling or dissection was encouraged but optional. Finally, this was the first group-wide study in which intensity-modulated radiation therapy (IMRT) could be employed. However, to use IMRT, the treating institution must have been credentialed by the Radiological Physics Center (including successfully irradiating a phantom within established criteria) and having the first IMRT case of each treating radiation oncologist reviewed by GOG experts prior to treatment. This study accrued quickly and has recently closed. Preliminary results should be available within the next 1-2 years.

The use of concurrent chemotherapy and whole abdominal radiation in endometrial cancer has prospectively been deemed tolerable but not further pursued in randomized trials.^{34,34a} Following completion of GOG 122 in the locally advanced population, the GOG opened GOG184, which evaluated whether the addition of paclitaxel to cisplatin and adriamycin chemotherapy could improve the recurrence-free survival compared with adriamycin and cisplatin in patients with locally advanced stage III/IV endometrial cancer treated with hysterectomy, optimal debulking and involved-field RT.¹⁴ Patients received 50.4 Gy to the pelvis, and 43.5 Gy to the para-aortic nodes if involved. Approximately 30% of patients developed distant recurrences, and there was a 10% locoregional recurrence rate at 36 months, without a significant difference between arms. In a subset analysis, the addition of paclitaxel benefited high-risk subsets including patients with gross residual disease and high risk histologies (clear-cell, serous and grade 3 endometrioid). A related Quality of Life study documented that patient-reported neuropathy was worse in patients receiving paclitaxel in addition to cisplatin and adriamycin, especially in the sensory component.¹⁵

In the locally advanced population, the GOG is currently conducting GOG 258, which randomizes patients with stages III and IVA endometrial cancer (<2 cm residual disease) between combination carboplatin and paclitaxel alone for six cycles versus a regimen of concurrent cisplatin and regional RT followed by four cycles of

additional chemotherapy with carboplatin and paclitaxel. The primary endpoint of GOG 258 is a comparison of RFS between the two arms.

Pelvic Only Recurrent Disease

Given the more selective use of pelvic RT as adjuvant treatment after hysterectomy for endometrial cancer resulting in a higher rate of vaginal cuff recurrences, the GOG opted to study a new population, not previously addressed in GOG trials – that of pelvic only recurrences in patients who had not received previous RT. This study (GOG 238) was designed as a randomized phase II study comparing pelvic RT and brachytherapy alone with pelvic RT and brachytherapy plus concurrent cisplatin chemotherapy. This study remains open to accrual.

Hormonal Therapy

Because of minimal toxicity and the potential for response, hormonal therapy has been a major therapeutic option in the treatment of advanced endometrial carcinoma. In the 1970s, efforts were underway to establish the role of hormonal therapy and chemotherapy in advanced disease. Since approximately one-fourth of patients did respond initially to hormonal therapy, which was much less toxic than any chemotherapy available at the time, the tendency was to first treat all patients with hormonal therapy, although later trials indicated that less than 5% had a long term benefit. To ease patients directly into chemotherapy trials, all patients did first receive standardized progestin therapy (GOG 0048). Attempts were made to assay estrogen and progesterone receptor content of tumors. This was not used to direct therapy, although it was recognized that patients with well differentiated tumors with high progesterone receptor values responded significantly better.

In 1989, to more clearly define the role of hormonal therapy, a prospective randomized trial was activated to compare lower dose (200mg) to high dose (1000mg) medroxyprogesterone acetate in endometrial cancer patients with advanced disease (GOG 0081).¹⁶ The response in both arms was similar, so no advantage for high dose progestin was identified. In a later study (1991-1992), high dose megestrol acetate (GOG 0121) was noted to be of similar benefit to low dose medroxyprogesterone.¹⁷

Tamoxifen has been utilized in the treatment of endometrial carcinoma, both in the salvage setting and as first-line systemic treatment. The largest trial, a recent GOG study involving patients who had never received systemic therapy for endometrial carcinoma, reported a 10% response rate.¹⁸ These data suggest that tamoxifen is not as active as progestins and is of little value as second-line therapy in patients who do not respond to progestins.

The GOG has evaluated combined therapy with tamoxifen plus a progestin given sequentially in the hope that tamoxifen may

increase progesterone receptor expression and, thus, increase the rate of response to progestins. Tamoxifen, 40 mg daily, with intermittent medroxyprogesterone acetate 200 mg daily on alternate weeks, had a 33% response rate with a median progression-free survival of three months and median survival of 13 months (GOG #119).¹⁹ A careful central assay of tumor ER alpha and PR isoforms A and B was performed on that trial. There was no statistically significant correlation of PR with response, but ER H core was related to both response and overall survival.^{19a} A subsequent A phase II trial of megestrol acetate, 160 mg orally for three weeks, alternating with tamoxifen, 40 mg daily for three weeks, until disease progression, showed an overall response rate of 27% with a median progression-free survival of 2.7 months and median overall survival of 14 months GOG #153.²⁰ As with prior hormonal studies, patients with well differentiated cancers were more likely to respond. Nevertheless, this trial was unusual in that 22% of patients with poorly differentiated tumors responded.

Further understanding of the antineoplastic effects and mechanism of the progestin, depo-provera were elucidated in GOG #211. In this study, Depo-Provera 400 mg was given intra-muscularly 21-24 days prior to hysterectomy for endometrial cancer. It was found that short-term progestin therapy induces partial histologic responses in most endometrioid adenocarcinomas, which is quantitatively and qualitatively different from that of benign endometrium. The mechanism appears to reflect increased differentiation of tumor and a diminished growth rate rather than tumor cell death. Stromal decidualization was confined to areas surrounding benign glands suggesting a paracrine effect. Down regulation of progesterone receptors by the progestin may limit its efficacy and duration of response.²¹

Other hormonal agents have been tested, but have not appeared superior to progestins. Anastrozole was evaluated in GOG #168, and found to produce a response rate of only 9%^{21a}. Faslodex, a pure estrogen antagonist, was evaluated in GOG #188. Patients with advanced, recurrent, or persistent endometrial cancer received 250 mg by intra-muscular injection every 4 weeks for at least 8 weeks, and until evidence of progression. Although toxicity was limited, there was little evidence of anti-tumor activity.²²

Chemotherapy

The GOG has successfully completed numerous phase II and III trials of chemotherapy in the treatment of advanced, persistent, and recurrent endometrial cancer. Prior phase II trials have demonstrated the activity of a number of single agents including doxorubicin, cisplatin, and paclitaxel. This has led to randomized phase III trials. From 1977-1979, the first completed chemotherapy randomized trial in endometrial cancer (GOG 0028) included megestrol acetate in both arms and compared melphalan and 5-fluorouracil to doxorubicin, cyclophosphamide and 5-fluorouracil.²³ The results were similar in each arm and not that different from prior experience with single agent therapy

with doxorubicin.²⁴

A randomized trial of pelvic radiation with or without subsequent doxorubicin (GOG 0034) in the higher risk patients with deep myoinvasion, cervical involvement or nodal metastasis did not detect benefit of post-radiation doxorubicin, possibly because of the small sample size and the number of patients lost to follow-up. The GOG compared doxorubicin with observation in 181 patients with high-risk, early-stage, endometrial carcinoma; at five years, there was no difference in recurrence rates.²⁵ From 1979-1985, a follow-up chemotherapy trial, GOG #48, compared single agent doxorubicin (60 mg/m²) to the combination of doxorubicin (60 mg/m²) plus cyclophosphamide (500 mg/m²), both administered intravenously every three weeks. The median age of women on the trial was 65 years of age (range 36-90), which underscores both the older age of most women with endometrial cancer, and the remarkable success of the GOG in accruing this elderly population to clinical trials. It should be remembered that in this trial, as well as in subsequent GOG endometrial carcinoma trials not employing granulocyte growth factors, women who were over the age of 64 years or who had prior pelvic radiotherapy (i.e. the majority of those on study) received initial dose reductions (25% in GOG #48). Although there were trends towards both improved response rate and improved survival with the combination therapy, the absolute magnitude of the survival increase was small, and not felt to justify the increased toxicity; doxorubicin therefore remained the GOG standard arm.²⁶ Interestingly, there were 14 women with clear cell carcinoma were entered on this trial, more than on many of the subsequent trials. Three (21%) responded, with response durations similar to that of the overall study patient population.

In 1985, a series of phase II trials (GOG 0086) was initiated to assess efficacy in chemotherapy naive endometrial cancer. Hexamethylmelamine, methotrexate, vincristine, ifosfamide, tumor necrosis factor, liposomal doxorubicin, paclitaxel and cisplatin were studied.²⁷⁻³¹ Later, the GOG0129 series of Phase II trials were opened to assess activity in previously treated patients. Agents evaluated included cisplatin, paclitaxel, topotecan, pemetrexed, ixabepilone, and gemcitabine.^{29,32,32a,b,c,d} The most active agents in the phase II trials was paclitaxel.

Because of these findings, subsequent combination clinical trials were designed. From 1988-1992, the first such major trial, GOG0107, used information gained in single agent GOG trials which demonstrated activity of cisplatin against endometrial cancer. Women were randomized to either doxorubicin (60 mg/m²) or the combination of doxorubicin (60 mg/m² plus cisplatin 50 mg/m²). The combination produced very significant improvements in both response rate and progression-free survival (PFS), but there was no improvement in overall survival. It is tempting to speculate that use of cisplatin in the salvage setting might have accounted for the lack of survival benefit. However information on salvage therapy was not collected, and results of platinum

agents used as second-line therapy against endometrial cancer have had mixed results; the GOG trial of cisplatin in previously treated patients yielded a response rate of only 4%. Despite the added toxicity of the combination regimen, the improvement in response rate and PFS led the GOG to adopt doxorubicin/cisplatin as their new standard therapy.³³

Animal data have frequently shown dramatic alterations in both toxicity and efficacy of a number of chemotherapeutic agents depending on the schedule of administration. A phase II (30 patient) GOG study was completed in which doxorubicin (60 mg/m²) was administered at 6:00 a.m. and cisplatin (60 mg/m²) was administered at 6:00 p.m.³⁵ The response rate of 60% appeared promising compared to the 42% response rate achieved with the same combination in GOG0107. GOG0139 was therefore undertaken to compare the circadian timed schedule with a “standard schedule” (i.e. both drugs given one right after the other at any convenient time) schedule. The completion of GOG0139 was a testimony to the dedication of GOG physicians, nurses, data managers, and patients; 6 AM doxorubicin is not convenient by any standard! However, the larger randomized trial demonstrated no difference between the two schedules of administration in terms of response rate, progression free survival, overall survival, or toxicity.³⁶ Again, the difficulty of comparing results across trials, particularly in comparing a small phase II trial with either other small trials or a larger randomized trial, is illustrated. Sources of bias are myriad. Of note, 60% of patients on the GOG phase II circadian trial had a performance status of 0 versus only 37% of patients on GOG0107.

In the early 1990’s the GOG demonstrated a striking 36% response rate to 24-hour infusion of single agent paclitaxel in endometrial cancer patients with no prior chemotherapy.²⁷ GOG0163 therefore compared the doxorubicin/cisplatin regimen (with the starting dose of cisplatin reduced to 50 mg/m² because of toxicities observed in the previous trials using 60 mg/m²) with a doxorubicin (50 mg/m²)/24-hour paclitaxel (150 mg/m²) combination. All patients on the paclitaxel arm received G-CSF support. Neither hematologic toxicities, response rate, PFS, nor survival differed between the arms, and the expense and inconvenience of a 24-hour infusion with growth factor support precluded its adoption for routine use.³⁷

While GOG0163 was ongoing, the GOG conducted a large Phase I trial, GOG9405, to determine tolerable doses of a combination of cisplatin, three-hour paclitaxel, and doxorubicin.³⁸ GOG0177 used the results of that phase I study, and randomized women to either doxorubicin/cisplatin or the combination of doxorubicin (45 mg/m²) plus cisplatin (50 mg/m²) plus paclitaxel (160 mg/m², given on day two) with G-CSF support (TAP). The three drug combination was superior in terms of response rate, progression-free survival, and overall survival, unequivocally demonstrating the value of paclitaxel in the treatment of endometrial carcinoma.

Hematologic and cardiac toxicities were similar between the two arms. However, there was more neuropathy with paclitaxel (12% vs 1% grade 3 peripheral neuropathy).³⁹

This triplet combination was also compared to doxorubicin and cisplatin in the adjuvant endometrial cancer setting. As mentioned earlier, GOG0184 was a randomized phase III study of tumor directed (pelvic plus or minus para-aortic) irradiation followed by cisplatin and doxorubicin or cisplatin, doxorubicin and paclitaxel for advanced endometrial carcinoma. This study was instituted following the completion of GOG #122 based on the assumption that combined modality therapy with radiation therapy and chemotherapy in advanced but optimally cytoreduced endometrial carcinoma may lead to a better result than either modality used alone. Patients with stage III and IV adenocarcinoma of the endometrium with less than 2 cm residual disease were treated with radiation therapy tailored to include the volume at risk followed by randomization to cisplatin plus doxorubicin or cisplatin, doxorubicin plus paclitaxel. Although the combination of doxorubicin, cisplatin, and paclitaxel is the most active regimen demonstrated to date in advanced endometrial carcinoma, patients are often treated with carboplatin and paclitaxel in the community.

The GOG completed a phase III trial to determine whether these regimens are of equal efficacy and whether there is an improvement in quality of life with the treatment in one arm of the study (GOG #209). Patients received either doxorubicin 45 mg/m² and cisplatin 50 mg/m² (day 1), followed by paclitaxel 160 mg/m² (day 2) with growth factor support (TAP) or paclitaxel 175 mg/m² and carboplatin AUC 6 (day 1) (TC) repeated every 21 days for 7 cycles. During the study, initial doses of TC were reduced (135 mg/m², AUC 5) for those with a history of pelvic/spine irradiation. Results have been reported in abstract form; neither overall survival nor progression-free survival differed between the arms, and the carboplatin/paclitaxel doublet was less toxic, and has therefore been taken forward in subsequent trials. This work has been submitted for publication.

Chemotherapy Plus Hormonal Therapy

Combinations of chemotherapy plus progestins have been studied in a number of phase II trials. The only large, randomized trial evaluating this approach (GOG protocol 29) allocated patients with advanced or recurrent disease to receive either cyclophosphamide, doxorubicin, cisplatin, and megestrol acetate or melphalan (Alkeran), 5-FU, and megestrol acetate. In pilot studies, these two regimens had been reported to yield response rates of 75% and 94%, respectively. The randomized trial produced response rates of 36% and 38%, respectively, with no evident advantage of either combination over prior studies of single-agent doxorubicin with regard to response rate, progression-free interval, or overall survival.²³ These results do not suggest any advantage for the combined use of chemotherapy and progestins.

Biologic Therapy

The GOG has performed phase II trials of a number of biologic agents in women with endometrial cancer. These include antiangiogenic agents, anti HER1 and HER2 agents, and mTOR inhibitors. Completed trials tested thalidomide [McMeekin *DS Gynecol Oncol* 105:508, 2007], gefinitib [Leslie *KK Gynecol Oncol* 129:486, 2013], lapatinib [Leslie *KK Gynecol Oncol* 124:569, 2012], trastuzumab [Fleming *Gynecol Oncol* 116:15, 2010] bevacizumab [Aghajanian *J Clin Oncol* 29:2259, 2011], Aflibercept [Coleman *et al Gynecol Oncol* 127:538, 2012], the combination of bevacizumab and temsirolimus [Alvarez *EA, Gynecol Oncol* 129:22, 2013], the combination of megestrol acetate and temsirolimus, AZD 6244, brivanib, AMG 386, Cediranib and BIBF1120. Bevacizumab (13.5% response rate in patients with 1-2 prior regimens) and temsirolimus appeared particularly promising, and were moved to large front-line randomized phase II trial in women with advanced or recurrent disease.⁴⁰

Molecular studies have accompanied many of these trials; for example, in the trial of lapatinib three mutations in EGFR among 30 participants were identified. Two of these, L688F and K754E, were not associated with response or PFS. However, a newly identified mutation in exon 18, E690K, occurred in the one patient with a partial response and progression-free survival extending past six months. [Leslie *KK Gynecol Oncol* 127:345, 2012]

While awaiting the results from GOG 209, the group opened GOG 248, a randomized phase II trial of mTOR inhibitor temsirolimus (25 mg IV weekly) versus a combination of megestrol acetate 80 mg twice a day for three weeks alternating with Tamoxifen 20 mg twice a day for three weeks plus temsirolimus at the same dose in women with advanced or recurrent endometrial carcinoma. This study was the first randomized trial undertaken by the Corpus Committee to evaluate the role of biologic therapy in endometrial cancer. The combination arm was closed to accrual early due to a higher than expected incidence of thrombo-embolic events in this arm. This completed study was the group's first randomized trial to evaluate the role of biologic therapy in endometrial cancer.⁴²

The GOG also conducted a phase III randomized 3 arm study incorporating different biologic agents (GOG 86P). Arm 1 included paclitaxel 175 mg/m², carboplatin at AUC 6, and bevacizumab 15 mg/kg every three weeks for 6 cycles; Arm 2 included the same dose of paclitaxel, carboplatin at AUC 5, plus temsirolimus 25 mg days 1 and 8 for 6 cycles given every 21 days; and Arm 3 included carboplatin at AUC 6 plus ixabepilone 30 mg/m² plus bevacizumab 15 mg/kg, for 6 cycles given every 21 days. This study is closed to patient entry and results are pending.

Tumor Biology

The valuable GOG database of multiple large randomized trials in endometrial cancer will allow us to answer other questions about the disease. For example, by pooling patients on accrued GOG

107, 139, 163, and 177 it was possible to evaluate the importance of histology in the chemotherapeutic treatment of advanced or recurrent disease. The probability of response was not related to histologic subtype (endometrioid, papillary serous, clear cell, mixed). Patients with clear cell tumors tended to have poorer progression free survival and overall survival.⁴³

In 2003, the GOG embarked on gaining a better understanding of the risk factors related to outcomes in endometrial cancer, but this time at the molecular level (GOG 210). By doing this, the group hoped to develop more accurate models of risk, identify candidate targets for therapeutic intervention, and utilize individualized treatments based on molecular characteristics identified in tumor tissue, normal tissue and/or in readily accessible biological fluids, like serum and urine. This required the establishment of a repository of clinical specimens (tissue, urine, and serum) with detailed clinical and epidemiologic data from patients with surgically staged endometrial carcinoma. This repository has been utilized to perform genomic, proteomic and immunoassay testing for the purpose of class prediction and class discovery in endometrial carcinoma to identify and validate molecular characteristics associated with risk of endometrial cancer recurrence, clinical and histological characteristics, and epidemiologic factors. This information, along with the clinical, histological and epidemiologic data obtained for this research study, is potentially valuable as a means to identify candidate characteristics to target or exploit that would help prevent and/or treat endometrial carcinoma, and to expand the current understanding of the biology, progression, metastasis and responsiveness of endometrial carcinoma. This study completed all accrual in 2011, and there have been multiple outstanding translational investigations that have arisen from multiple investigators and institutions and facilitated by this tissue repository and data base, some of which have already been published.⁴⁴

Quality of Life

Does hormone replacement therapy (HRT) increase the likelihood of recurrence? Several retrospective reports had shown no adverse outcomes. Thus, the GOG undertook a large randomized placebo controlled trial of HRT after treatment for earlier stage endometrial cancer. HRT was not associated with a significant incidence of recurrent disease or mortality.⁴⁵

In GOG 122, a detailed QOL analysis revealed significantly greater toxicity in the chemotherapy arm, particularly peripheral neuropathy persisting up to six months.⁴⁶

GOG LAP2 contained a Quality of Life (QOL) survey component as well. Although only 225 patients completed the sexual function items in the QOL survey, there were no significant differences reported in sexual function.⁴⁷

Quality of Life (QOL) endpoints have always been important in GOG trials, and they are increasingly included in study objectives.

Most current phase III studies contain QOL endpoints.

Imaging

In collaboration with the American College of Radiology Imaging Network (ACRIN), the GOG is conducting GOG 233, to evaluate the preoperative utility of FDG-PET scanning in detecting retroperitoneal nodal metastasis in high risk endometrial and cervical cancers.

Summary

The first decades of endometrial cancer investigation by the GOG began with a meticulous prospective, surgicopathologic staging study that was the platform for development of all subsequent trials. The resultant statistical model of low risk, intermediate risk, and high risk groups of patients led to trials where therapeutic modalities were best targeted at disease spread. Hormonal therapy was thoroughly investigated and led to combination hormonal therapy trials. A clear role for chemotherapy was established, at least for advanced disease. It was realized that greater advances might be achieved with the advent of newer anti-neoplastic agents and these agents were subjected to extensive phase II testing. These agents later were integrated into comparison chemotherapy trials for advanced endometrial cancer. Multimodality therapy is in the early stages of investigation and shows promise. Newer agents, including biologics are under active study, as well as the potential contribution of modern imaging techniques. Finally, GOG 210 established a repository of clinical specimens with detailed clinical and epidemiologic data from patients with surgically staged endometrial carcinoma. This should provide for a much greater understanding of molecular characteristics associated with risk of endometrial cancer recurrence clinical and histological characteristics, and epidemiologic factors.

Uterine Sarcomas

Sarcomas arising in the uterus have often already metastasized before surgery or then recur.⁴⁸⁻⁴⁹ However, in patients with apparently localized disease, the optimal adjuvant postoperative therapy has been, and continues to be, under active investigation.

Surgery

Surgery is the mainstay of treatment for uterine sarcomas. For carcinosarcoma,

this usually consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy with washings to be obtained for peritoneal cytology. The GOG prospective staging study reported a 17% incidence of nodal metastasis for this histologic subtype, so retroperitoneal nodes should be sampled as for poorly differentiated endometrial cancers. In a prospective surgical staging trial by the GOG, the recurrence rate for early-stage carcinosarcoma was 53% and for LMS was 71%.⁴⁹

Radiotherapy

Uterine sarcomas represent only 2%-5% of all uterine malignancies. These patients have a high incidence of distant, as well as pelvic, recurrences. In a nonrandomized prospective GOG study, patients with stages I and II mixed mesodermal sarcomas and LMSs had fewer pelvic recurrences following irradiation than did those patients who did not undergo pelvic irradiation. No difference in overall or disease-free survival was noted.⁵⁰

The GOG completed a randomized study for patients with stages

Table 1. GOG Randomized Chemotherapy Trials in Advanced/Recurrent Endometrial Carcinoma

GOG#	Years of Accrual	Agents	n	RR	Median OS	p (OS)	Reference
48	1979-1985	Dox vs.	132	22%	6.7 mos	P= .048 (one – sided)	Thigpen, 1994 ¹
		Dox/Ctx	144	30%	7.3 mos		
107	1988-1992	Dox vs.	150	25%	9.2 mos	NS	Thigpen, 2004 ²
		Dox/Cis	131	32%	9.0 mos		
139	1993-1996	Dox vs.	169	46%	11.2 mos	NS	Gallion, 2003 ³
		Circadian Dox/Cis	173	49%	13.2 mos		
163	1996-1998	Dox vs.	157	40%	12.6 mos	MS	Fleming, 2004 ⁴
		Dox/24 hr paclitaxel	160	43%	13.6 mos		
177	1998-2000	Dox vs.	129	34%	12.3 mos	P =.037 (one – sided)	Fleming, 2004 ⁵
		Dox/Cis/3 hr paclitaxel	134	57%	15.3 mos		

Table 1 summarizes the past 25 years of GOG trials attempting to optimize front-line chemotherapy for women with advanced or recurrent endometrial carcinoma. Clearly, the median overall survival of women entered on these trials has improved over time, from about 7 months in GOG #48 to over a year in GOG #177. Some portion of this is due to changes in supportive care and patient selection. For example, the improvement in median survival with doxorubicin alone from 6.7 months on GOG #48 to 9.2 months on GOG #107 may be related to the fact that 11% of women on GOG #48 had a performance status (PS) of 3. Patients with PS 3 were excluded from GOG #107. Such differences in survival with identical regimens serve as a reminder of the critical importance of randomized trials in determining if a therapy is truly superior and underscore the value of what the GOG has accomplished in this area. Unknown selection factors make comparisons of results across studies very unreliable.

I-IV mixed mesodermal sarcomas, GOG 150. Following resection of gross disease, 232 patients were randomized to either cisplatin 20 mg/M²/d for four days plus ifosfamide 1.5 gm/M²/d for four days every three weeks for three cycles (CIM) or whole abdominal radiation (WAI) to a total dose of 3,000 cGy, and the pelvis was treated to a total dose of 4,980 cGy. The abdomen received 150 cGy per fraction with 5 fractions per week. The pelvis was boosted an additional 11 fractions at 180 cGy per fraction. No statistically significant difference was identified for CIM over WAI. However, when adjusting for stage and age, the recurrence rate was 21% lower in the CIM arm. Furthermore, the estimated death rate was 29% lower in patients randomized to receive CIM chemotherapy.⁵¹

Chemotherapy

A GOG study, #20, looking at adjuvant doxorubicin vs no further therapy, showed no differences in recurrence rate, progression-free survival, or overall survival.⁵² The response rate to doxorubicin alone is 20% or less, and no significant improvement has been seen when it was combined with dacarbazine (DTIC) or cyclophosphamide.^{53,54} Consequently, the GOG embarked on a series of Phase II trials to identify potentially active cytotoxic agents. Only two of the agents were active. Cisplatin showed definite activity as a first- and second-line agent, with response rates of 19% and 18% respectively, against malignant mixed müllerian tumors (MMMTs).^{55,56} Ifosfamide also has activity against carcinosarcomas. In chemotherapy naive patients, responses were seen in 32% and in 18% of those previously treated with chemotherapy.^{57,58} In previously treated patients, paclitaxel had “moderate activity,” with responses seen in 18% that lasted a median of four months.⁵⁹ The anti-angiogenic agent, thalidomide, had a 4% response rate in measurable persistent or recurrent carcinosarcoma.⁶⁰ There was an 18% progression-free survival at six months, which was considered as showing potential activity, but with more active agents identified further investigation was not initiated. Another phase II study tested for activity of imatinib mesylate (600 mg daily oral dose) but found minimal activity in patients with measurable pretreated carcinosarcoma.⁶¹ Consequently, cisplatin, ifosfamide, and taxol were selected for further evaluation in Phase II and III trials.

The addition of cisplatin to ifosfamide in GOG0108 appeared to offer a small improvement in progression-free survival but not overall survival over ifosfamide alone.⁶² Because of this, GOG 0161 randomized patients with measurable disease to ifosfamide, 2.0 g/M²/d for 3 days every 3 weeks for 8 cycles versus ifosfamide 1.6 g/M²/d for 3 days plus paclitaxel, 135 mg/M² by 3 hour infusion on day 1 repeated every 3 weeks for 8 cycles. Of 214 patients enrolled, 179 were eligible. The addition of paclitaxel increased the crude response rate from 29% to 45%. Hazards of death and disease progression decreased 31% and 29%, respectively, favoring the combination arm. These results were obtained at the expense of a significantly higher rate and severity of sensory neuropathy.⁶³

In the 232 series, novel combinations were tested in the phase II setting in patients who had received no prior chemotherapy. In GOG 232B, combination paclitaxel and carboplatin was given to 55 patients with advanced, persistent, or recurrent measurable disease carcinosarcoma. Partial and complete response rates were 41% and 13%, respectively, and toxicity was deemed acceptable.⁶⁴ In GOG 232C, the PARP inhibitor, iniparib, was added to the paclitaxel-carboplatin backbone, generating a response rate of 23.5% in 17 evaluable patients. This was felt to be insufficient to warrant further study.⁶⁵

All this work has contributed knowledge to the design of the current Phase III randomized study currently open for newly diagnosed stage I-IV, persistent, and recurrent carcinosarcomas of the uterus, fallopian tube, peritoneum, or ovary, GOG0261. This two-arm study randomized between combination paclitaxel (175 mg/m² day 1) plus carboplatin (AUC 6 day one) versus a combination of ifosfamide (1.6 mg/m² days 1-3 plus mesna) and paclitaxel (135 mg/m² day 1) with G-CSF support. Dose reductions are built in if patients have had prior pelvic RT, and dose escalation is built in to arm 2 based on hematologic tolerance.

Although early uterine sarcoma studies in the GOG included both carcinosarcoma and leiomyosarcoma (LMS), it was clear that these diseases had different characteristics and needed to be studied separately. An early phase II trial of bolus etoposide in advanced and recurrent LMS showed approximately a 111% response rate,⁶⁶ and a subsequent study of prolonged oral etoposide showed minimal activity.⁶⁷ Similar minimal response rates were observed with paclitaxel⁶⁸ and trimetrexate.⁶⁹ However, in GOG 131E, gemcitabine was tested as second-line therapy in measurable LMS, and an encouraging response rate of 20.5% was observed.⁷⁰ Subsequently, in GOG 131G, the combination of gemcitabine and docetaxel was evaluated as second-line treatment, and the response rate increased to 27%. The median progression-free survival was 5.6 months. As in carcinosarcoma, the GOG tested the biologic agents thalidomide and sunitinib in LMS, and neither showed significant activity.^{71,72}

All this work has informed the design of two Phase III trials currently underway in the GOG. GOG 250 accrues patients with measurable recurrent or advanced LMS between 2 regimens. Arm I consists of gemcitabine followed by placebo on day 1 plus gemcitabine and docetaxel on day 8 of each 3 week cycle. Arm II consists of the same regimen, except that instead of placebo in arm I, bevacizumab is given. Treatment continues until progression or adverse effects prohibit further therapy.

As there is no established role for adjuvant systemic therapy in uterus-limited LMS, GOG 277 is a randomized phase III study with an observation arm. For patients with high-grade FIGO stage I LMS who have undergone hysterectomy, no further therapy is compared with combination chemotherapy including gemcitabine,

docetaxel, and doxorubicin for 4 cycles, with GCSF support.

Gestational Trophoblastic Neoplasia

The gestational trophoblastic diseases are unique in the spectrum of human disorders. The fertilized ovum develops not into a fetus but, rather, an abnormal proliferation of trophoblastic cells. Occurring in about 1/1000 recognized gestations, this most commonly manifests in the more benign form, hydatidiform mole that can be successfully treated with uterine evacuation or hysterectomy. However, in 20% of these patients the more malignant form, gestational trophoblastic neoplasia (GTN) develops, as it can very rarely after other gestational events. Recognized histologically as invasive mole, gestational choriocarcinoma, or placental site trophoblastic tumor, GTN can spread locally and metastasize.⁷³ Prior to the development of chemotherapy, GTN was almost always fatal. Gestational choriocarcinoma was one of the first malignancies to be cured with chemotherapy. There subsequently was established, in this country and others, recognized regional Trophoblastic Disease Centers that had the expertise and resources to treat GTN with chemotherapy. Over the course of the following decade chemotherapy regimens were developed that were capable of achieving cure in the vast majority of cases. The therapeutic success of these centers contributed to the development of NCI designated cancer centers. The regimens developed by these centers became progressively more complex and resource intensive, limiting their utility in developing countries and other low resource settings where GTD and fatal GTN remain an unsolved problem.⁷⁴ The peculiarity and rarity of the GTDs created the phenomenon of a few anointed “experts” and unvalidated dogma and ritual. In addition, there was little collaboration and no small amount of competition between the centers with each claiming its regimens to be superior.

Into this fray entered the G.O.G. Its Uterine Corpus Committee has sought to develop simpler and, hopefully, less expensive treatment regimens and to confront dogma with evidence. One such dogma was that oral contraceptives were contraindicated after evacuation of a hydatidiform mole because they might stimulate trophoblastic tissue. There was no data to support this.⁷⁵ The G.O.G. performed a randomized trial (GOG0055) that showed that oral contraceptives were the preferred method after molar evacuation.⁷⁶

By the late 1970's, the prevailing chemotherapy regimens for non-metastatic GTN championed by the various trophoblastic disease centers included 5 day methotrexate IM or IV, methotrexate with folinic acid rescue, and 5 day dactinomycin. While effective, these regimens were inconvenient for patients and labor intensive for providers. The G.O.G. conducted two phase II trials, which showed that a single dose of dactinomycin every other week (GOG0069) or weekly IM methotrexate (GOG0079) had good compliance, comparable activity, and tolerable toxicity.⁷⁷⁻⁷⁹ A randomized phase III trial, GOG0174, of either 30 mg/M2 weekly in-

tramuscular methotrexate versus “pulsed” intravenous actinomycin-D, 1.25 mg/M2 every two weeks as primary management for low risk gestational trophoblastic neoplasia was reported. Both regimens were well tolerated. Only two patients experienced grade 4 toxicity, one hematologic the other neutropenia, and no patient experienced grade 5 toxicity. Among eligible patients, complete response was observed in 53% of those given methotrexate and 69% of those given dactinomycin (P=0.015). This study demonstrates that biweekly dactinomycin at 1.25 mg/m² is statistically superior to weekly parenteral methotrexate at 30 mg/m² as initial management for low-risk GTN.⁸⁰

Recent single institution reports have claimed that a second D&C when persistent trophoblastic neoplasia is diagnosed might obviate the need for chemotherapy in some patients. GOG 0242 “A Phase II Study to Determine the Response to Second Curettage as Initial Management for Persistent Low Risk, Non-Metastatic Gestational Trophoblastic Neoplasia”, is designed to test this observation and to determine which subset(s) of patients might be most likely to benefit from a second curettage rather than immediate chemotherapy. Going forward, the Committee on Cancers of the Uterine Corpus has tasked the Trophoblastic Subcommittee to collaborate with the international trophoblastic disease centers to develop a chemotherapy study to build on the results of GOG 0174. That study “GOG0275 A Phase III Randomized Trial of Pulse Actinomycin-D versus Multi-day Methotrexate for the Management of Low Risk Gestational Trophoblastic Neoplasia” has opened.

The GOG has also been involved in developing second line therapies for the 10-20% of patients with low-risk gestational trophoblastic neoplasia who develop resistance to primary therapy. GOG #0176 was a phase II trial that addressed the efficacy and toxicity of actinomycin-D, 1.24 mg/M2 IV every two weeks for patients who had failed primary therapy with methotrexate. Pulse actinomycin-D is an active regimen.⁸¹

The complexity of the regimens developed was especially seen in those used in high risk metastatic GTN and culminated in a letter salad of acronyms such as CHAMOMA and CHAMOCA utilizing several drugs that had no single agent activity. Consequently, the G.O.G. undertook a prospective randomized comparison of methotrexate, dactinomycin, and chlorambucil (MAC) versus methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine (CHAMOMA) in “poor prognosis” metastatic gestational trophoblastic disease (GOG0057) and showed that the more complicated regimen was also more toxic and not as effective.⁸²

Conclusion

For over thirty years the GOG has driven the progress in treating uterine corpus malignancies. Thus, the continued leadership of the G.O.G. is necessary for evidence-based progress to be made against these diseases.

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Developing New Approaches in the Treatment of Carcinoma of the Cervix



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Studies in Early Stage Cervical Cancer

Preinvasive Disease

Patients with cervical intraepithelial neoplasia (CIN) generally have been treated with local surgical ablation. The overall cure rates are high. GOG investigations in this area consist only of GOG 31 and GOG 32, both of which were active between 1978 and 1981. GOG 31 compared local excision to cryosurgery in patients with CIN-I and CIN-II, while GOG 32 compared surgical conization to cryosurgery in patients with CIN-III. Both studies were designed to evaluate morbidity and cost. Neither study could be successfully completed.

In retrospect, it appears that there were several reasons for the failure of these two studies:

1. *Access to patients:* Some GOG institutions that have adequate numbers of patient referrals with invasive disease, but see comparatively few patients with CIN. As such, these patients are managed successfully at the community level by general gynecologists.
2. *Patient willingness:* Some patients declined to be randomized between an outpatient and an inpatient procedure, as in GOG 32.
3. *Inability to obtain sufficient follow up:* Both populations were difficult to follow because of problems with follow up appointments and compliance. This is characteristic of patients with CIN. Individuals who are in the lower socio economic strata or have a transient lifestyle have the fewest resources available to them. The data from both studies have been published¹.

Stage IA/IB1 Disease

Stage I accounts for approximately 39% of all cervix cancer patients world-wide and perhaps 60% of previously-untreated patients in GOG institutions. There has been only one study conducted for patients with stage IA (early invasive) disease: a surgical pathological study that was active between 1971 and 1976 (GOG 5). Protocol 5 evaluated the characteristics of stage IA, or “microinvasive” cervical carcinoma. These results have contributed to the generally accepted working definition of “microinvasive” cervical cancer used in North America².

In patients with stage IB disease, the GOG conducted a large prospective surgical pathological study (GOG 49) between 1981 and 1984 in which patients underwent an exploratory laparotomy, bilateral pelvic and para aortic lymph—adenectomy, and if para aortic nodes were negative on frozen section—radical hysterectomy. There were 1,003 patients entered on this study. The data from this trial underwent intensive analysis to define risk groups that would form the basis for future phase III therapeutic trials. Pre operative clinical factors that were evaluated included:

- Cell Type
- Histologic Grade
- Patient Age
- Performance Status
- Maximum Clinical Tumor Diameter
- Gross Description of the Neoplasm
- Number of Quadrants Involved

Post operative pathologic factors analyzed included:

- Pelvic and Para-Aortic Node Status
- Capillary-Lymphatic

- Space Involvement
- Depth of Invasion
- Parametrial Extension
- Uterine Extension
- Positive Pelvic Washings
- Surgical Margin Status

The pathologic risk factors defined by the GOG in Protocol 49 were then used to determine the need for post-operative therapy. Even in the absence of nodal metastases, patients with large tumors, deep stromal invasion, or capillary-lymphatic space (CLS) involvement were shown to be at risk for tumor relapse and death^{3,4}. This analysis provided the database on which subsequent GOG studies of stage IB disease were based. The results of the study also notably contributed to the understanding of significant prognostic factors in early cervical carcinoma. Patients with stage IB disease who did not have large tumors, deep stromal invasion or capillary-lymphatic space invasion, are adequately treated with either radical operation or radiation, with excellent rates of control and almost always resulting in a cure. Thus, there is little opportunity to improve survival for these patients.

With the background of the database from GOG 49, the GOG identified subsets of Stage IB patients which might benefit from additional therapy. Based on the multivariate analysis of risk factor data from GOG 49, two protocols were developed to examine the role of multi-modal therapy in patients with Stage IB disease and unfavorable prognostic features. A randomized phase III study (GOG 92) examined the role of adjuvant pelvic radiation therapy in patients with Stage IB disease, who are found to have intermediate risk factors such as CLS involvement, deep invasion of the cervical stroma, and lesion size. Patients were randomized after radical hysterectomy and pelvic lymphadenectomy to receive either no adjuvant therapy versus pelvic radiation therapy. This trial was designed to answer a question that had been debated in gynecologic oncology for years. Open from March 1988 to August 1993, this trial determined that the addition of radiation improved local control and progression-free survival. However, there were increased adverse effects observed in the irradiated group⁵. An update of the results of this clinical trial were published in 2006, confirming the longterm benefits of adjuvant radiation in the setting of “intermediate risk factors” following radical hysterectomy. Interestingly, this post-hoc analysis suggested that pelvic radiation appeared to be particularly beneficial for patients with adenocarcinoma or adenosquamous histologies⁶.

In 2010, the GOG, in collaboration with Korean GOG, activated GOG 263 (ClinicalTrials.gov Identifier:NCT01101451). This randomized phase III trial is set to enroll 480 subjects, and investigates the role of adding weekly IV cisplatin to these “GOG 92-like” patients with post-operative “intermediate risk factors.”

Post-operative pelvic radiation therapy has become standard ther-

apy for patients with occult parametrial extension. Though much has been written on this subject, these patients are uncommon and represent a varied population. GOG 109 was performed as an intergroup study with the Southwest Oncology Group (SWOG). Opened to patient entry in October 1990, this phase III trial evaluated post-operative pelvic radiation therapy following radical hysterectomy with versus without cisplatin and infusion 5-FU to determine if concurrent chemotherapy improved local control and survival⁷. This study was reported after the three studies in locally-advanced disease (see below) and the ensuing NCI Clinical Alert confirmed that the benefits of chemoradiation extended to these patients as well. This study has also been updated. A post-hoc hypothesis generating analysis suggested that the prognostic significance of histological type, tumor size, number of positive nodes, and parametrial extension in the radiation alone group was less apparent when chemotherapy was added. The absolute improvement in 5-year survival for adjuvant chemotherapy and radiation in patients with tumors < or =2 cm was only 5% (77% versus 82%), while for those with tumors >2 cm it was 19% (58% versus 77%). Similarly, the absolute 5-year survival benefit was less evident among patients with one nodal metastasis (79% versus 83%) than when at least two nodes were positive (55% versus 75%)⁸.

Moving forward, as the benefits of chemotherapy in treating cervical cancer become more apparent, additional cycles of adjuvant chemotherapy are being investigated (also see GOG 274 below). GOG 0724 (ClinicalTrials.gov Identifier:NCT00980954) is collaboration between the GOG and the RTOG. This study opened in 2009 seeking to enroll 400 subjects. Patients with “high risk factors” similar to those treated on GOG 109 are randomized to either standard external beam radiation or intensity modulated radiation therapy to the pelvis once daily 5 days a week for 5-6 weeks with concurrent IV cisplatin weekly for 6 weeks versus the same regimen along with additional 4 cycles of IV paclitaxel and carboplatin every 21 days. The results of this as well as GOG 263 are eagerly awaited.

Stage IB2 Disease

Patients with bulky stage IB disease (> 4 cm), or barrel shaped tumors, are considered by some to be poor candidates for primary radical hysterectomy. GOG 71 was a randomized phase III trial which compared radiation therapy with and without adjuvant extrafascial hysterectomy. This trial was based on published data suggesting that adjuvant surgery in this patient group was beneficial. Opened in late 1984, this trial accrued patients very slowly at first. The study subsequently accrued patients well and reached its accrual goal in 1991. The combination of radiation followed by operation had an advantage over radiation alone with respect to local (central pelvic) tumor control. With longer term follow-up, however, there was no survival advantage observed for the group who underwent hysterectomy after radiation therapy⁹. This protocol represents one of the few studies comparing single modality to combined modality therapy in this patient population.

When the GOG was ready to proceed to the next trial, only the data on local control were mature; thus, the GOG retained adjuvant hysterectomy in the next study in this population. GOG 123 opened in February 1992. This phase III trial compared pelvic radiation therapy followed by extra-fascial hysterectomy with and without weekly cisplatin to determine if cisplatin improved local control or survival¹⁰. This report accompanied two other trials in prompting an NCI Clinical Alert and changing the standard of care in this patient population.

A pilot study (GOG 89-03) evaluated an accelerated course of neoadjuvant cisplatin and vincristine prior to radical hysterectomy in therapy-naïve patients with suboptimal stage IB2 cervical carcinoma to determine the response rate of this regimen. There were 35 patients accrued. The response rate was high (~85%) and this regimen was incorporated as the study regimen of GOG 141. GOG 141 opened to patient entry in August 1993. This phase III trial compared radical hysterectomy alone to the same operation following an accelerated course of cisplatin and vincristine, and failed to show any additional objective benefit to the added neoadjuvant chemotherapy. Survival and operability were not improved and the use of postoperative adjuvant radiation was not decreased¹¹.

Pretreatment Surgical Staging

The GOG undertook a careful prospective evaluation of surgical staging for locally-advanced cervical cancer (GOG 19). Between November 1973 and June 1976, there were 290 evaluable patients who underwent surgical staging (para-aortic lymphadenectomy). It was confirmed that clinical staging underestimated the true extent of disease in a large number of patients (Table 1).

There were, however, added surgical adverse effects as well as the additional complications of radiation after operative manipulation¹². Following up on this demonstrated inaccuracy of clinical staging, the GOG conducted a prospective evaluation of imaging of the para-aortic nodes. From October 1982 to February 1988, 264 eligible and evaluable patients with stages IIB-IVA disease underwent CT scan, ultrasound and lymphangiogram, followed by surgical staging. There were 64 patients (24%) with confirmed positive PA nodes. Both CT and ultrasound had a very high negative predictive value, but low sensitivity. Lymphangiogram had the highest sensitivity (79%)¹³. In addition, a non-randomized comparison (GOG 24) of extraperitoneal and transperitoneal sur-

Table 1.

Clinical Stage	# Patients	% Upstaged	% with + PA nodes
IB	143	24%	6%
II	80	52%	29%
III	63	45%	30%
IV	4	50%	33%

gical staging procedures showed similar accuracy and similar intraoperative complications. However, the extraperitoneal approach was associated with a lower frequency of postirradiation regional enteric complications, and has since been the preferred method of surgical staging¹⁴.

Interestingly, with recent advances in body imaging, including widespread use of positron emission tomography with fluorine-18 fluorodeoxyglucose (FDG-PET/CT), surgical staging has been largely abandoned in routine clinical practice¹⁵. However, a recent retrospective GOG analysis of GOG 85, GOG 120 and GOG 165 showed an improved four-year survival rate (54.3% vs 40%) among patients with locally-advanced cervical cancer treated with chemotherapy and radiation after surgical evaluation of the para-aortic lymph nodes¹⁶, compared to negative imaging (mostly CT) alone. In collaboration with ACIN, GOG 233 is a prospective evaluation of preoperative FDG-PET/CT scanning prior to primary chemoradiation therapy to detect retroperitoneal lymph node metastasis in participants with locoregionally advanced carcinoma of the cervix (ClinicalTrials.gov Identifier:NCT00416455).

Studies in Advanced Cervical Cancer

GOG research in cervical cancer is broad based and constantly evolving over time. It encompasses a spectrum of clinical studies, from phase I to phase III, on the treatment of advanced disease; subset analyses of the large phase III randomized trials have generated hypotheses to be tested in subsequent trials. Ongoing translational research accompanying the randomized phase III studies leads to exploration of new strategies in future randomized trials. Completed studies also have delineated tumor and treatment-related prognostic and predictive factors for outcomes in relation to specific therapeutic interventions. The GOG research in advanced cervical cancer has contributed significantly to broad and international acceptance of concurrent chemotherapy and radiation as the standard of care in advanced disease.

Approaches to Locally-Advanced Cervical Cancer:

Earlier GOG Investigations

In 1979, the GOG was pioneering in its exploration and reporting of various treatment strategies which combined treatment concurrent with radiation. The first evidence of benefit to this strategy resulted from a phase III study (GOG 4) in which the role of concurrent hydroxyurea versus placebo with pelvic radiation was examined in the treatment of stage IIIB and IV cervical cancer¹⁷. Studies in this early era of group-wide research were not necessarily statistically powered and designed as they are currently. However, this study demonstrated that although the use of hydroxyurea was accompanied by increased toxicity over radiation alone, it led to apparent improvements in progression-free and overall survival. Concurrent hydroxyurea became a standard in the GOG to which other concurrent chemotherapy would be compared in future trials. Another innovative study (GOG 24), reported in 1986, examined the role of a nonspecific immune stimulant,

Corynebacterium parvum, as concurrent and adjuvant therapy to standard pelvic irradiation. Improved outcomes in advanced cervical cancer were not achieved¹⁸.

Subsequent studies of the GOG became more rigorous in their design, were more carefully conducted, and statistical methods for analysis became more sophisticated. Pursuant to ongoing studies of concurrent therapies with radiation, the GOG performed the first study of a “targeted therapy.” Concurrent hydroxyurea was compared to the use of concurrent misonidazole, a hypoxic cell radiosensitizer. Given the fact that hypoxic cells are known to be present in a majority of cervix cancers and their presence causes relative radiation resistance, this was a rational targeting strategy to explore. The results of this trial (GOG 56) demonstrated that misonidazole in tolerable doses did not improve outcomes over those using concurrent hydroxyurea and radiation¹⁹.

Ancillary data analyses of the large phase III trials have contributed significantly to our understanding of advanced cervical cancer. A multivariate analysis of prognostic variables in the three previous trials (GOG 24/56/59) of concurrent therapies with radiation demonstrated that patient age, performance status, para-aortic lymph node status, tumor size and pelvic node status were all significantly associated with progression-free survival; in addition to the FIGO stage, bilateral parametrial extension or sidewall disease were also significant factors²⁰. Such analyses allow stratification of patients into groups with varying risks, thus contributing to future trial design, conduct and analyses.

Chemoradiation Therapy: 1999 NCI Clinical Alert

In pursuit of identification of more effective concurrent therapy regimens, the GOG has sequentially examined a number of agents in differing regimens (Table 2).

These agents were selected because *in vitro* and *in vivo* trials demonstrated a positive interaction when they were used in con-

junction with radiation. These trials were conducted in the adjuvant therapy setting in earlier disease (GOG 109)⁷, as definitive treatment in stage IB2 cervical cancer (GOG 123)¹⁰, and in surgically staged patients with negative para-aortic nodes stage IIB-IVA (GOG 85 and GOG 120)^{21,22}. These studies in conjunction with an intergroup study with the RTOG²³ showed such an important, positive impact on progression-free survival, overall survival, and local control for patients with advanced cervical cancer that the results stimulated a rare NCI Clinical Alert suggesting that all patients receiving radiation for cervical cancer should be considered for receiving cisplatin-based chemotherapy concurrently with their radiation treatment²⁴. These studies demonstrated absolute improvements in survival of 8-18%, and a very consistent risk reduction in death due to disease of approximately 40%. The first randomized trial (GOG 85) in advanced disease compared a combination of cisplatin and 5FU every 21 days versus hydroxyurea, and demonstrated better progression-free and overall survival for the 5FU/cisplatin arm²¹. Following a phase I study (GOG 113) to define the tolerability of the 3-drug combination of hydroxyurea, 5FU and cisplatin²⁵, a subsequent three-arm randomized trial compared the results of the “standard” of hydroxyurea and radiation to the three-drug combination concurrent with radiation, and to a more simple regimen of weekly cisplatin 40 mg/m² (total maximum dose of 70mg) and radiation as used in the positive trial (GOG 123) in stage IB2 cervical cancer¹⁰. This important and definitive three-arm study (GOG 120) demonstrated an improvement in progression-free and overall survival for the three-drug combination and the single-agent weekly cisplatin compared to hydroxyurea²². Because there was significant grade III and IV toxicity associated with the three-drug combination, the conclusion was drawn that weekly cisplatin offered the best therapeutic ratio for a concurrent chemoradiation scheme. Weekly concurrent cisplatin at 40 mg/m² (total maximum dose of 70mg) with radiation appears to be the regimen of choice and is now accepted internationally. The weekly cisplatin regimen, however, has never been directly compared to combinations of 5FU and platinum. However, the

GOG conducted another randomized trial comparing a protracted venous infusion of 5FU versus the weekly cisplatin regimen (GOG 165). This study was prematurely closed at a planned interim analysis because there was a statistical demonstration that the 5FU would never yield improved results over those of weekly cisplatin alone²⁶.

In pursuit of more effective concurrent regimens with radiation in the management of advanced disease and in pursuit of more specifically targeted therapies, the current study of the GOG in stage

Table 2. Randomized GOG Studies in Locally Advanced Cervical Cancer.

1971

- Protocol 004 (1971-1976) - RT + Placebo vs. RT + H
- Protocol 024 (1977-1981) - RT vs. RT + C. Parvum
- Protocol 056 (1981-1985) - RT + H vs. RT + Misonidazole
- Protocol 085 (1986-1990) - RT + H vs. RT + CDDP + 5FU
- Protocol 120 (1992-1997) - RT + H vs. RT + CDDP vs. RT + 5FU + CDDP + H
- Protocol 165 (1997-2000) - RT + CDDP vs. RT + PVI 5FU
- Protocol 191 (2001-2003) - RT + CDDP vs. RT + CDDP + Hgb support
- Protocol 219 (2005-2009) - RT + CDDP vs. RT + CDDP + TPZ
- OUTBACK (0274) (2011-?) - RT + CDDP vs. RT + CDDP + 4 cycles of Carbo/Paclitaxel

2013

IB2-IVA disease compares the combination of tirapazamine, a specific hypoxic cell cytotoxin, plus cisplatin and radiation versus a standard weekly cisplatin and radiation alone. Although the design of this study acknowledges that tumor hypoxia remains a significant problem limiting local control and survival in cervical cancer since hypoxia causes both chemo and radiation resistance and stimulates angiogenic pathways and tumor growth, it did not show any improvement in PFS or OS (Paul A DiSilvestro-Personal Communication). This study is accompanied by related translational studies examining the angiogenic pathway and these results are eagerly anticipated.

The GOG has recognized as have others that a subset of patients with cervical cancer metastatic to para-aortic nodes may be cured with radiation alone. Attempts to improve cure rates in this group of patients resulted in an observational study (GOG 125) in which concurrent 5FU plus cisplatin chemotherapy was added to extended field radiation to encompass the pelvis and para-aortic nodes²⁷. This study demonstrated that a tolerable concurrent chemotherapy regimen could be given with extended field irradiation. The hypothesis generated is that some advantage may accrue to the addition of chemotherapy to radiation over radiation alone, although no study comparing these two regimens directly has been conducted in this patient group. During the evolution of the multiple phase III studies of the GOG in advanced cervical cancer, important modifications have been made over time in radiation treatment protocols of the GOG. The GOG accepted that a large body of observational data support that brachytherapy using high-dose rate (HDR) has a similar therapeutic ratio to low-dose rate brachytherapy (LDR), i.e., local control and treatment complications are comparable. The GOG now allows use of either HDR or LDR in its protocols for the treatment of advanced disease. This allows broader trial participation as LDR declines in usage. In addition, the importance of other radiation factors such as treatment time and tumor volume have been recognized by the GOG; strict limitations have been placed on acceptable overall treatment times for radical pelvic irradiation (eight weeks). Adequate pelvic radiation volumes aided by CT or MRI tumor delineation better encompass disease particularly posteriorly in the pelvis. Ancillary data analyses in the study of Lanciano et al (GOG 165) has clearly identified that cigarette smoking is an independent predictor for significantly worse outcome in patients being treated with locally advanced cervical cancer²⁸.

Currently, the GOG is participating in a worldwide study investigating the impact of additional cycles of chemotherapy following definitive cisplatin concurrent with pelvic radiation. Led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG), GOG 274, otherwise known as the OUTBACK trial, is a randomized phase III trial of cisplatin and radiation therapy together with or without carboplatin and paclitaxel among patients with locally advanced cervical cancer. This trial opened in 2012 and is scheduled to enroll 780 subjects (ClinicalTrials.gov Identifier:

NCT01414608).

In summary, 42 years of GOG multidisciplinary research in advanced cervical cancer has markedly influenced the worldwide management of patients and has resulted in significant improvement in patient survival²⁹ and improved our understanding of locally advanced cervical cancer.

Chemotherapy for Advanced, Recurrent, Metastatic Cervical Carcinoma

When cervical cancer cannot be treated with surgery and/or radiation therapy with curative intent, the prognosis is poor. However, major advances in systemic therapy have led to marked improvements in this setting. The need to identify an effective chemotherapy for these patients has been one of the primary goals of the Cervix Committee for three decades, and is yet another area where only the GOG has been able to advance clinical science. Only through the conduct of well-designed phase III studies may the merits of drugs or combinations be evaluated, compared, and discarded versus selected for further study and community adoption.

Platinum Compounds

Because of its recognized activity against other solid tumors, the GOG initiated a phase II study of cisplatin 50 mg/m² at an infusion rate of 1 mg/min every three weeks in patients with stage IVB or recurrent cervical cancer. Among the 22 patients who had not received prior chemotherapy, the response rate was 50% (3 CR, 8 PR). The response rate was 17% (0 CR, 2 PR) in the group of 12 patients who had received prior chemotherapy³⁰. Although later series with larger patient numbers reported lower response rates, generally in the 20-30% range, the activity of cisplatin was confirmed. To further explore the use of cisplatin in the treatment of cervical carcinoma the GOG conducted a study of cisplatin at three dose schedules to determine if improved results could be achieved through increased dose intensity. There were 581 women entered on this trial and 497 were considered evaluable. Although the objective response rate increased from 21% to 31% ($p = .015$) by increasing the cisplatin dose from 50 mg/m² to 100 mg/m² every three weeks, there was no associated improvement in the complete response rate, progression-free interval or overall survival; furthermore, higher cisplatin doses were associated with greater nephrotoxicity and myelosuppression³¹. In a subsequent GOG study, 380 patients were randomized to receive 50 mg/m² cisplatin given as a short (1 mg/min) versus 24-hour infusion. The overall response rate was essentially identical (18%) in each group. Although GI toxicity (nausea and emesis) was lower in the prolonged infusion group, the incidence of other adverse effects—nephrotoxicity, myelosuppression, neurotoxicity—did not differ³².

Recognizing the activity and associated toxicity profile of cisplatin, the GOG initiated a randomized phase II study of the platinum analogs carboplatin and iproplatin. Clinical experience indicated minimal nephrotoxicity or neurotoxicity, and both drugs

could be administered in an outpatient setting without prior hydration. The study was conducted from July 1984 through July 1987, and 394 patients were entered. The starting dose of carboplatin (400 mg/m²) was reduced to 340 mg/m² in patients who had received prior radiation therapy. Similarly, the starting dose of iproplatin (270 mg/m²) was reduced to 230 mg/m² doses in previously irradiated patients. Both treatments were repeated every 28 days. The objective response rates were 15% for carboplatin and 11% for iproplatin. Although the study was not designed to compare either analog to cisplatin, these response rates were lower than what had been reported for cisplatin. Furthermore, after treatment failure there were several patients who subsequently went on to receive cisplatin. For 22 of these patients, follow-up data were available, and the secondary response rate to cisplatin (18%) was higher than the primary response rate to either analog. The GOG concluded: “this finding seems to be further evidence that cisplatin must remain the drug of choice for advanced squamous cell cancer of the cervix”³³.

The Development of Cisplatin Combinations

Given the modest activity of cisplatin and consequent lack of a meaningful impact on survival, the GOG strove to identify other drugs that were either more effective than, or could be used in combination with cisplatin. These studies represented an effective collaboration between Developmental Therapeutics and the Cervix Committee. A number of agents were studied and proven inactive. However, the GOG conducted a phase II study of mitolactol (dibromodulcitol or DBD) and reported a 29% response rate³⁴. Other phase II studies—conducted both by GOG and other groups—identified ifosfamide as an active agent with response rates ranging from 16–40%^{35–37}. After subsequent phase I studies determined the feasibility of administering these agents in combination with cisplatin, the GOG conducted a phase III trial (GOG 110) of cisplatin versus cisplatin plus DBD versus cisplatin plus ifosfamide (Table 3). Compared to cisplatin alone, cisplatin plus ifosfamide had a significantly higher response rate (33% versus 19%)

Table 3. Platinum-Based Phase III GOG Studies in Recurrent and Metastatic Cervical Cancer.

Study	Agent	RR	OS
43 (1987) (n=497) ¹	CDDP 50 mg/m ²	21%	7.1 mos
	CDDP 100 mg/m ²	31%	
	CDDP 20 mg/m ² × 5d	25%	
64 (1989) (n=331) ²	Rapid CDDP	18%	6.2 mos
	24 hr CDDP	18%	
77 (1989) (n=394) ³	Carboplatin	15%	6.2 mos
	Iproplatin	11%	

¹ Bonomi, P. et al; *J Clin Oncol*, 1985, 3: 1079-85.

² Thigpen, JT et al; *Gynecol Oncol*, 1989; 32: 198-202.

³ McGuire III, WP et al; *J Clin Oncol*, 1989; 7: 1462-8.

and progression-free interval (4.6 versus 3.2 months) with no significant improvement in survival. Furthermore, adverse side effects were significantly higher in the ifosfamide-containing arm. Peripheral and central neurotoxicity were more frequent and more severe with cisplatin plus ifosfamide versus cisplatin alone. CNS toxicity ranged from confusion to somnolence to coma and/or seizures. There were two treatment-related deaths in patients receiving cisplatin plus ifosfamide: one patient had a cardiorespiratory arrest while comatose and the other developed renal failure and refused dialysis. The eligibility criteria for the study were modified to include only patients with serum albumin > 3.0 g/dL and serum creatinine within normal limits for the institution. Patients with bilateral hydronephrosis were made ineligible. There were no further cases of fatal CNS toxicity, but lesser degrees of encephalopathy were still observed in patients receiving cisplatin plus ifosfamide³⁸.

Several studies had suggested the addition of bleomycin to the combination of cisplatin plus ifosfamide yielded higher response rates and may also improve survival. The GOG initiated a phase III study comparing the combination of cisplatin plus ifosfamide with versus without bleomycin (Table 4). These regimens proved essentially identical in terms of objective response rates (approximately 32%), progression-free survival, and overall survival³⁹.

GOG Protocols 169 and 179

Discordant results from GOG protocol 110 (improved response rates and progression-free survival versus increased toxicity and no improvement in overall survival) combined with increasing expertise in the group to assess quality of life, prompted a fundamental change in the design of future prospective trials in patients with recurrent/metastatic cervical cancer. Patient-reported quality of life was deemed an essential study endpoint in this patient population with poor median survival. These ultimately successful endeavors were the result of an effective collaboration between the Cervix Committee and the expertise of the Quality of Life Committee.

The first randomized controlled study of palliative chemotherapy

Table 4. Platinum-Combination Phase III GOG Studies in Recurrent and Metastatic Cervical Cancer.

Study	Agent(s)	RR	OS
110 (1997) (n=454) ¹	CDDP	18%	8.0 mos
	CDDP/MTL	21%	7.3 mos
	CDDP/IFEX	31%	8.3 mos
149 (2002) (n=287) ²	CDDP/IFEX	32%	8.4 mos
	CDDP/IFEX/BLEO	31%	8.5 mos

¹ Omura, GA et al; *J Clin Oncol*, 1997; 15: 165-71.

² Bloss, JD et al; *J Clin Oncol*, 2002; 20: 1832-7.

in cervical cancer to prospectively obtain quality of life measurements, in addition to traditional clinical outcomes measures, was the phase III trial (GOG 169) of cisplatin plus paclitaxel versus cisplatin. The GOG had previously reported a 17% response rate for paclitaxel against advanced squamous cell carcinoma of the cervix⁴⁰. The combination of cisplatin and paclitaxel was subsequently evaluated in a phase II study. Among the 47 patients enrolled in the study, there were 41 evaluable for response (and 40 had received prior radiation therapy). The most frequent dose-limiting toxicity was neutropenia and two patients died from neutropenic sepsis. There were 19 patients who responded to treatment, including five complete responders, for an objective response rate of 46%⁴¹. There were 264 eligible patients randomized on GOG 169. Objective response rates were 19% (6% CR, 13% PR) for cisplatin versus 36% (15% CR, 21% PR) for cisplatin plus paclitaxel ($p = .002$). The median progression-free survival was also improved with the addition of paclitaxel but overall survival was not improved (8.7 months for cisplatin versus 9.7 months for cisplatin plus paclitaxel). Although toxicity, particularly myelosuppression, was more common in the group of patients receiving paclitaxel, this did not result in worsening quality of life⁴².

A GOG phase II study identified topotecan as a drug with significant activity against cervical carcinoma⁴³. In vitro studies showed that topotecan and cisplatin are synergistic⁴⁴. According to studies conducted by the North Central Cancer Treatment Group (NCCTG), the MVAC (methotrexate plus vinblastine plus doxorubicin plus cisplatin) regimen yielded a 66% response rate in 19 patients with advanced/recurrent cervical cancer with a median overall survival of 11.5 months. Three patients survived more than three years⁴⁵. Other investigators also reported objective tumor responses in more than half of patients with MVAC chemotherapy^{46,47}. The GOG initiated a phase III trial (GOG 179) comparing cisplatin versus cisplatin plus topotecan versus MVAC, again with quality of life included among the outcomes measures. The MVAC arm was closed by the Data Safety Monitoring Board following four treatment-related deaths among 63 patients. There were 293 eligible patients randomized to receive one of the cisplatin-containing regimens. Objective response rates were 13% (3% CR, 10% PR) for cisplatin versus 26% (10% CR, 16% PR) for cisplatin plus topotecan ($p = .004$). Progression-free survival was also better among patients receiving combination chemotherapy. Median survival for patients receiving cisplatin versus cisplatin plus topotecan was 6.5 months versus 9.4 months, respectively ($p = .014$). This was the first prospective trial—conducted by the GOG or any group—to identify a chemotherapy drug/regimen yielding a survival advantage for this patient population⁴⁸. Furthermore, despite increased toxicity, the cisplatin plus topotecan combination did not significantly reduce patient-reported quality of life⁴⁹.

Although GOG 179 resulted in a statistically-significant improvement in overall survival with the cisplatin plus topotecan combination, median survival in this study was not appreciably different than that for the two previous GOG phase III trials (Table 5).

Reasons for this may include an increasing use of concurrent chemotherapy for patients with locally-advanced cervical cancer undergoing primary radiation therapy. For example, there was an approximate two-fold increased use of concurrent chemotherapy among patients who received cisplatin plus topotecan on GOG 179 (58%) versus cisplatin plus paclitaxel on GOG 169 (31%) (Table 6).

Two recent phase II trials have identified vinorelbine as an active agent against cervical carcinoma^{50,51}. The GOG conducted a phase II study of cisplatin plus vinorelbine (GOG 76-Z) and reported a response rate of 30% and only mild toxicity⁵². Gemcitabine has been shown to have limited activity against cervical cancer⁵³; however, studies have demonstrated synergy between gemcitabine and cisplatin in vitro and in vivo⁵⁴ and the combination has been reported to result in response rates of 40 - 95% in small phase II trials in advanced cervix cancer patients⁵⁵⁻⁵⁸. As a follow-up to these studies, the GOG has initiated a randomized phase III study (GOG 204) of cisplatin plus one of four drugs: paclitaxel (PC), topotecan (TC), vinorelbine (VC), or gemcitabine (GC) in stage IVB, recurrent or persistent carcinoma of the cervix. A total of 513 patients were enrolled when a planned interim analysis recommended early closure for futility. The experimental-to-PC hazard ratios of death were 1.15 (95% CI, 0.79 to 1.67) for VC, 1.32 (95% CI, 0.91 to 1.92) for GC, and 1.26 (95% CI, 0.86 to 1.82) for TC. The hazard ratios (HRs) for progression-free survival (PFS) were 1.36 (95% CI, 0.97 to 1.90) for VC, 1.39 (95% CI, 0.99 to 1.96) for GC, and 1.27 (95% CI, 0.90 to 1.78) for TC. Response rates (RRs) for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection and alopecia. The trend in RR, PFS, and OS favored PC making this the global standard in this setting⁵⁹. Importantly, this was the first study where the median survival for these high-risk patients eclipsed one year. Finally, patient-reported quality of life was not different among the four

Table 5.

Protocol	Regimen	#Pts	OR	CR	PFS (mos)	OS (mos)
GOG 110	P	140	19%	6%	3.2	8.0
	P + IFX	151	31%	13%	4.6	8.3
GOG 169	P	134	19%	6%	3.0	8.9
	P + T	130	36%	15%	4.9	9.9
GOG 179	P	145	13%	3%	2.9	7.0
	P + Topo	148	26%	10%	4.6	9.2

Table 6.

GOG Protocol 169	Response Rate	Prior Cisplatin	Median Survival
CDDP	19%	30%	8.8 mos
CDDP/Paclitaxel	36%	24%	9.7 mos

GOG Protocol 179	Response Rate	Prior Cisplatin	Median Survival
CDDP	13%	56%	6.5 mos
CDDP/Topotecan	27%	58%	9.4 mos

treatment arms⁶⁰.

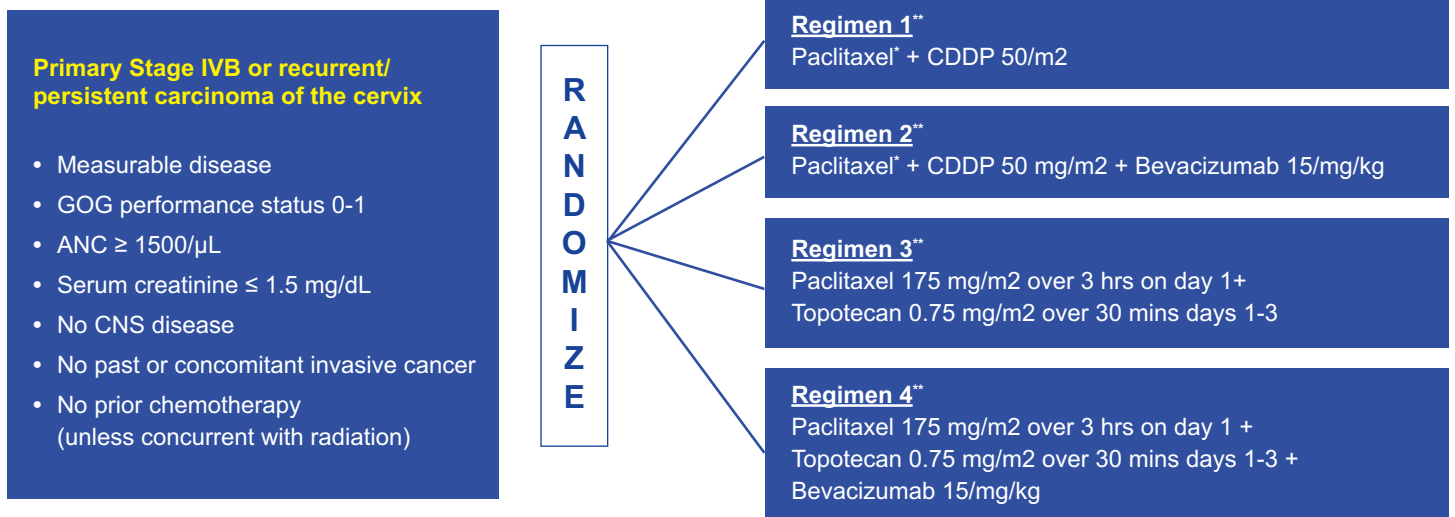
The first targeted agent to show activity in treating recurrent cervical cancer was bevacizumab, a humanized monoclonal antibody targeting vascular-endothelial growth factor (VEGF). GOG 227C studied single-agent bevacizumab at 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity among women with recurrent cervical cancer who had measurable disease, and a GOG performance status < or = 2. Eleven patients (23.9%; two-sided 90% CI, 14% to 37%) survived progression-

free for at least six months, and five patients (10.9%; two-sided 90% CI, 4% to 22%) had partial responses. The median response duration was 6.21 months (range, 2.83 to 8.28 months). The median PFS and overall survival times were 3.40 months (95% CI, 2.53 to 4.53 months) and 7.29 months (95% CI, 6.11 to 10.41 months), respectively⁶¹. This result was not surprising since an earlier translational companion study of GOG 109 showed the independent prognostic significance of tumor angiogenesis for both PFS and OS in high-risk, early-stage cervical cancer⁶². The inactivation of p53 by HPV E6 in these metastatic lesions appears to increase VEGF, angiogenesis and drive tumor progression making this a viable therapeutic target⁶³.

In 2009, the GOG launched protocol 240 to prospectively investigate the role of anti-angiogenesis therapy in treating metastatic and recurrent cervical cancer. In addition, the non-platinum doublet of paclitaxel plus topotecan was compared to the PC winner of GOG 240 since retreatment with cisplatin is less effective after primary concurrent radiation and chemotherapy (Table 7).

Although GOG 240 did not show an improvement associated with

Table 7. GOG 240

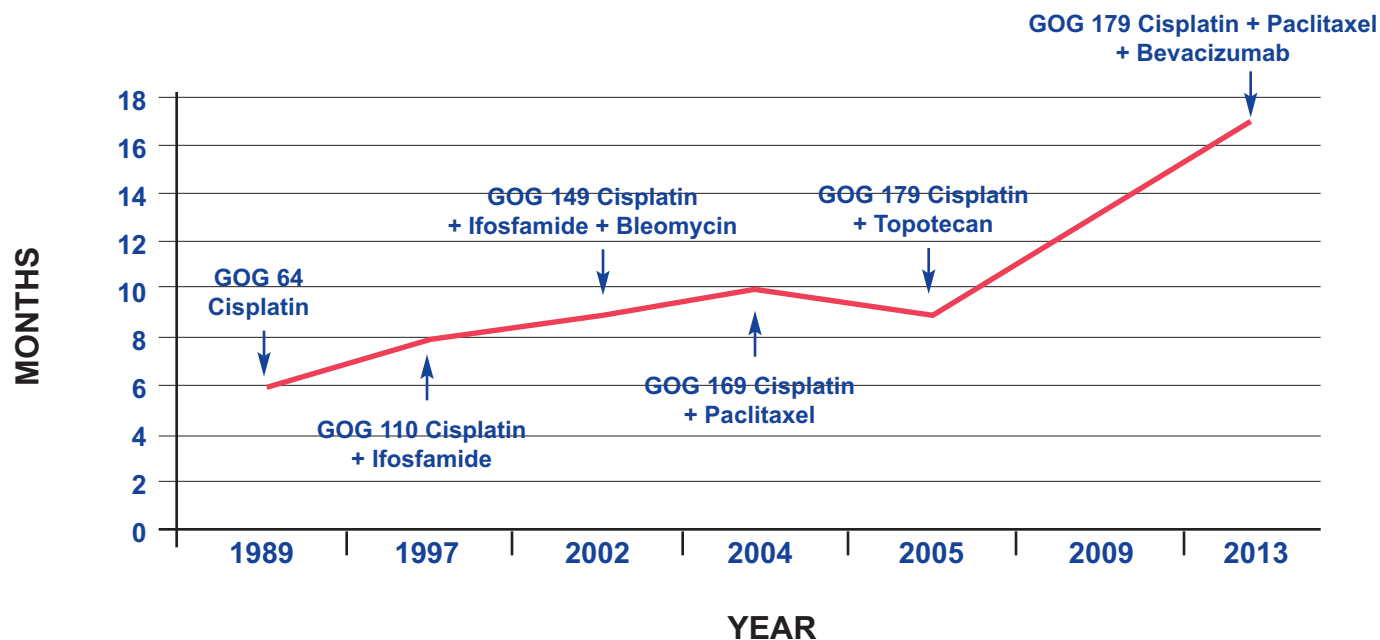


Open to enrollment April 6, 2009
 Closed to enrollment Jan 3, 2012
 Sample size = 452
 Study Chair: KS Tewari

All Regimens
Quality of Life Assessment

- Baseline
- Before cycle 2
- Before cycle 5
- 9 mos after study entry at follow-up visit

* 135 mg/m2 over 24 or 175 mg/m2 over 3 hours
 ** Cycles repeated q21 days to progression toxicity

Table 8. Progress in Survival in Advanced and Recurrent Cervical Cancer.

paclitaxel plus topotecan, it met its other primary endpoint of improving OS with the addition of bevacizumab. The bevacizumab-to-no-bevacizumab hazard ratio of death was 0.71 (97.6% CI 0.54-0.95; 1-sided $p=0.0035$). Median OS was 17 months (chemotherapy plus bevacizumab) and 13.3 months (chemotherapy alone). The RRs were 48% (chemotherapy plus bevacizumab) and 36% (chemotherapy alone) ($p=0.0078$). Treatment with bevacizumab was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%). This remarkable result again changed the global standard (Table 8).

Future Directions

With the well-documented success of radical surgery, radiation and systemic therapy, an increasing focus is being placed on survivorship as women with cervical cancer are being cured more often and living longer. Accordingly, the GOG Cervical Cancer Committee has launched its first survivorship clinical trial (ClinicalTrials.gov Identifier: NCT01649089). GOG 278 is a prospective evaluation of quality-of-life in patients undergoing surgery for cervical cancer to determine the intermediate-term and long-term effects of surgery. Moving forward, novel technologies to more effectively deliver radiation and other targeted systemic therapies will be studied.

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The Developmental Therapeutics Committee of the Gynecologic Oncology Group: Setting the Bar in Phase I and Phase II Studies



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Abstract

The Developmental Therapeutics Committee (DTC) is responsible for phase I and II evaluation of novel therapies in women with gynecologic cancers in collaboration with the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and the pharmaceutical industry. The Phase I Subcommittee (PIS) of DTC oversees safety-lead-ins for phase II studies and disease-oriented phase I trials in collaboration with GOG Site Committees, with an aim toward future randomized phase II and phase III trials. Biomarkers and translational research in phase I and II studies involves a team science approach with active collaboration with members of the Committee on Experimental Medicine (CEM), GOG Core Laboratory facilities, SPORE/PO1 sites, cancer centers and other funded laboratories. Throughout the protocol development process, the Committee also interacts with the Medical Oncology, Nursing, Data Management, and Radiation Oncology Committees. The DTC has a strong mentoring focus; often serving as the entry point for new investigators. Mentoring is accomplished both within and across institutions. Junior investigators are matched with experienced investigators/mentors (who function as study co-chairs and senior authors) to advise, counsel and guide through concept and protocol development, safety report reviews, study result evaluation, and ultimately manuscript preparation. The historical evolution of DTC and the key accomplishments that have contributed to clinical and translational science are reviewed.

Introduction

Due to the rarity of each individual type and disease state of gynecologic cancers, few individual centers have the patient resources to conduct independent phase II and randomized phase II trials of gynecologic cancers within a reasonable timeframe. Scientific, regulatory and administrative details require thoughtful prioritization of new concepts. The GOG provides

an effective multicenter infrastructure to rapidly prioritize and complete studies.

At this time, clinical trial paradigms are being driven by molecular targeted and immunomodulatory agents. Molecular profiling of tumor genotype, DNA methylation status, mRNA and protein expression patterns, and pharmacogenomics pathways of drug metabolism are being incorporated into clinical trials offering a more personalized approach to treatment for women with these malignancies. The Developmental Therapeutics Committee with its Phase I Subcommittee is tasked with incorporating new treatment paradigms in the phase I/II and randomized phase II setting prior to incorporation of these agents into phase III trials.

History

In 1975, early drug development was performed as pilot studies in the Disease Site Committees. In 1977, Dr. J. Tate Thigpen, the then co-Chair of the Protocol Committee, proposed that a pilot study be defined as a phase I or II study and reside under the jurisdiction of the Protocol Committee. Later that year, it was felt that these studies should be under the auspices of the Chemotherapy Committee chaired by Dr. George Omura. By 1978, the New Drug Liaison Committee, chaired by Dr. Milan Slavik, was formed based on a recommendation from Dr. William McGuire then at CTEP to GOG leadership indicating that GOG should be actively involved in the evaluation of new drugs through phase II trials.

The first phase II study (GOG Protocol 26) was actually a series of disease-specific sections on a master protocol evaluating the same drug (cisplatin) in multiple disease settings, with activity demonstrated in each of the three major tumor types (ovarian, cervical and endometrial). A representative of the New Drug Liaison Committee attended NCI Phase I meetings to identify drugs of po-

tential interest for evaluation within the GOG phase II framework. Dr. McGuire transitioned from NCI to a full member institution of GOG, and he joined the New Drug Liaison Committee as co-Chair in January 1982. Other agents and tumor types were added as GOG Protocol 26 became a master phase II template for the entire program. The New Drug Liaison Committee became the New Drug Committee in 1985, chaired by Dr. James Arseneau, as it began to evaluate agents in previously untreated patients. Protocols 76 (cervical cancer) and 86 (endometrial cancer), and 87 (uterine leiomyosarcomas) were created to provide an opportunity for a subset of institutions to explore new front-line treatments in phase II studies while the remaining sites participated in Group-wide phase III studies. In 1988, Dr. McGuire was charged with development of a Pilot Subcommittee (which changed its name to the Phase I Subcommittee with Phase I Working Group institutions in 1990) of the New Drug Committee with the intent of looking at potential drug combinations and concurrent chemoradiation.

The GOG leadership under Dr. Robert Park formed the Developmental Therapeutics Committee in 1996, to achieve the goals of working alongside both the pharmaceutical industry and the NCI, maximizing opportunities for evaluation of new drugs in gynecologic malignancies. Dr. McGuire was appointed Chair, with primary responsibility for phase I studies and Dr. Michael Bookman co-Chair, with primary responsibility for phase II studies.

In 1999, Dr. McGuire became co-Chair of the Ovarian Committee and Dr. Bookman transitioned to Chair of DTC. Dr. Gini Fleming was nominated to replace Dr. McGuire as co-Chair of the Phase I Subcommittee (PIS) and Dr. David Spriggs was subsequently added as a second co-Chair to facilitate integration of translational scientific objectives and provide oversight of the core pharmacokinetic laboratory. Under Dr. Bookman's leadership a system was put in place to evaluate cytotoxic chemotherapies and biologic and/or targeted therapies within distinct queues. The 227 (cervical cancer), 229 (endometrial cancer), 170 (ovarian cancer), 230 (carcinosarcoma) and 231 (leiomyosarcoma) were created to evaluate biologic and/or targeted therapies. A protocol shell was created and maintained for each treatment category/queue. The consistency in eligibility and primary endpoint analysis across studies within a queue allowed for development of an extensive historical controls data base.

In view of the increased number and complexity of phase I and II studies, a proposal was made to designate Section Leaders for each of the major disease sites to work in collaboration with the relevant GOG site Committees. During 2002, Section Leaders were appointed for ovarian cancer (Dr. Robert Burger), cervical cancer (Dr. Peter Rose), endometrial cancer (Dr. R. Scott McMeekin) and gynecologic sarcomas (Dr. Gregory Sutton), drawing on experienced GOG members and past study chairs with an active interest in these sites. In conjunction with this organizational change, Dr. Spriggs stepped down as co-chair.

In 2004, Fleming was recruited to serve as co-Chair for the Ovarian Committee, and in 2005, Dr. Paula Fracasso was nominated to serve as co-Chair of DTC and Chair of the Phase I Subcommittee (PIS). In 2006, Dr. Bookman stepped down as Chair of DTC and Dr. Carol Aghajanian was nominated for this position. At present, Dr. Aghajanian remains active as Chair of DTC and Dr. Fracasso is Chair of the Phase I Subcommittee with Drs. Robert Burger and Charles Kunos as Co-Chair of DTC and PIS, respectively. In addition, Drs. Don Dizon, D. Scott McMeekin, Robert Coleman, and Martee Hensley are the DTC Section Leaders of cervical cancer, endometrial cancer, ovary cancer and gynecologic sarcoma sections, respectively. Dr. Aghajanian represents the GOG at the CTEP Early Drug Development Meetings and as a member of the Investigation Drug Steering Committee (IDSC) of the National Cancer Institute.

Accomplishments

A summary of treatment categories (queues or series) are included in Table 1.

Cervix Cancer

Chemoradiation in cervical cancer (Phase I). With the demonstration that concurrent platinum-based chemoradiation can improve survival in patients with locally advanced cervical cancer, there has been increased interest in developing new treatment regimens. This poses some unique challenges, such as the monitoring of acute and chronic toxicities, which exceeds the usual scope of phase I trials. In addition, there is no validated phase II paradigm (endpoint) for demonstration of efficacy. As such, historically, a promising regimen would need to move from phase I directly to phase III. As such, safety and feasibility are key considerations. The Phase I Subcommittee has focused on combinations of radiation with cisplatin and paclitaxel (9803 and 9804), cisplatin and gemcitabine (9912), cisplatin and topotecan (9913), and cisplatin with cetuximab (9918), reflecting emerging experience in the management of advanced cervical cancer. More recently, the Phase I Subcommittee has become interested in treatment following standard chemoradiation in women with locally advanced disease with a high risk of recurrence. In two on-going trials, GOG9926 and 9929, patients are treated with cisplatin and chemoradiation followed by cytotoxic agents ("outback chemotherapy" with paclitaxel and carboplatin in node positive disease) and an immunomodulatory agent, ipilimumab, respectively.

Incorporation of cytotoxic therapy including paclitaxel, topotecan, and other agents; practice changing advances for advanced, recurrent or persistent cervical cancer (76 and 127 series). In GOG-76S, paclitaxel was found to have activity in squamous cancer of the cervix with a response rate of 17%. This was followed by GOG-76X, a phase II evaluation of paclitaxel and cisplatin in combination, which had a response rate of 46% among patients without prior chemotherapy for advanced or metastatic disease. A phase III trial (GOG-169) then compared cisplatin with or without pa-

clitaxel, showing cisplatin plus paclitaxel was superior to cisplatin alone with respect to response rate and progression-free survival with sustained quality of life.

Topotecan was established as an active agent in squamous cell carcinoma of the cervix, achieving an overall response rate of 19% in patients with no prior chemotherapy (GOG-76U) and 12.5% in patients with one prior therapy (GOG-127F). This was rapidly translated to a phase III trial (GOG-179) comparing cisplatin with and without topotecan. This was the first randomized phase III trial to demonstrate a survival advantage for combination chemotherapy over cisplatin alone in advanced cervical cancer. On June 14, 2006 the US Food and Drug Administration approved topotecan in combination with cisplatin for the treatment of stage IVB, recurrent or persistent cervical cancer based on the results of GOG-179.

In patients with one prior therapy, vinorelbine showed evidence of modest single agent activity with response rate of 14% in GOG-127-L. When vinorelbine was combined with cisplatin in patients with no prior therapy for advanced or recurrent disease in GOG-76Z a response rate of 30% was achieved. In patients with one prior therapy, the activity of single agent gemcitabine in GOG-127K was limited (8%), although when combined with cisplatin showed promise with a response rate of 22% (GOG127-Q).

These studies provided the basis for a four-arm phase III trial (GOG-204) comparing platinum doublets and showing that vinorelbine/cisplatin, gemcitabine/cisplatin, and topotecan/cisplatin were not superior to paclitaxel/cisplatin in terms of overall survival. The trend in response rate, progression free survival and overall survival favored paclitaxel/cisplatin. Thus, paclitaxel/cisplatin remains the standard chemotherapy backbone for this disease.

Incorporation of targeted therapy in cervical cancer (227 series). To date, bevacizumab is the only biologic/targeted therapy to show significant activity in cervical cancer. In GOG-227C, bevacizumab resulted in a response rate of 11% with 24% of patients progression-free at 6 months. These results contributed to the development of GOG-240, a phase III trial of chemotherapy with and without bevacizumab in stage IVB, recurrent or persistent cervical cancer that showed an overall survival advantage to the addition of bevacizumab. Paclitaxel/cisplatin plus bevacizumab is now defined as a standard care option.

Endometrial Cancer

Incorporation of paclitaxel in the treatment of endometrial cancer (86 and 129 series). Paclitaxel was shown to be the most active single agent therapy tested to date in advanced and recurrent/persistent endometrial cancer with a 36% response rate in chemotherapy naïve patients (GOG-86O) and a 27% response rate in patients having received one prior therapy (GOG-129C). This led to incor-

poration of paclitaxel into the initial therapy regimen for endometrial cancer, initially as part of a 3 drug regimen in GOG-177 (paclitaxel, doxorubicin, cisplatin or TAP) and then as a platinum-doublet in GOG-209 (paclitaxel/carboplatin). Paclitaxel/carboplatin is the standard initial chemotherapy for advanced, recurrent or persistent endometrial cancer.

Incorporation of targeted therapy in endometrial cancer (229 series). The GOG established the promise of anti-angiogenesis agents in endometrial cancer with GOG-229E, a phase II trial of bevacizumab in patients with advanced endometrial cancer and one to two prior lines of therapy. This trial showed a response rate of 14% with 40% of patients surviving progression free for 6 months or more. In collaboration with the Corpus Committee and CTEP, a three arm randomized phase II study of paclitaxel/carboplatin plus bevacizumab, paclitaxel/carboplatin plus temsirolimus and ixabepilone/carboplatin plus bevacizumab as initial therapy for measurable stage III or IVA, stage IVB, or recurrent endometrial cancer has been completed (GOG 86-P). This trial builds on work within the GOG evaluating anti-angiogenesis agents (229B – Thalidomide; 229E – bevacizumab; 229F – aflibercept; 229-G – bevacizumab/temsirolimus), taxanes (86O and 129C – paclitaxel; 129P – ixabepilone) and work by the GOG (248 - A Randomized Phase II Trial of Temsirolimus or the Combination of Hormonal Therapy Plus Temsirolimus in Women with Advanced, Persistent, or Recurrent Endometrial Carcinoma), CTEP investigators and others evaluating rapamycin analogues (mTOR inhibitors) in endometrial cancer.

Uterine Sarcomas

Evaluation of gemcitabine and docetaxel in uterine leiomyosarcoma (87 and 131 series). The first phase II trial of gemcitabine and docetaxel in uterine LMS was a single arm, single center experience. The GOG ran two GOG phase II trials of gemcitabine and docetaxel, one in first-line (87-L) and one in second-line therapy (131-G) confirming the activity of this regimen. A randomized phase II trial was then led by the Sarcoma Alliance for Research through Collaboration (SARC 002), to allow for inclusion of all patients with metastatic soft tissue sarcomas (not just uterine LMS), that confirmed the superiority of docetaxel/gemcitabine to single agent gemcitabine both in terms of PFS and OS, and effected a change in standard practice for this disease. The GOG has recently completed a phase III trial of gemcitabine and docetaxel with and without bevacizumab (GOG-250).

In addition, an adjuvant single arm phase II trial of chemotherapy for uterine LMS has completed through the SARC consortium (SARC 005), and due to promising results, has led to a recently launched a multi-national randomized phase III trial of adjuvant chemotherapy versus observation in uterine LMS through the International Rare Cancer Initiative (GOG-0277, A phase III randomized trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus limited, high grade uter-

Table 1. Phase I and II Study Queues

Tumor Type	Ph	GOG	Description	Primary Endpoint	Participants
<i>Cervix</i>	II	127	Recurrent or persistent, one prior therapy (in addition to prior cis-RT)	Response	Group-wide
	II	227	Targeted therapy, recurrent or persistent, 1-2 prior therapies (in addition to prior cis-RT)	Response and PFS6	Group-wide
	II	76	Front-line studies of new combinations, no prior therapy (prior concurrent cis-RT allowed)	Response	Limited access (Cervical cancer phase II working group)
	I	(n/a)	Front-line chemoradiation pilots	DLT-MTD Acute and Chronic	Limited access (Phase I working group)
<i>Endometrium</i>	II	86	Randomized phase II, front-line studies of new combinations, no prior chemotherapy	PFS	Group-wide
	II	129	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	229	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide
	I	(n/a)	Studies of new combinations	DLT-MTD Feasibility	Limited access (Phase I working group)
	I	(n/a)	Front-line chemoradiation pilots	DLT-MTD Acute and Chronic	Limited access (Phase I working group)
	<i>Ovarian, Fallopian Tube, Primary Peritoneal</i>	II	126	Platinum-resistant, recurrent or persistent, one prior therapy	Response
II		170	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide
II		186	Randomized phase II, recurrent or persistent, 1-3 prior therapies	PFS	Group-wide
I		(n/a)	Front-line studies of new combinations, no prior therapy	DLT-MTD Feasibility	Limited access (Phase I working group)
I		(n/a)	First platinum-sensitive recurrence, studies of new combinations, 1 prior therapy	DLT-MTD Feasibility	Limited access (Phase I working group)
I		(n/a)	Recurrent or persistent, multiple prior therapies	DLT-MTD	Limited access (Phase I working group)
<i>Uterine Leiomyosarcoma</i>		II	87	No prior therapy	Response
	II	131	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	231	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide

(Table continued on next page)

Table 1. (Continued)

Uterine Carcinosarcoma	II	232	No prior therapy	Response	Group-wide
	II	130	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	230	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide

PFS6 = Percent of patients progression free at 6 months

Notes:

- Published results for each study performed can be reviewed using the GOG Publication Search Engine, which is available through the GOG website at: <https://gogmember.gog.org/PublicationSearch>
- The GOG Phase I Procedures Manual can be reviewed on the GOG website at: <https://gogmember.gog.org/Manuals>

ine leiomyosarcoma, activated June 4, 2012).

Establishing the standard of care for treatment of carcinosarcomas (232 and 130 series). Paclitaxel was shown to have single agent activity (response rate of 18%) in recurrent carcinosarcoma patients who had received one prior therapy in GOG-130B. The combination of paclitaxel and carboplatin in chemotherapy naïve patients with advanced or recurrent carcinosarcoma had a high level of activity in GOG-232B (response rate of 54%). These studies led to the ongoing GOG-261, comparing paclitaxel and carboplatin to ifosfamide and paclitaxel in newly diagnosed patients with stage I-IV carcinosarcoma. GOG-261, when complete, will establish the standard initial therapy for this rare disease.

Ovarian Cancer

Initial therapy pilot studies. The usual initial therapy of ovarian cancer involves treatment with a taxane and a platinum agent. This therapy is either delivered in the form of paclitaxel and carboplatin, dose dense (weekly) paclitaxel and carboplatin or intraperitoneal therapy. Despite an NCI clinical announcement in 2006 (following the publication of GOG-172) declaring intraperitoneal therapy the preferred method of treatment for stage III, optimally debulked ovarian cancer; use of this treatment remained low. DTC prioritized the development of intraperitoneal (IP) regimens with the goal of reduced toxicity, while maintaining or increasing efficacy. The Phase I Subcommittee completed three phase I studies incorporating dose/schedule modifications, IP carboplatin (instead of IP cisplatin), docetaxel (instead of paclitaxel), and an assessment of the safety and feasibility of adding IV bevacizumab on Day 1. GOG-9916 evaluated three regimens, Part A (Day 1: IV paclitaxel and IP carboplatin, Day 8: IP paclitaxel), Part B (Day 1: IV docetaxel and IP carboplatin, Day 8: IP paclitaxel), and Part C (bevacizumab successfully added to Part A regimen). Part B cycle 1 MTD was not feasible over 4 cycles due to bone marrow toxicity.

GOG-9917 established chemotherapy doses (Day 1: IV paclitaxel 175 mg/m² and IP carboplatin AUC 5 +/- bevacizumab) of an every 3 week regimen. Of note, GOG9917 includes a successful collaboration with the Kawasaki Medical School in Kurashiki-City, Japan, a member of the Japanese GOG consortium. GOG-9921 successfully identified a modified GOG 0172 regimen of IV/IP paclitaxel and IP cisplatin (Day 1: IV paclitaxel 135 mg/m² over 3 hours and IP cisplatin 75 mg/m², Day 8: IP paclitaxel 60mg/m²) that allowed for 95% of patients to complete all 6 cycles of therapy. Only 42% of women on the IP arm of GOG-0172 completed the planned 6 cycles of therapy. 9916 and 9917 contributed to the IP carboplatin arm used for phase III testing by the Ovarian Committee (GOG0252) and the 9921 (modified 172 regimen) has become a standard therapy and control arm (GOG0252).

In preparation for the group's next phase III trial, the Phase I Subcommittee is currently enrolling GOG9923, a phase I study of chemotherapy and veliparib (PARP inhibitor) in patients with previously untreated ovarian, fallopian tube and primary peritoneal cancer. This study was awarded a CTEP Career Development LOI (CRDL) and an American Reinvestment and Recovery Act Award (ARRA). In addition, the DTC performed GOG-280, a phase II trial of veliparib in the proof of principle (BRCA germ line mutation) population, establishing activity.

Single arm phase II trials in platinum resistant ovarian cancer (126 series). The GOG has demonstrated the activity of retreatment with taxanes in platinum-taxane resistant ovarian cancer. In the GOG 126 series, patients with one prior therapy (initial taxane plus platinum-therapy) who progress within 6 months of their last platinum dose are entered. Docetaxel (126J), weekly paclitaxel (126N) and weekly albumin bound paclitaxel (126R) have all shown activity, with response rates of 21-23%. This consistent and reproducible activity of taxane retreatment has contributed to weekly paclitaxel being a common usual care option for patients

and serving as a chemotherapy backbone for development of novel combinations in randomized phase II and III trials. Pemetrexed also showed activity in the 126 series with a 21% response rate (126Q).

Randomized phase II trials in platinum resistant ovarian cancer. In collaboration with CTEP and the pharmaceutical industry, the GOG completed a phase I trial (GOG-9925) of VTX-2337 in combination with pegylated liposomal doxorubicin or weekly paclitaxel. One of the most basic mechanisms for activation of the immune system is through Toll-like receptors (TLRs). The combination of a specific TLR agonist with the capacity to activate dendritic cells and monocytes can be shown in pre-clinical models to provide synergy with chemotherapy and stimulate a variety of immune pathways relevant to generation of anti-tumor immunity. VTX-2337 is a novel small molecule TLR8 agonist. After establishing safety and recommended phase II dose in 9925, GOG-3003, a randomized phase II trial of pegylated liposomal doxorubicin with VTX-2337 versus placebo, has been launched. Randomized phase II trials (186 series). In 2002, the 186 series was initiated for patients with 1-3 prior lines of chemotherapy. The initial studies in this series were single arm studies that required measurable disease and had a traditional response rate endpoint. In 2010, the 186 series evolved from serial evaluation of single agents to randomized phase II trials. These randomized phase II trials allow for more effective evaluation of efficacy (as compared to relying on historical controls), the ability to evaluate novel combinations, and the ability to evaluate different doses and schedule. The endpoint for these studies is progression free survival (PFS). The first five of these randomized studies are on-going or recently completed and under followup and include studies with either a weekly paclitaxel backbone or bevacizumab backbone. These include weekly paclitaxel with and without Reolysin (186H), weekly paclitaxel with pazopanib versus placebo (186J), weekly paclitaxel versus cabozantinib (186K), bevacizumab with everolimus versus placebo (186G) and bevacizumab with and without fosbretabulin (186I). The 186 series randomized phase II trials will begin to report mature results in 2014.

Future trials in the 186 series may be either randomized phase II studies, or if appropriate, single arm phase II studies using the acquired historical data sets as benchmarks. The randomized phase II program allows evaluation of novel combinations and to draw in the accrual power of the entire GOG membership as many sites decline participation in smaller phase II studies due to the complexity of opening the studies with limited accrual.

Incorporation of targeted therapy and immunomodulatory agents in ovary cancer (170 series). The 170 series is a series of phase II trials of targeted and immunomodulatory agents in patients with recurrent ovarian cancer who have received one to two prior lines of therapy. Overall, this series of studies has been disappointing in terms of demonstrating activity. The only truly positive phase

II trial performed to date in this series is GOG-170D, a phase II trial of bevacizumab. This trial resulted in an impressive 21% response rate with 40% of patients surviving and progression free at 6 months. With this activity, a front-line Phase III trial (GOG0218) which evaluated chemotherapy with or without bevacizumab, as well as maintenance bevacizumab, was performed. This Phase III trial documented a significant improvement in progression-free survival with the addition of bevacizumab. Future studies in the 170 series will only proceed if new science dictates and a selection biomarker is available.

Future Plans

The Developmental Therapeutics Committee will continue to provide GOG (and soon to become NRG Oncology) with a diverse portfolio of cytotoxic, targeted, and immunomodulatory agents for Phase I and Phase II studies for women with gynecologic cancers in collaboration with NCI's CTEP and the pharmaceutical industry. These studies will evaluate new investigational agents and combinations of agents, novel scheduling and dosing of investigational and non-investigational agents, and novel concurrent chemotherapy and radiation therapy regimens, based on preclinical or early clinical data. The DTC disease-site section leaders will actively facilitate collaboration with Disease Site Committees, to ensure that appropriate agents are prioritized for development with an aim toward future randomized phase II and phase III trials. Integral biomarkers and translational research in these trials will continue to evolve and strengthen as scientific information becomes available.

In 2012, the Pharmaceutical Research and Manufacturers of America website reported that there were almost one thousand agents in clinical development for cancer. In addition, there has been an explosion of genomic data across many solid tumors demonstrating that these tumors are molecularly complex often containing more than one driver mutation. Taken together, it is critical to consider innovative trial designs. In concert with the members of the Committee on Experimental Medicine and the GOG biostatisticians, these designs often require tumor tissue, blood and plasma. Moreover, these designs will necessitate: 1) Randomized trial designs that allow for early introduction of combinations, a necessary shift from serial evaluation of single targeted agents, 2) Adaptive trial designs that allow for randomization of multiple treatment options based on pre-defined molecular biomarkers of the tumor with treatment changes based on emerging results from the trial, and 3) Novel trial designs that allow for diseases with similar histologic and/or molecular characteristics (i.e., serous ovarian cancer and serous endometrial cancer or HPV-positive squamous cell carcinomas of the cervix, vagina, and vulva) to receive the same treatment in a single trial.

These complex phase I-II studies require specialized staff, and the overall process has benefited from designation of key individuals in both the Administrative Office and the Statistical and Data Cen-

ter devoted to protocol development, translational objectives, and statistical endpoints. Furthermore, the unique web-based GOG Phase I infrastructure, which effectively monitors patients and manages the GOG Phase I trials in real-time, ensures the safety of all patients on Phase I trials and Phase II safety lead-ins and allows for the appropriate dose escalation. Furthermore, biweekly Phase I and Phase II safety-lead in conference calls involving Study Chair, Phase I Subcommittee Chair, SDC biostatistician, SDC Clinical Data Coordinator, and representation from all sites with patients accrued (investigator and/or research nurse); allows for in depth review of all data including safety information (AdEERS Reports) in real time. Thus, the current DTC is well-positioned to assist GOG (and soon to be NRG Oncology) in the development of innovative Phase I and II regimens for future randomized Phase II and Phase III studies in women with gynecologic cancers.

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Chapter 7 |

Translational Research in the GOG and the Committee on Experimental Medicine



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Translational Research: The Problems

Translational Research. The goals of translational research (TR) in the context of cancer clinical trials include (1) identifying individuals at risk, (2) preventing cancer development, (3) identifying early primary disease, (4) predicting which patients will likely respond to specific therapies and the durability of the response, (5) predicting recurrence prior to symptoms, and (6) determining why tumors become refractory to a given therapy. The challenges to successfully achieving these goals vary widely among the gynecological malignancies; however, there are several themes common to the different tumor types. These challenges are frequently related to the specific scientific/clinical question being addressed.

Identifying Gynecologic Cancer Risk. Perhaps the greatest strides in gynecologic cancer translational research have been made in the identification of patients at high risk for cancer development. Less than 20 years ago, the only indication of inherited gynecologic cancer risk was a family history of the disease. Currently, it is known that germline mutations in BRCA1 and BRCA2 and a series of genes in the fanconi DNA repair pathway, as well as the mismatch repair family of genes, account for the majority of inherited ovarian and endometrial cancer risk¹. Germline DNA can be screened for mutations in these genes and inherited risk ascertained. Despite this, several major challenges remain.

Outstanding Issues in Identifying Risk. To date, the gene(s) responsible for inherited risk in individuals with a strong family history of gynecologic cancer and no mutations in characterized genes remain(s) unidentified. Additionally, and perhaps more importantly, is the inability to determine the precise degree of risk in mutant gene carriers, as it varies widely in different families. Addressing these issues requires tracking very large numbers of

individuals at inherited risk of gynecologic cancer. Such an effort in the Gynecologic Oncology Group (GOG) is hampered by the fact that the required population is generally healthy women, who are not usually seen by gynecologic oncologists. Further, the collection of tissue specimens and clinical data is a time consuming and expensive challenge.

Prevention. In an ideal world, the best strategy to eliminate death from gynecologic cancer is to prevent its occurrence. The question is how to test potential prevention strategies. To truly test a drug's ability to decrease gynecologic cancer development requires a large number of women treated for a prolonged period of time. This number could be decreased somewhat if only high risk women were studied; however, even with this approach, the number required is large. For instance, large-scale phase III trials using HPV vaccines or potential chemoprevention agents are not practical in GOG. As an alternative, smaller phase II studies can be designed using surrogate endpoint biomarkers as an indication of a preventive effect. In such a setting, women can be treated with a preventive agent for a limited time prior to surgery. After such time, biopsies can be obtained and analyzed for modulation of the appropriate biomarkers.

Challenges to the Surrogate Endpoint Approach to Prevention. The validation of appropriate biomarker endpoints is critical to these trials and requires significant laboratory-based effort coupled with the careful collection of specimens. Since many of these patients are essentially "normal" (i.e., without cancer), the ethics involved in treating these patients - performing invasive procedures and perhaps delaying treatment - needs to be carefully considered. It is important to note, based on these assumptions, current and proposed surrogate endpoint biomarker studies are likely underpowered. Furthermore, it must be noted that these high-risk women

are healthy, making it difficult to identify and recruit them to such trials.

Early Detection. A major scientific/clinical goal is to identify cancer early during its development or recurrence. This is less of a problem for cervical and endometrial cancers than for ovarian because of the early symptoms and adequate screening for the former. Critical to the development of better screening assays for ovarian cancer is the development of new technologies and proper storage of clinically-relevant specimens.

Early Detection of Ovarian Cancer. One approach to improved ovarian cancer screening is to add additional biomarkers to CA125 in an attempt to improve sensitivity and specificity². Another approach, proteomic profiling is being validated after an initial promising study³. A third approach utilizes detection of abnormal DNA in serum or plasma as an indication of cancer⁴.

Procedural Problems Hindering Early Detection. There are a variety of practical problems with conducting these types of studies in a timely fashion. The obvious samples required are serial specimens from a population-based study where women are followed over time until disease occurred. The overall incidence of ovarian cancer is modest compared to breast cancer; thus, these studies would need to be quite large.

The good news is that such samples do exist, having been collected in a number of large population-based studies. The problem is that there is limited sample volume available and the laboratory testing methods (with the exception of proteomic profiling) require one half or more of the specimen. Hence, the groups controlling the samples from these population-based studies have been reluctant to release samples without some preliminary evidence of the detection strategy robustness. In lieu of collecting another set of samples in a population-based setting, investigators are faced with developing an alternative - for example, collecting samples from individuals undergoing surgery for a pelvic mass or a risk-reducing oophorectomies and age-matched, apparently healthy individuals. The goal is then to differentiate cancer from normal and benign disease in the pelvic mass cases and detect the rare cases of preclinical cancer in the prophylactic oophorectomy specimens.

Based on estimates of malignancy incidence in these settings, it is estimated at least 2000 samples will be needed. The issue here is whether validation in this setting will be at all predictive of a positive outcome in a population-based setting. There is also concern as to whether markers predictive of clinical disease will be the ones that detect preclinical disease and whether markers that detect sub-clinical cancer in individuals with genetic risk are the same as those needed to detect sub-clinical sporadic disease.

One possible exception is the use of abnormal serum DNA, since

an abnormality is hypothesized to be pathognomonic for cancer. This approach has additional appeal in that it is possible to calculate what the tumor burden must be for an abnormal DNA molecule to be detected in a background of normal serum DNA (assuming tumor and normal tissues shed DNA at equivalent rates). Currently the sensitivity of this technology allows detection of one abnormality in the background of 10,000 normal molecules. This should allow detection of a five gram tumor in a 50 kilogram individual. This is quite good sensitivity, but since all available data suggest tumors shed DNA more rapidly than normal tissues, sensitivity is likely greater.

The last major question relates to the natural history of ovarian cancer. That is, does early stage/curable disease exist sufficiently long enough that a highly sensitive and specific test performed on an annual basis will be effective at reducing mortality? This will be an important question to answer in the GOG in the coming years.

Prediction of Response. The ability to predict response to therapy requires the availability of predictive markers and suitable patient material. At this time, highly predictive markers have yet to be identified. The greatest progress is in the use of microarrays to interrogate tumors for gene expression patterns and gene copy number; the goal being to identify differences that track with treatment outcome and survival⁵. Progress in this effort is impeded by insufficient numbers of high quality tumor specimens with adequate follow up from women receiving similar treatment. Currently, the ideal specimens are frozen tumors collected at the time of primary surgery from patients entered on Phase III clinical trials. The problem is that most often tumor tissue is not frozen at the time of surgery because the surgeon is uncertain whether the patient will be entered on a phase III trial. Furthermore, primary surgery is often performed at non-GOG institutions and patients are later referred to GOG institutions for entry on protocols.

These issues are further complicated in recurrent disease and with experimental therapy. In the case of recurrent disease, there is most often no surgical specimen available at the time of recurrence. In the case of experimental therapy, especially with agents targeting specific components of signal transduction pathways, there rarely are specimens available pre- and post-treatment. Hence, one cannot know whether the pathway has been perturbed and, if so, whether it correlates with clinical outcome. Some of these impediments, especially in prediction of primary response, may be alleviated in the future based on technological advances and theoretical possibilities. For instance, progress is being made in the use of formalin-fixed, paraffin-embedded tissue for molecular analysis. Further, there is the theoretical possibility that serum/plasma proteome may predict response and that polymorphisms in the individual's germline DNA may be predictive.

Therapy Resistance. The mechanism(s) involved when tumors be-

come resistant to therapy is of both scientific and clinical interest. Obviously, if critical mechanisms for loss of sensitivity to drugs could be found, they would be prime drug target candidates. Much work has gone into trying to identify drug resistance mechanisms; however, most has been done in cancer cell lines and has not reliably translated to clinical material. The material needed for such studies would involve primary tumor specimens from individuals with a broad range of response to therapy. Work is proceeding in this area, but it is surprising how few specimens of this type are available. The more interesting question relates to acquired drug resistance. In this case, the patient might become apparently disease free for a period of time (e.g., 1.5 to 5 years), but ultimately recur. To ascertain resistance, mechanisms operating in such tumors require a primary tumor specimen matched to one obtained at recurrence. Since surgery is often not warranted for recurrent disease, there are few paired specimens of this type and even fewer from equivalently treated patients. How to design phase III clinical trials to address this need for specimen collection at primary surgery and at recurrence is a major ethical and economic challenge.

The GOG Solution:

The Committee on Experimental Medicine

Origins and Goals. To address the critical importance of translational research in clinical trials, the GOG established a separate committee to provide the expertise and direction needed to fully integrate this new effort into its clinical trials structure. The Committee on Experimental Medicine (CEM) is the successor of the Tumor Biology and Science Committee (TuBaSCo). TuBaSCo was charged with bringing basic and translational research to the GOG. In that context, TuBaSCo initiated several protocols, provided seed money for translational research grants, and convened a multidisciplinary translational research retreat in 1995. Based upon the recommendations of that retreat, CEM was established. In 1997, CEM became GOG's translational research committee and was chaired by William Beck, PhD, and co-chaired by Thomas Hamilton, PhD. The goals of CEM were (and remain today) to integrate strong laboratory-based, hypothesis-driven translational research into GOG clinical protocols. Thus, CEM's aims and responsibilities were designed to (1) generate novel translational research ideas, (2) provide scientific consultation to GOG membership, (3) approve scientific content in concepts and protocols, (4) fund seed grants using NIH-type review, (5) develop and oversee core labs, and (6) organize annual scientific meetings with experts from outside and within the GOG.

Composition. CEM is composed of individuals with varying scientific expertise and designed to cover all major areas of scientific endeavor (e.g., molecular biology, cell biology, pharmacology, radiation biology). Scientists are selected on the basis of being independently funded and having international reputations. Throughout the years, CEM has maintained a diverse membership, balancing scientists with clinicians whose expertise spans all as-

pects of gynecologic cancers, as well as representatives from the administrative and statistical offices.

Organization. In 2004, as part of GOG's evolving administrative structure, Michael Birrer, MD, PhD, was appointed CEM Chair, with Drs. William Beck and Thomas Hamilton serving as Co-Chairs. As previously discussed, GOG committee members are selected to bring expertise from all major areas of scientific endeavor. CEM committee members are also jointly appointed on other GOG committees including Developmental Therapeutics (DT), Rare Tumor (RT), Cancer Prevention and Control (CPC), and the disease site committees (ovary, corpus, cervix)

At this time, the oversight and use of the GOG Tissue Bank was also strengthened by changes in the administration and utilization of banked specimens. This included a close, integrated relationship between CEM and the Tissue Utilization Subcommittee (TUS). TUS was directly responsible for the creation and implementation of the bank's tissue acquisition and use rules. All members of TUS were also members of CEM; thus, there was a seamless integration between the two.

In 2011, TUS was transformed after much discussion regarding ways to improve the management of projects involving tissue requests. A monthly management call (described below) was implemented. Currently CEM, chaired by Dr. Birrer and co-chaired by Dr. Beck, works directly with the GOG Tissue Bank to prioritize and manage specimen distribution. CEM also provides feedback to the GOG Tissue Bank regarding standard operating procedures and quality control issues. Integral to this relationship is the translational research staff at the statistical center.

Concept and Protocol Review Procedures. Early on, CEM initiated new review procedures for protocols and concepts. Each proposal was assigned a primary and secondary reviewer as discussion leaders. This procedure, with brief introductory remarks by the Principle Investigator (PI), permitted the appropriate review of concepts and protocols, but proved to be cumbersome and time consuming.

Accordingly, at the summer 2002 meeting, CEM changed the process to streamline the procedure. The new format was to discuss all concepts and protocols in a closed door session on the first evening of the meetings. Reviewer assignments were made several weeks before the meeting and reviewers were asked to send their critiques to the CEM Chair prior to the closed door session. Where it could be done, concepts and protocols were approved or disapproved at the closed door session. The results were subsequently reported at the open session the following day, at which time PIs were allowed to respond to any specific questions that arose. The results (and any pertinent information from the reviews) were presented to the Protocol Development Committee and assigned prioritization.

This process ensured that all protocols and concepts were thoroughly reviewed at each semi-annual meeting and that all proposed translational research was scientifically sound. Further, this process afforded CEM an opportunity to integrate translational research endpoints and the appropriate tissue collections into GOG trials. As a result, there was a dramatic increase in translational research in phase III trials. This included all ovarian phase III trials (GOG 218, 212, 213, 262), endometrial trials (GOG 209, 210), cervical cancer trials (GOG 219, 239), and multiple phase II trials. This method proved efficient; however, at the summer 2013 meeting, changes were made to the CEM meeting structure to accommodate the increasing need for interaction between CEM and the Developmental Therapeutics (DT) committee.

In recent years, given the increasing focus on targeted molecular therapies and the pursuit of personalized medicine, it became evident that the roles and expertise of CEM and DT were of utmost importance to GOG clinical trials. Accordingly, the closed door CEM session was replaced with an open, joint CEM and DT meeting. This allowed CEM and DT to convene prior to the disease site committees and review and prioritize the science and drugs of interest that should be designated as high priority by the site committees. CEM protocol review subsequently took place the following day after the disease site committees met. This allowed CEM to review newly submitted concepts and protocols with some knowledge of the disease site committees' reviews and critiques of the proposals (an element that was missing from the previous review method).

Review of Banked Specimen Applications. To further streamline the development and implementation of translational research studies, a bank application was developed that allows investigators to apply for use of clinically-annotated and non-annotated banked specimens. This resource was formerly referred to as the GOG internal and external bank, respectively. The banked specimen application is easy to complete, yet provides sufficient information for reviewers to adequately assess scientific content. Applications for non-annotated specimens are reviewed directly by the GOG Tissue Bank, whereas all applications for clinically-annotated specimens are reviewed by CEM. CEM reviews these applications at semi-annual meetings and electronically in between meetings. Once approved, all applications for clinically-annotated specimens are developed into GOG protocols. These protocols are given the support of the GOG infrastructure and their progress tracked by the group. Investigators are expected to present the on goings of their research using GOG specimens at semi-annual meetings and publish the final results.

Monthly Management Calls. Throughout the years, CEM's efforts resulted in the integration of translational research into nearly all phase II and III protocols and several phase I protocols. This, coupled with standalone translational research protocols and banked specimen applications, resulted in a queue of approximately 100

protocols including translational research at any given time. To successfully execute the translational research in a GOG protocol requires close and constant interaction between CEM, the statistical center, the tissue bank, the administrative and finance offices, and the investigator. It became evident that given the workload, additional management meetings (outside of the semi-annual and interim meetings) would be necessary to maximize efficiency. In the summer of 2011, CEM began monthly conference calls to aid in the management of translational research projects. Calls include representatives from CEM, the statistical center, the tissue bank, and the administrative office. Each call provides an opportunity to discuss logistical and operational issues, as well as provide progress reports for all translational research studies.

Pilot Study Funding. A past goal of CEM was to fund pilot studies leading to national funding and/or publication. Although limited by the amount of funding available, the Group Chair's discretionary fund provided small amounts of money for scientific projects. As such, CEM proposed to fund scientific grants via a Request For Abstracts (RFA) mechanism. In 1997, three RFA grant recipients submitted final progress reports to GOG in 1999 and were able to obtain independent funding based upon their preliminary results. In 1999, with additional funding from the Group Chair, CEM initiated two additional RFA competitions (translational research and genomics) that were responsive to the National Cancer Institute "Director's Challenge" to develop genomic approaches to understand cancer. Two subcommittees of the CEM were empanelled to review the applications. There were nine translational research applications and six genomic applications. For the translational research applications, preference was given to those that best combined the efforts of basic and clinical scientists. In July 1999, CEM made two translational research awards of approximately \$50,000 each and one genomics award of \$86,000. All of these awards eventually led to publications and independent federal funding⁵⁻⁷.

In 2004, CEM reevaluated utilization of the RFA mechanism and concluded the best way to foster the scientific goals of GOG was to design and fund more translational research efforts. This meant directing all monies to those proposals which involve scientific hypotheses that were directly applicable to questions of clinical importance. Additionally, CEM decided to focus on supporting peer-reviewed funding and industry monies for GOG translational research initiatives.

This new effort has been successful in two regards. First, and most importantly, it has allowed GOG to continue to incorporate translational research into its clinical trials. CEM members have successfully competed for seven NIH-funded grants and have several pending. Included in these applications are several large programmatic applications including two endometrial Specialized Programs of Research Excellence (SPOREs). CEM members' success rate for grant applications has been approximately 25%. CEM has

also successfully engaged industry in supporting its translational research efforts. This has provided critical monies to test important translational research hypotheses. Secondly, this effort has provided an independent peer review evaluation of many scientific proposals. NIH study section review has been important as an external validation of the scientific value of these efforts. Further, industry supported projects are required to go through several levels of scientific review ensuring that the goals of the effort are important and scientifically sound.

Scientific Symposia. Another key element in CEM scientific efforts is the organization and hosting of annual scientific symposia. These symposia have been viewed as quite valuable from an education standpoint and have provided a basis for scientific direction within the group. Past scientific symposia topics include: ovarian carcinoma (1997), chemoprevention (1998), angiogenesis (January 1999), molecular biology of gynecologic malignancies (June 1999), cDNA arrays (2000), tumor vaccines (2001), proteomics (2002), new therapeutic agents (2003), drug resistance (July 2004), mouse models (January 2005), bevacizumab and angiogenic biomarkers (January 2006), pharmacogeomics (January 2007), hormone therapy (July 2007), reliable measurement of gene expression in formalin-fixed tissues (January 2008), novel methods of aCGH analysis (July 2008), Young Investigator presentations (January 2009), clinical application of genomic medicine (July 2009), cancer stem cell research and applications (January 2010), microRNA (January 2011), pathway identification (July 2011), new strategies to identify and screen women at risk for ovarian cancer (January 2012), and targeting genomic chaos in gynecologic cancer (July 2012).

Work in Progress Presentations. In recent years, CEM dedicated its final open session at the semi-annual meetings to “Work in Progress” presentations. These presentations allow investigators receiving GOG specimens to discuss the progress of their research with CEM. It affords the investigators an opportunity to receive feedback from the committee and discuss future directions.

Core Laboratories. Despite GOG efforts to develop protocols that improve treatment of women with gynecologic malignancies, there are many trials that do not improve the overall survival of these women. Of concern, the biologic and/or pharmacologic mechanism(s) responsible for the success or failure of chemotherapy is not understood. Phase I/II studies have toxicologic and therapeutic end points, but little laboratory support to help explain the biologic basis for the result. Early on, there was little translational research, especially laboratory correlates, in most GOG protocols. Thus, it was difficult to make sense of the clinical results of some protocols, as there was no information regarding the expression of the drug target. In most cases, it was not even known whether the drugs administered actually reached their targets in adequate amounts to be effective. In addition, very little pharmacokinetic data were available.

As a consequence, CEM proposed that GOG establish core laboratories to run various molecular and analytical assays in support of selected protocols. In 1997, CEM established the Molecular Pharmacology and the Clinical Pharmacology core laboratories and obtained permanent funding for them with the 1999 grant renewal. In January 2001, with approval from group leadership, CEM established an additional core laboratory, the Hormone Receptor core laboratory.

In 2005, the Molecular Pharmacology and Clinical Pharmacology core laboratories were merged into one Pharmacokinetic (PK) core laboratory and the Hormone Receptor core laboratory was renamed the Receptors and Targets core laboratory to more adequately describe its function.

The GOG Tissue Bank. The GOG Tissue Bank has been funded and managed as a direct subcontract with GOG since 1991. The bank is housed at the Biopathology Center, part of The Research Institute at Nationwide Children’s Hospital, in Columbus, OH. The GOG Tissue Bank is among the best gynecologic cancer tissue repositories in the world. Specimen acquisition currently occurs via GOG treatment protocols; thus, all incoming specimens are highly annotated. All GOG protocols with specimen collection and translational research include a protocol-specific specimen appendix detailing required specimens, standard operating procedures for collection and shipment, and instructions for optimal banking. Specimen collection and shipping kits are provided for most GOG protocols. In addition, training sessions occur at GOG semi-annual meetings and translational research and bank staffs are available on a daily basis to assist sites with specimen collection and translational research issues. The GOG translational research infrastructure has a track record of collecting nearly 800,000 high-quality, clinically-annotated and non-annotated specimen aliquots. On average, approximately 51,000 specimen aliquots are submitted to the GOG Tissue Bank each year; almost 18,000 specimen aliquots are distributed to investigators for testing.

In 2004, in response to the GOG progress review, state of the science meetings, and site visit recommendations, translational research objectives and tissue collection were instituted on all major GOG trials. This effort resulted in a greater than 40-fold increase in total clinical trial specimen type accrual over the next grant period. A large majority of these specimens (i.e., tissue, plasma, and serum) were collected for GOG 199, A Prospective Study of Risk-Reducing Salpingo-Oophorectomy and Longitudinal CA-125 Screening among Women at Increased Genetic Risk of Ovarian Cancer (described below). This trial provided a unique opportunity to prospectively collect clinically-annotated serial specimens from high risk women, establishing a valuable resource for future translational research.

Regardless of GOG 199, efforts beginning in 2004 to incorporate translational research and/or tissue acquisition in GOG trials have

resulted in a nearly 90-fold increase in total clinical trial specimen type accrual to date (from approximately 2000 to 178,000). Specifically, acquisition of formalin-fixed, paraffin-embedded tissue increased 85-fold (from approximately 400 to 34,000); plasma increased over 140-fold (from approximately 250 to nearly 35,000); serum increased 100-fold (from approximately 600 to almost 60,000 specimens); and the acquisition of other specimens including ascites, peritoneal wash, lymphocytes, cervical cells, buccal cells, and urine, increased approximately 23-fold (from just over 150 specimens to nearly 3,500).

In addition, recent GOG initiatives have called for the collection of whole blood for DNA isolation in all phase III trials. Since 2004, blood acquisition has increased 75-fold (from approximately 200 to nearly 15,000). This effort will in no doubt continue to build upon the GOG biorepository of clinically-annotated specimens available for translational research.

In 2012, the GOG Tissue Bank was the first biorepository to be accredited by the College of American Pathologists (CAP) Biorepository Accreditation Program. CAP accreditation is a peer-based program designed to drive the adoption of standards through consistent application of best practices and evidence-based standards. The accreditation process occurs in a three year cycle, with on-site inspections by qualified biorepository peer reviewers occurring at the beginning of each cycle. The goal of this accreditation is to continue to accomplish best practices for ensuring biospecimen handling to support clinical research, personalized medicine, and cures for genetic diseases. The CAP has been accrediting medical laboratories for more than 50 years and is well recognized as the gold standard in laboratory accreditation. The Biopathology Center, which includes the GOG Tissue Bank, was one of the first ten biorepositories in the United States to earn its certificate of accreditation. This institutional accreditation process benefits the GOG Tissue Bank, ensuring that it is managed in a manner that results in the procurement, storage, and distribution of quality specimens that can be used to support new emerging technologies, cutting-edge medical research and strengthen the quality of patient care.

The GOG Tissue Bank remains at the cutting edge of cooperative group banking and is the premier gynecologic cancer tissue repository in the world.

A Biorepository of Gynecologic Malignancies. GOG 136, the GOG's sole banking study, opened to enrollment in 1992 and collected fixed and frozen tissue and pre-operative serum from women with a diagnosis of ovarian cancer. Enrollment was opened to endometrial and cervical cancer patients in 1997. In 2009, the protocol was amended to extend enrollment to several important populations – rare tumors and women with recurrent disease. The specimen requirements were also updated to accommodate the era of genomics and each patient was required to submit a whole blood

specimen for DNA extraction. The protocol was given a major overhaul to conform to updated GOG translational research standard operating procedures and, as a result, enrollment increased to over 2,000 registrations per year. Unfortunately, in 2011, the Cancer Therapy Evaluation Program decided to cease funding for banking protocols. As such, GOG 136 closed to patient accrual at the end of 2011 with more than 14,000 registrations over nearly 20 years.

Specimens collected from women enrolled solely on GOG 136 (n~11,000) are associated with very limited clinical data. These non-annotated specimens (formerly referred to as “External Bank” specimens) are available to investigators after review and approval by the GOG Tissue Bank. In some cases, women have enrolled on both GOG 136 as well as another GOG treatment trial (n~3,000). Thus, there is clinical information available for these specimens. These GOG 136 cases, along with all other specimens collected on GOG treatment trials, are considered clinically-annotated specimens (formerly referred to as “Internal Bank” specimens) and are available to investigators after review and approval by CEM.

To date, the GOG biorepository of gynecologic malignancies remains the premier collection of this kind in the world. Undoubtedly, the continued collection of clinically-annotated specimens on GOG trials will continue to build this invaluable resource.

GOG 199. A large majority of banked specimens (tissue, plasma, and serum) have been collected for GOG 199, A Prospective Study of Risk-Reducing Salpingo-Oophorectomy and Longitudinal CA-125 Screening among Women at Increased Genetic Risk of Ovarian Cancer. This trial, opened in 2003 and closed to patient accrual in 2006, provided a unique opportunity to prospectively collect clinically-annotated serial specimens from high risk women and will undoubtedly prove a valuable resource for future translational research.

It has become clear that individual investigators cannot amass the number of well-characterized samples required to perform definitive studies in a methodologically sound fashion. The Consortium of Investigators of Modifiers of BRCA-Associated Cancer (CIMBA) was formed to permit pooling of such scarce materials by multiple investigators. The GOG 199 resource allows the GOG to play an important role in a number of CIMBA research studies.

GOG 210. GOG 210 is a molecular and surgico-pathological staging study of endometrial carcinoma. The overall goal of this protocol is to improve outcome and/or quality of life for patients with endometrial cancer. This fundamental goal will be accomplished through the development of more accurate risk models and identification of targets for therapeutic intervention and individualized treatments based on molecular characteristics identified in patient specimens. The specific objectives of this molecular staging study are to (1) establish a repository of clinical specimens with detailed

clinical and epidemiologic data from patients with surgically staged endometrial carcinoma, (2) utilize genomic, proteomic, and immunoassay results from specimens to predict and discover molecular characteristics of endometrial carcinoma and to validate those characteristics associated with recurrence risk, clinical and histological characteristics, and epidemiologic factors, (3) improve the accuracy and resolution of the risk assessment models for predicting endometrial cancer recurrence using informative genomic, proteomic, and immunoassay results in combination with clinical, pathologic, and epidemiologic factors, (4) use the genomic, proteomic, and immunoassay results, along with the clinical, histological and epidemiologic data obtained for this research study, to identify targets of endometrial cancer prevention and/or treatment, and (5) to expand the current understanding of the biology, progression, and responsiveness of endometrial carcinoma. To satisfy these objectives, tissue, serum, and urine were collected.

Over a dozen translational research projects have utilized GOG 210 specimens to date. There have been several abstracts and publications generated from these research studies. Additionally, several publications are in development or in press. CEM continues to review and evaluate translational research projects utilizing GOG 210 specimens.

The Cancer Genome Atlas (TCGA). Project The GOG was called upon to serve as one of the major sources for ovarian, endometrial, and cervical cancer specimens for TCGA. The GOG was selected as the main provider of ovarian cancer specimens for the initial pilot study. GOG was selected due to CEM involvement in the design of GOG clinical trials and the collection of high quality, clinically-annotated specimens. The CEM Chair, Dr. Michael Birrer, served as PI of the project and a member of the TCGA steering committee and ovarian cancer working group. Additionally, the GOG Tissue Bank served as one of the Biospecimen Core Resources.

GOG analyzed 315 ovarian specimens for inclusion in the study. Pathologic review consisted of histology (papillary serous), percent tumor (>70%), percent necrosis, and total sample size (200mg). Sectioning and pathology review was completed for all TCGA specimens; these efforts were led by gynecologic oncology pathologist, Nilsa Ramirez, MD, Director of the GOG Tissue Bank. GOG was the largest contributor of ovarian cancer specimens (n=85). In total, GOG submitted 85 ovarian, 119 endometrial, and 41 cervical cancer specimens to this effort.

All TCGA specimens will be analyzed for copy number differences (CGH), expression profiling (Affymetrix 133 plus 2), methylation analysis, and genomic sequencing. This project has the potential to identify genomic events that are critical for the development of ovarian cancer and/or potentially important therapeutic targets. The existing translational research infrastructure of the GOG, ideally positions the group to translate these re-

sults into clinical advances.

Bench to Bedside. CEM has made a major effort to utilize work from its member's laboratories to affect GOG clinical trial efforts. In ovarian cancer, Dr. Michael Birrer's laboratory has conducted large-scale genomics studies on a large number of tumor specimens collected via GOG initiatives. The data from Dr. Birrer's laboratory strongly suggest that ovarian tumors of different histologies have completely differently genomic make-ups and that tumors of similar histology, regardless of organ of origin, are very similar with respect to genomics⁸. These data were discussed with the GOG and provided a paradigm shift in the group's approach to ovarian cancer trials. All rare histology groups such as clear cell and mucinous tumors were removed from randomized phase III trials and are now the focus of histology-specific trials.

Further, work from Dr. Birrer's laboratory demonstrated that ovary tumors of varying grade have very different gene expression patterns⁹. Low-grade tumors have expression patterns that are very similar to borderline tumors suggesting that these are separate tumors and different from high-grade serous cancers. Based on these results, low-grade tumors were also removed from the phase III trials. Perhaps more importantly, these data identified rare tumors as a separate tumor group worthy of study and provided the rationale for a major change in the GOG committee structure and the creation of the Rare Tumor Committee, currently chaired by David Gershenson, MD.

GOG 239 examined the effects of a MEK inhibitor on low-grade serous tumors of the ovary. This trial was specifically based upon the finding that the MAP kinase pathway is activated in these tumors and all biomarker endpoints in this trial are genes, which were previously identified in Dr. Birrer's studies. GOG 239 also included a translational research objective designed to investigate the relationship between BRAF and KRAS mutations and tumor response in patients given selumetinib. The results of GOG 239 suggested that selumetinib is an active agent, but not necessarily because of BRAF or KRAS mutational activation. This finding is important given recent recommendations for clinical trial designs restricting patient enrollment based on mutation status. Unless there is compelling evidence to restrict patient enrollment, trial designs should allow for adequate hypothesis testing.

In endometrial cancer, several CEM members have played important roles in identifying genetic factors that contribute to endometrial cancer risk. As a result of these research efforts, there have been changes in the clinical genetic management of patients with endometrial cancer and their family members. Paul Goodfellow, PhD, and his group have demonstrated inherited (germline) mutations in MSH6 that are common among endometrial cancer patients. The validation of this finding by the Goodfellow laboratory has paved the way for a change in the clinical management of HNPCC patients. In addition, Dr. Goodfellow and colleagues

(Pamela Pollock, PhD, and Matthew Powell, MD) have recently taken a genomics discovery from laboratory to clinical trial. Drs. Goodfellow, Pollock, and Powell identified FGFR2 activating mutations in patients with inherited genetic disease (craniosynostosis and skeletal dysplasia syndromes). The translational research component of GOG 229I will examine whether activating mutations in FGFR2 are associated with survival, tumor response, or endometrioid histology in patients treated with brivanib.

The Future of the CEM: Challenges

The future direction of CEM will involve the full integration of translational research into all gynecologic cancer clinical trials. Integral to this process is the accomplishment of three separate goals - (1) identification of appropriate laboratories and accomplished investigators with the required expertise, (2) obtaining adequate funding to conduct these studies, and (3) identification and prioritization of scientific areas of extraordinary opportunity.

Outreach to the Gynecologic Oncology Community. To effectively conduct translational research, it is necessary to involve the entire gynecologic cancer research community. This is necessary to actively and effectively engage established gynecologic cancer research programs including program project, Specialized Program of Research Excellence (SPORE), and mouse modeling groups. These programs involve multiple peer-reviewed funded investigators organized into interactive projects centered on an important biologic and clinical question involving gynecologic cancers. Thus, these are ideal groups to integrate into GOG clinical trial structure to address important translational research questions. Moreover, it is critical to engage individual investigators with a proven track record of outstanding scientific investigation in gynecologic cancers. The composition of CEM will assist in these efforts by including members who participate on SPORE and program project grants and have fully funded laboratories conducting gynecologic cancer research. This will ensure a seamless integration of GOG projects with outside research efforts. Further, CEM will provide scientific forum where researchers (GOG and non-GOG) can present and exchange “cutting edge” scientific concepts and new technological developments. This will include scientific retreats, semi-annual meeting symposia, and Work in Progress (WIP) presentations at semi-annual CEM committee meetings. Finally, CEM will provide an efficient and fair review process by which outstanding translational research proposals utilizing GOG clinical trial specimens can be selected. This process, described above, involves a simplified bank application that provides sufficient information to judge the quality of the proposal, but simple enough so as to encourage applicants. These applications are reviewed quickly by CEM and the GOG Tissue bank and approved applications are provided with the necessary statistical and administrative support.

Funding Challenges. The success of translational research within the GOG is critically dependent upon adequate funding. It is an-

anticipated that funding will remain a major challenge over the next several years. The major funding sources for translational research are the National Cancer Institute, industry, and philanthropic sources. CEM will facilitate the preparation of grant applications for translational research from qualified investigators by providing administrative support, letters of collaboration, statistical collaboration, and most importantly, efficient access to the GOG Tissue Bank. Grant applications utilizing GOG resources (e.g., clinically-annotated specimens) and receiving GOG support will be stronger and thus, in a better competitive position. A transparent and efficient process will be created to assist investigators through the grant writing process. Our industrial colleagues are also collaborators in the effort to translate scientific discoveries into clinical successes. Biotechnology and pharmaceutical companies are developing many of the new therapeutic agents that will be available for clinical testing. Thus, CEM will work closely with industry to design and implement the appropriate clinical trial protocols to effectively test these new agents. Further, this process will require research funds from these companies to specifically support the laboratory-based science attached to these clinical trials. This effort will include utilization of, and collaboration with, drug company research laboratories. CEM will work with leadership to raise philanthropic monies dedicated to translational research efforts. This will involve organized fundraisers that emphasize translational research efforts, along with the potential clinical impact. These events will be organized around the group’s semi-annual meetings and other events.

Prioritization and Areas of Opportunity. Perhaps the biggest challenge to conducting successful translational research within a cooperative group is to effectively prioritize specific research areas that offer extraordinary opportunities. Many avenues of research are possible, but only a few can be reasonably achieved with available trials and resources. Thus, CEM will make a major effort to prioritize translational research directions. We have identified and prioritized three areas of extraordinary opportunity for translational research, including angiogenesis, molecular targets and genomics. **Angiogenesis** With better understanding of the mechanism(s) involved in the development of the blood supply of tumors and the development of effective anti-angiogenesis agents, angiogenesis will be an important area of translational research. CEM will utilize the expertise of several of its members who are recognized experts in angiogenesis to fully integrate anti-angiogenesis and appropriate translational endpoints into GOG clinical trials. This will involve a major phase III trial testing avastin in advanced stage ovarian cancer, exploring the relationship of hypoxia and angiogenesis in cervical cancer in phase II trials, and the importance of angiogenesis in endometrial cancer. CEM will use several established laboratories (within CEM) to create, test, and standardize assays to measure important angiogenesis endpoints. It will be critical to establish the important biologic characteristics of tumors that predict response to anti-angiogenesis therapy. **Molecular targets** New molecular targets have also been priori-

tized by CEM as an important area of investigation for GOG. With the identification of the molecular basis of many gynecologic cancers, critical activated pathways can be identified effectively in these tumors and targeted with novel agents. Indeed, the advent of small molecule inhibitors that target these pathways will form the basis of many phase II and phase III trials. It will be important in these trials to analyze intermediate molecular endpoints to determine adequate drug dosing and proper interpretation of clinical trial results. CEM will utilize its membership's broad scientific expertise to evaluate all phase II trials for appropriate translational research endpoints. Further, CEM will use the R01-funded laboratories of its members and those of SPORC investigators to conduct these studies. In addition, CEM-supervised Core Laboratories will be used to provide assays for use in phase II trials. These studies should validate any biomarkers as appropriate biologic endpoints for these experimental agents and provide standardized assays for phase III trials.

Genomics. The final area prioritized by CEM for scientific investigation is genomics. Recently evolved technologies (e.g., expression profiling by microarray, SNP) allow for a broad, in-depth genomic analysis of gynecologic and clinical correlation. These technologies are critical for a complete understanding of the molecular basis of gynecologic cancers. Additionally, these technologies can now be applied to formalin-fixed, paraffin-embedded tissue and thus, testing of large numbers of clinical specimens. Testing such large numbers provides the statistical strength needed to address important clinical questions (e.g., risk, early detection). Further, application of these technologies to clinical trials has the potential for prognosis and prediction of the clinical course of patients. In addition to genomic technologies, proteomic technologies have the potential to detect ovarian cancer when present in small volumes, such as during early tumor development and during recurrence. Integrating these technologies into phase III trial design will be of critical importance. CEM will ensure that all phase III trials require tissue collection; thus, providing adequate specimens to validate gene expression signatures and protein patterns needed to stratify patients for future trials. Ultimately, these investigations will lead to dramatic changes in phase III trial design in which patients are stratified according to their genomic/proteomic profile. These results can also be used to identify potential therapeutic targets. These translational research efforts will require peer review funded laboratories with the experience in these technologies to participate.

Conclusions. In order to significantly impact the diagnosis, prevention, and treatment of women with gynecologic cancers, it is clear that translational research is a critical element of all future studies. Empiric clinical trials will no longer be the standard approach. Trials with carefully selected and validated translational endpoints will be needed. Utilizing the expertise of CEM mem-

bership and the infrastructure CEM has created, GOG has and will continue to successfully apply translational research to its clinical trials structure. This will usher in a new and exciting era where the rational application of new agents and individualization of care will become the standard.

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Chapter 8 |

Investigating Quality of Life



Lari B. Wenzel, PhD and Wui-Jin Koh, MD

The GOG Quality of Life (QOL) committee was formed in 1992 to evaluate Phase III studies for their appropriateness for a QOL component, and develop this component with the highest scientific rigor. Under the initial co-leadership of Drs. David Cella and Donald Gallup from 1992 – 2004 this Committee excelled, as evidenced by site visit review scores in the outstanding – excellent range. This report updates the previous 2006 publication, and will provide brief overviews of the breadth and scope of the committee, key accomplishments, new initiatives, and future directions.

The QOL committee serves to prioritize concepts, develop and co-author protocols, educate staff and monitor compliance, provide scientific direction, and interpret and disseminate knowledge gained from QOL studies. To meet these responsibilities we have selected high-priority (usually Phase III) trials where QOL data are important, and collaborate in interpretation of GOG trials which include QOL. The committee is Chaired by a psychologist and Co-Chaired by a gynecologic oncologist, which provides an optimal balance from which to guide QOL measurement in priority state of the science studies. The QOL committee composition is multidisciplinary, to include gynecologic oncologists, psychologists and behavioral scientists, nurses, radiation and medical oncologists, data managers, patient representatives and biostatisticians. As the scope of work has expanded over time, so too has the need for an increasingly diverse multidisciplinary representation. This growth is reflected in our steadily-increasing publication and study participation rates. From 2000 - 2005, the QOL committee generated 25 peer reviewed publications or published abstracts. Additionally, QOL members have been involved in 8 phase III studies, which have identified QOL as a major component of the studies.

As new therapeutic approaches for gynecologic cancer are developed and tested, it is important that advances in traditional clinical endpoints (such as response rates, progression-free survival and

overall survival) are balanced against careful, quantitative, and reproducible assessments of QOL. Our contribution to key Phase III trials has advanced the field of QOL measurement and clinical trial data analysis/interpretation. For example, in GOG protocol 177, the FACT/GOG-NTx subscale was refined and further validated. This included 11 items assessing sensory, motor, hearing symptoms and possible functional impact, which was administered to 263 advanced endometrial cancer patients prior to each of 7 courses of chemotherapy (TAP: paclitaxel/doxorubicin/ cisplatin vs AP: doxorubicin/cisplatin). Results of this study indicated that the patient-reported sensory symptom scores (sum of 4 item scores) increased significantly over the treatment duration ($p < 0.001$) in TAP compared to AP. Ultimately, in this study we were able to conclude that as few as 4 sensory symptoms in the FACT/GOG-NTx subscale can be used to reliably and sensitively assess cisplatin-paclitaxel induced neurologic symptoms in clinical oncology without compromising the psychometric properties of the overall scale¹. In protocol 172, examination of abdominal discomfort as an important QOL endpoint associated with intraperitoneal therapy has led to the validation of the FACT/GOG-Abdominal Discomfort (AD) subscale². These are two examples in which the advancement of QOL measurement science has occurred as an outgrowth of Phase III QOL results. Studies of this type will permit greater application of streamlined QOL measures for targeted assessment in clinical trials, to improve informed decision-making.

Contributions to studies of advanced disease have been numerous. GOG 169, which randomized eligible patients with recurrent/metastatic cervical cancer to cisplatin vs cisplatin/paclitaxel, was one of the first chemotherapy trials in cervical cancer to formally incorporate a QOL component. It was determined that there was no significant difference between groups in QOL scores; however, a disproportionate number of patients receiving cisplatin alone (C; N = 48) compared to those receiving cisplatin plus pa-

clitaxel (CP; N = 33) dropped out of the QOL component, likely due to progressing disease, deteriorating health status, or early death. Although there was greater toxicity in the combination regimen, there was no statistically significant difference in overall quantitative QOL scores between treatment arms. This finding, combined with the increased response rate and PFS in the CP arm and the higher drop-out rate in the C arm, suggests a worse outcome for the single-agent regimen. QOL measurement contributed to the conclusion that cisplatin plus paclitaxel is superior to cisplatin alone with respect to response rate, PFI and sustained or improved QOL and this combination regimen remains a widely used standard of care³. In a subsequent phase III chemotherapy study for recurrent/metastatic cervical cancer (protocol 179), we prospectively assessed the impact of treatment with cisplatin alone (C), versus C in combination with topotecan (CT) on quality of life (QOL) in patients with advanced or recurrent cervical cancer, and explored the prognostic value of baseline QOL scores. Importantly, results from this study indicated there were no statistically significant differences in QOL up to nine months post-randomization despite more hematological toxicity in the combination arm. The Baseline FACT-Cx was associated with survival and this was the first advanced cervical cancer study to note that patient-reported QOL measures may be an important prognostic tool in advanced cervix cancer⁴.

Our contribution to GOG protocol 122 assisted in determining if QOL outcomes should be considered when evaluating two markedly different treatment-intense regimens for advanced endometrial cancer. Following treatment, significant differences in patient symptom patterns between the 2 cohorts were evident, with whole abdominal irradiation (WAI arm) patients reporting significantly higher fatigue than those on chemotherapy (AP arm: doxorubicin + cisplatin for 7 courses, with an additional 8th cycle of cisplatin alone). Significant differences in functional alterations due to changes in elimination were identified at the end of treatment ($p < .01$), and 3 month follow-up ($p < .01$), with WAI having poorer scores. However, the AP group showed significantly higher peripheral neuropathy scores at end of treatment and 3 and 6 month follow-up compared to the WAI group ($p < .01$). While fatigue and elimination problems were acutely worse for patients on the WAI arm, these level off at 6 months, nearing pre-treatment levels. However, marked peripheral neuropathy was sustained for at least 6 months for patients on the AP arm. Given the disparate treatment approaches tested in GOG 122, it was important to measure and understand the QOL outcomes associated with each modality, to achieve better patient communication and education.⁵

The committee was also instrumental in establishing the importance of QOL measures in advanced ovarian cancer. GOG 152, which evaluated the role of interval secondary cytoreduction, was the first multicenter randomized trial in ovarian cancer to longitudinally examine self-reported QOL, and it also established a predictive value of baseline QOL on survival, attributed primarily to

the lowest scoring quartile. Although interval secondary cytoreduction resulted in no notable long-term difference compared to the control arm, a clinically significant improvement in QOL was seen in both arms at 6 and 12 months after starting therapy. Of interest were fewer complaints of neurotoxicity at 6 months among patients who did versus did not undergo interval secondary cytoreduction⁶. In protocol 172, which evaluated IV vs IP chemotherapy, we noted that although QOL differences favored the IV arm during and shortly after treatment, at one year post treatment health-related quality of life and abdominal pain scores were similar between the two arms, with the exception of paresthesias, which were more likely to persist at moderate levels among the patients who receive IP chemotherapy⁷. These findings suggest that the additional toxicity which may be observed with IP delivery is generally transient and not a long-term issue for most patients.

As a demonstration of our contribution to early stage disease, protocol 8003 examined and evaluated the reliability of an instrument, the Vaginal Sound, designed to measure vaginal length. In this study we noted that the Vaginal Sound instrument is a simple yet reproducible measure of vaginal length and adds methodological rigor to studies of vaginal stenosis.

As of 2004, the QOL committee has been chaired by Dr. Lari Wenzel, a psychologist and behavioral scientist at the University of California, Irvine. Since the previous report in 2006, the committee has maintained its goal of providing state-of-the-science outcome measurements for selected phase III and randomized phase II clinical trials, where it has been determined that quality of life and patient-reported outcomes should be embedded as key study endpoints. During 2006 to 2013, the committee has generated additional peer-reviewed publications or published abstracts, and QOL members have been involved in the design, conduct, and analysis of virtually all recent phase III trials.

In July 2011, the QOL committee was combined with the Comparative Effective Research working group, to form the Health Outcomes Research Committee (HORC), with Dr David Cohn, a gynecologic oncologist, serving as co-chair of this newly formed committee. In addition to its focus on QOL measures, this committee is also now tasked with providing a forum through which comparative effectiveness and cost-effectiveness outcomes can be incorporated into clinical trials. Furthermore, with the impending merger of the NSABP, RTOG, and GOG into NRG Oncology, the GOG HORC has led the way in collaboration with outcomes research initiatives in the other cooperative groups, and since January 2013 has become integrated as the Patient Centered Outcomes Research Committee (PCORC) within the NRG structure.

QOL measures and endpoints have continued to inform analysis of recently completed large GOG trials, and allow appropriate implementation into clinical practice. In GOG 204, which was a 4-arm study of chemotherapy platinum-containing doublets in

recurrent/metastatic cervical cancer, it was reported that health-related quality of life outcomes were not significantly different among the four treatment cohorts. The QOL assessment supported the selection of cisplatin and paclitaxel as the continued systemic treatment regimen of choice, except in patients with significant pre-treatment neuropathy⁸. GOG 218 was a randomized, double-blinded, placebo-controlled trial in advanced ovarian cancer, which showed improvement in progression-free survival with the addition of concurrent and maintenance bevacizumab to carboplatin and paclitaxel chemotherapy, compared to chemotherapy alone or to bevacizumab added only during cycles 2-6 of chemotherapy. A formal analysis among the three groups showed that while the additional of bevacizumab slightly decreased QOL during chemotherapy, there was no prolonged effect on QOL after completion of the chemotherapy phase, when single-agent bevacizumab was continued as a single agent. QOL and abdominal discomfort was noted to improve from baseline to cycle 13 for all treatment groups. This QOL evaluation confirms the safety and tolerability of protracted bevacizumab given concurrently with carboplatin/paclitaxel, followed by subsequent maintenance bevacizumab alone⁹. In endometrial cancer, the committee has attempted to evaluate a previously understudied area of QOL, that of sexual function and its related factors following surgery¹⁰, which may be helpful in designing future trials in early stage endometrial and cervical cancer.

To further advance the science of patient-reported outcome measurement, supplemental funding has been obtained through the Essential Biomarker, Imaging and Quality of Life Supplemental Funding Program (BIQSFP), in developing a QOL study which is integral to the GOG 249 Phase III clinical trial in early stage endometrial cancer. GOG 249, which has just recently completed planned accrual, is designed to determine if treatment with vaginal cuff brachytherapy followed by three cycles of chemotherapy reduces the rate of recurrence or death (i.e. increases recurrence-free survival) when compared to pelvic radiation therapy. Comprehensive patient-reported outcomes are ongoing. Analysis will ultimately include comparisons of physical functioning, fatigue and neurotoxicity between the two treatment groups, review of associations between primary comorbid illnesses and obesity on survival, fatigue and physical functioning, evaluation of the psychometric properties (such as construct validity, reliability, sensitivity to treatment and responsiveness over time) of the PROMIS Fatigue Short form 1, and assessment of fatigue measurement equivalence between women with endometrial cancer and age-matched non-cancer women from the general US population.

In addition to quantifying and reporting QOL measures associated with different therapies in gynecologic cancers, we are interested in identifying useful interventional approaches that can impact QOL, and perhaps even survival. Recent analyses by this committee has shown that poorer pre-treatment QOL scores, especially in the physical well-being domain, are associated with poorer overall

survival following treatment for advanced cervical and ovarian cancer, even after adjusting for other known prognostic factors^{11, 12}. Attempts are ongoing to try and define modifiable pre-treatment characteristics where interventional support may improve outcomes. Other examples of QOL interventional initiatives include GOG 244, which will evaluate lower extremity lymphedema following pelvic surgery and possible mitigating factors, as well as GOG 259, which will evaluate the role of specific nursing case in symptom management in ovarian cancer. There are also ongoing developmental efforts on protocols to study the efforts of tailored weight loss intervention in endometrial cancer survivors, as well as ovarian transposition in young cervical cancer patients who will undergo pelvic radiotherapy.

The cost, and cost-effectiveness, of medical care has become an increasingly critical area of investigation, and is reflected in the new HOCR committee structure and its added primary aim. In 2011, GOG 8030 (CPC1012) was approved by the National Cancer Institute as the first comparative effectiveness research study of the GOG. This trial “A Comparative Effectiveness Study of Cancer Risk Management for Women at Elevated Risk of Ovarian Cancer” will be based on data from GOG 199, a non-randomized natural history study of risk-reducing salpingo-oophorectomy and ovarian cancer screening for women at increased genetic risk of ovarian cancer. HOCR investigators have begun accessing the primary data from GOG 199, and incorporating this data into a Markov model which evaluates the incidence of ovarian cancer, breast cancer, surgical complications, cardiac complications, and quality of life in patients enrolled on GOG 199. Results from GOG 8030 will help to inform future decision making for women at increased genetic risk for ovarian cancer. Efforts are also underway to develop prospective cost-effective analysis studies, partnered with new phase III trials (with potential funding through the BIQSFP mechanism).

In summary, the importance of quality of life evaluation as part of clinical trials has been convincingly established. QOL endpoints and measures are now incorporated into the majority of randomized GOG trials. The committee has evolved, with expanded aims, priorities, and expertise. Future directions include continued advances in QOL measurement science, contribution to trial interpretation to aid in treatment decision-making, the introduction and assessment of key interventions to enhance quality of life, and increased focus on comparative and cost effectiveness analysis.

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Chapter 9 |

Prevention of Gynecologic Cancer



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Introduction

Cancer is the leading cause of death among women under the age of 85. In 2013, over 28,000 deaths are expected from gynecologic cancers alone in the United States (U.S). A cancer patient is not well one day and sick the next, but undergoes a gradual process of cancer progression that begins with the development of the first cancer cell. It is estimated that at least 10 years elapse between the development of that first cell and the onset of metastatic gynecologic cancer. This translates to nearly 300,000 women in the U.S. who currently harbor conditions that will ultimately result in gynecologic cancer death. These women desperately need effective prevention strategies to save their lives. The central goal of the Cancer Prevention and Control (CPC) Committee is to prevent these gynecologic cancers from ever occurring. To reach this goal, we have developed an innovative structure and research strategy specifically with these women in mind.

Very few clinical investigators would disagree with the concept that it is better to prevent cancer than treat cancer. Gynecologic oncologists, in particular, have established a strong tradition of cancer prevention research, leading to major reductions in both the incidence and mortality of cervix and endometrial cancers. With this in mind, Dr. David Alberts (Arizona Cancer Center) approached the leadership of the Gynecologic Oncology Group (GOG) in 1994 to establish a Cancer Prevention and Control Working Committee. Two workshops were held at the Gynecologic Oncology Group Semi-Annual Meetings that led to the ini-

tiation of the Cancer Prevention and Control Committee in 1995, which continues to be chaired by Dr. Alberts and is co-chaired by Dr. Joan Walker (Oklahoma University Health Sciences Center). Initial and continued National Cancer Institute funding for Cancer Prevention and Control research within the GOG has come from the Community Clinical Oncology Program (CCOP) in the Division of Cancer Prevention with oversight from Drs. Leslie Ford, Lori Minasian, Terri Cornelison and Joseph Kelaghan.

The research focus of the CPC Committee in the GOG is multidisciplinary, focusing on cancer epidemiology, prevention, early detection, screening, and supportive care with special emphasis on minority and underserved populations. The CPC Committee is organized according to organ sites (i.e. cervix, uterine corpus, ovary, and vulva subcommittees) as well as disciplines (i.e. health disparities, epidemiology, biomarkers, early detection, chemoprevention and survivorship subcommittees). These subcommittees are given the challenge of developing the scientific direction of the CPC Committee within their respective research areas. To further the research mission of the CPC Committee, mini-retreats are sponsored by this Committee, focusing on the development of new research proposals in the organ site and discipline subcommittees.

Prevention of Ovarian Cancer

The pathogenesis of epithelial ovarian cancer is now better understood and divided into a low grade pathway and a high grade pathway. Simplistically, the low grade pathway may originate as

endometriosis then transforming into an endometrioid, often low stage, or clear cell carcinoma, or borderline and low grade serous carcinoma. This current explanation helps explain the benefit of oral contraceptives and progestins as protective against some types of ovarian cancer. This may also correlate with obesity and infertility associations with ovarian cancer.

The CPC committee has completed a trial, GOG 214, led by Gus Rodriguez, M.D., which comprehensively evaluated the effects of levonorgestrel on ovarian epithelium. The data analysis is ongoing.

The second pathway found causing “ovarian cancer” is the tubal hypothesis which proposes that the neoplastic cell is transformed in the fallopian tube and these cells are exfoliated into the peritoneal cavity and all peritoneal surfaces grow these cells including the surface of the ovary and omentum. This explains the challenge finding any differences between the behaviors of primary peritoneal, ovarian, and fallopian tube cancers. The surface spreading high grade serous cell type is found in genetically predisposed women with BRCA 1 & 2 mutations. Also, young relatives of ovarian cancer patients having prophylactic bilateral salpingo-oophorectomy have demonstrated a 90% risk reduction of future high grade serous cancer, but those where peritoneal carcinomatosis occurs it is explained by failure to adequately evaluate the fallopian tubes. Now the protocol of SEE-FIM (serial sectioning of the entire fallopian tube) at the time of prophylactic BSO has demonstrated precursor lesions (STIC= serous tubal intraepithelial carcinoma) and early fallopian tube cancers. Retrospective, reevaluation of women’s tubes who were originally diagnosed with ovarian cancers has also demonstrated precursor or neoplastic lesions in the fallopian tubes. It is now expected that removal of fallopian tubes could prevent most high grade serous cancers. Removal of ovaries is required to reduce the risk of breast cancer in BRCA 1 & 2 patients. The age at which these procedures should occur continues to be under debate and further research.

A clinical trial under development in the CPC committee will remove the fallopian tubes of women at high risk with BRCA 1 & 2 and who have chosen to refuse oophorectomy or delay oophorectomy until closer to menopause. Women age 30 until age 50 will be eligible and tissue will be saved for basic science investigations into the cell of origin of ovarian cancer. The patient’s perspective to this treatment plan will be assessed with evaluation of treatment effects. A quality of life and delay of menopausal symptoms will be studied in the typical BRCA 2 woman who chooses the scheduling of two surgeries the first at age 30, bilateral salpingectomy after completion of childbearing, and then removal of ovaries at age 40 to induce menopause and help prevent breast cancer. The NCI agrees with the proposed single arm protocol with tissue banking, and comparison to the GOG 199 population which has already completed the quality of life instruments. The goal is to be better than screening at reducing mortality, and not expected to be

better than risk reducing salpingo-oophorectomy at preventing breast cancer. The quality of life outcomes are expected to be better than BSO. The data from this study should help women with medical decision making. The tissue banking is expected to help determine the timing of interventions and document the etiology of ovarian cancer. Collection of cervical, endometrial and pelvic fluid will be performed as well as blood, to see if precursor lesions can correlate with molecular screening.

It is commonly believed, however, that the process of recurrent ovulation (incessant ovulation) causes genetic damage in ovarian epithelial cells and that sufficient genetic damage can lead to ovarian cancer in susceptible individuals. Under this model, it has been suggested that reproductive and hormonal factors such as pregnancy and oral contraceptive use decrease ovarian cancer risk, mainly via their inhibitory effects on ovulation. The “incessant ovulation model” is attractive in that it is supported by a large volume of epidemiologic evidence linking ovulation with ovarian cancer risk in humans, and by the observation that poultry hens, which ovulate daily, have a high incidence of spontaneous ovarian cancer. Unfortunately, the model falls short in that it fails to explain the markedly protective effect conferred by pregnancy and oral contraceptive use against ovarian cancer. For example, oral contraceptive use for three years, which inhibits less than 10% of the number of ovulatory cycles in a woman’s lifetime, confers a 50% reduction in risk of ovarian cancer, rather than 10%. Moreover, one pregnancy, which is associated with approximately one year of anovulation is associated with a 30-35% decrease in ovarian cancer risk. These data suggest that there may be biologic effects unrelated to ovulation that mediate the influence of reproductive factors on ovarian cancer risk.

There is mounting evidence that the ovarian epithelium is a hormonally responsive target organ the biology of which can be strongly influenced by the local hormonal environment. The normal ovarian epithelium expresses receptors for most members of the steroid hormone superfamily, including estrogen, progestin, retinoids, vitamin D, and androgens. In addition, the ovarian epithelium contains cyclooxygenase. Thus, there is the potential for reproductive and environmental factors to impact ovarian cancer risk via a direct biologic effect of hormonal and non-hormonal agents on the ovarian epithelium. Indeed, recent studies have demonstrated that reproductive hormones can have very potent biologic effects directly on the ovarian epithelium, thereby impacting ovarian cancer risk. Progestins, for example, induce apoptosis, one the most important molecular pathways *in vivo* for the prevention of cancer, and a pathway that mediates the action of a number of known chemopreventive agents. Therefore, it is possible that progestin-mediated apoptotic effects may be a major mechanism underlying the protective effects of pregnancy (a high progestin state) and oral contraceptive pill use. Similarly, retinoids, vitamin D, and non-steroidal anti-inflammatory agents (NSAIDs) may have biologic effects on the ovarian epithelium that are cancer preventive,

whereas androgens may have stimulatory effects on the ovarian epithelium, leading to an increased ovarian cancer risk.

Ultimately, the most promising chemopreventive agents for ovarian cancer will need to be critically evaluated in prospective randomized trials to demonstrate their efficacy and safety. This could be a formidable challenge if performed in the general population due to the generally low prevalence of ovarian cancer. A prospective trial of an ovarian chemopreventive in women of average risk would require tens of thousands of subjects, and many years to complete. On the other hand, the ideal study group may instead comprise women who have one first degree relative with ovarian cancer. These women have a higher incidence of the disease (three-fold increased risk of ovarian cancer versus women without family history), thus requiring a study of smaller size and fewer years to complete. In addition, in given that more than 22,000 new cases of ovarian cancer are diagnosed annually in the U.S., first-degree relatives of women with ovarian cancer comprise a large potential pool of subjects for study. Finally, women at increased risk of ovarian cancer are likely to be strongly motivated to enter clinical trials to evaluate ovarian cancer interventions, given their firsthand knowledge of the disease, and their personal inherent risk.

The CPC Committee of the Gynecologic Oncology Group approved two pilot protocols (GOG-190 and GOG-214) designed to gather preclinical evidence in support of retinoids and progestins as ovarian cancer preventives. In addition, several other agents with promise as ovarian cancer preventives are also being considered, and will probably be evaluated in due time. The protocols shared a similar design. Women at high risk of ovarian cancer who are planning to undergo prophylactic oophorectomy and who enroll were to be randomized to receive either the retinoids (GOG-190) or progestin (GOG-214) for four to six weeks prior to surgery. In addition to meticulous examination of ovaries to rule out occult cancer, the ovarian epithelium were examined for evidence of induction of surrogate endpoint biomarkers relevant to cancer prevention and outcomes compared between those women who received a chemopreventive and those who did not.

GOG-190 (Retinoids)

The design of GOG-190 was for seventy women at high risk of ovarian cancer on the basis of a personal or family history of breast or ovarian cancer, or known alterations in BRCA1 or BRCA2 were to be randomized to either immediate oophorectomy (control arm) or to receive the retinoid, Fenretinide, for 4-6 weeks prior to undergoing oophorectomy. The ovaries from control versus Fenretinide-treated subjects would be compared with regard to several surrogate endpoint biomarkers, including markers of ovarian epithelial dysplasia, as well as ovarian epithelial cell proliferation and apoptosis.

Retinoids are natural and synthetic derivatives of vitamin A. They have great potential for cancer prevention, due to a broad range of

important biologic effects on epithelial cells, including inhibition of cellular proliferation, induction of cellular differentiation, induction of apoptosis, cytostatic activity, and induction of TGF- β . The use of vitamin A analogues has been limited by the requirement for large pharmacological doses in order to reach therapeutic efficacy. In addition, high dosages of naturally occurring retinoids produce significant side effects.

By modifying the basic retinoid structure, analogues with reduced toxicity have been developed. An example of such a compound is Fenretinide (N-4-hydroxyphenyl retinamide), or 4-HPR, a retinamide derivative of vitamin A, which has been a promising chemopreventive compound with therapeutic efficacy in a variety of carcinogenesis models.

Epidemiologic and laboratory evidence suggests a potential role for retinoids as preventive agents for ovarian cancer¹. A high dietary intake of β -carotene has been associated with a decreased ovarian cancer risk, whereas low serum retinol levels have been associated with an increased risk of ovarian cancer. In vitro, it has been reported that the growth of human ovarian carcinoma cell lines and normal human ovarian epithelium is inhibited by retinoids. The mechanism underlying this effect may involve induction of TGF- β and/or apoptosis in ovarian epithelial cells. The most significant evidence supporting a rationale for retinoids as chemopreventives for ovarian cancer is that of a published Italian study suggesting an ovarian cancer preventive effect from the retinoid 4-HPR. Among women randomized to receive either 4-HPR or placebo in a trial designed to evaluate 4-HPR as a chemopreventive for breast carcinoma, significantly fewer ovarian cancer cases were noted in the 4-HPR group as compared with controls². Unfortunately, slow accrual (related to concerns for potential 4HPR toxicities) resulted in early trial closure. Safer chemopreventive agents are required for this relatively young, anxious group of women.

GOG-214 (Progestins)

In GOG-214, women at high risk of ovarian cancer on the basis of a personal or family history of breast or ovarian cancer, or known alterations in BRCA-1 or BRCA-2 were randomized to either to receive either placebo or the progestin, levonorgestrel, for four to six weeks prior to undergoing oophorectomy. The rationale for evaluating progestins as ovarian cancer chemopreventives is based on a strong preclinical evidence collected to date in primates and humans (summarized below). The ovaries from control versus progestin-treated subjects will be compared with regard to several surrogate endpoint biomarkers. These will include markers of proliferation, apoptosis, and transforming growth factor- β (TGF- β).

The well-known association between oral contraceptive pill (OCP) use and lower subsequent ovarian cancer risk suggests that an effective chemopreventive approach using contraceptive hormones is possible. The reduction in the risk of ovarian cancer in women

who have used combination estrogen-progestin OCPs for at least three years is approximately 30-40 percent, and this protective effect increases with the duration of use and persists for up to two decades after discontinuation of use³⁻⁷. Strong epidemiological evidence linking ovulation with ovarian cancer risk has led to the widespread belief that the protective effect of OCP use is due to the ability of these agents to inhibit ovulation, thereby decreasing the risk of epithelial damage related to ovulation in OCP users^{8,9}. This presumption has been questioned, because routine oral contraceptive use results in a disproportionately greater protective effect than that which can be attributed solely to ovulation inhibition. For example, OCP use for three years, which would inhibit less than 10 percent of total number of ovulations in a woman's lifetime, confers a 30 to 50 percent reduction in the risk of ovarian cancer, rather than 10 percent. It has been proposed that these data are more consistent with the hypothesis that OCPs exert a protective effect through some other profound biologic effect on the ovary unrelated to ovulatory inhibition.

In search of biologic effects of OCPs that have the potential to confer protective effects against ovarian cancer, a study in primates has shown that the OCP has a potent apoptotic effect on the ovarian epithelium, mediated by the progestin component¹⁰. In addition, in the same primate study, the progestin component of the OCP was shown to markedly differentially regulate expression of TGF- β in the ovarian epithelium^{10,11}. TGF- β is a peptide growth factor that inhibits proliferation of many cell types, and under some circumstances induces apoptosis.

With regard to cancer prevention, the apoptosis pathway is one of the most important in vivo mechanisms that functions to eliminate cells that have sustained DNA damage and which are thus prone to malignant transformation¹². In addition, a number of well-known chemopreventive agents have been demonstrated to activate the apoptosis pathway in the target tissues that they protect from neoplastic transformation¹³⁻²⁸. Similarly, TGF- β pathway has been shown to play an important role in cancer prevention. The finding that progestins activate these critical pathways in the ovarian epithelium raises the possibility that progestin-mediated biologic effects underlie the protection against ovarian cancer afforded by routine OCP use, and not ovulation inhibition as has been previously assumed. This forms the basis for an investigation of the progestin class of drugs as chemopreventive agents for epithelial ovarian cancer.

Published human data are further supportive of the notion that a biologic effect related to progestins may be a major mechanism underlying the cancer preventive effect for both the OCP as well as pregnancy, which confers potent protection against subsequent ovarian cancer and which is associated with high serum progesterone levels:

- An analysis of the data from the Cancer and Steroid Hormone

Study (CASH), has demonstrated that progestin-potent OCPs confer greater protection against ovarian cancer than OCPs containing weak progestin formulations²⁹.

- A re-analysis of data from the WHO has demonstrating a 60% reduction in the risk of non-mucinous ovarian cancer in women who have ever used depo-medroxyprogesterone acetate, a progestin-only contraceptive³⁰. Progestin-only OCPs do not reliably inhibit ovulation, but are nevertheless contraceptively effective, presumably due to direct biologic effects on the reproductive tract. Up to 40% of women using the progestin-only OCPs can ovulate³⁰. Thus, the 60% reduction in ovarian cancer from a progestin-only OCP is further evidence that progestins have a direct chemopreventive effect on the ovary.
- Epidemiologic evidence has shown that twin pregnancy is more protective against subsequent ovarian cancer than singleton pregnancy. Previously, it was presumed that women who have twins would be at greater risk of ovarian cancer, presumably due to an increased likelihood of more lifetime ovulatory events as compared with women who do not have twins, and the notion that increased ovulation would confer greater risk of ovarian epithelial damage. Because women with twin pregnancy have higher progesterone levels than women with singleton pregnancy, it has been proposed that the data regarding the marked protective effect of twin pregnancy are supportive of the notion of a biologic effect of progesterone as conferring ovarian cancer protection, and that the effect is dose dependent³¹.
- Finally, pregnancy at a later age is more protective than pregnancy early in life. In fact, a pregnancy after the age of 35 is twice as protective against ovarian cancer as a pregnancy prior to the age of 25. It has been proposed that this would suggest a protective effect of pregnancy that is unrelated to effects on ovulation, and supporting the notion that pregnancy may clear premalignant or damaged cells from the ovary^{31, 32}.

GOG-214 was completed in late 2012 with 62 fully evaluate patients. Final biomarker analysis should be completed in late 2013. In addition, a follow up will be developed to perform proteomics with the serum samples collected from this study.

GOG-0199 (Early detection/risk reduction)

GOG-0199 is a nationwide, multi-institution, prospective cohort study of women at increased genetic risk of ovarian cancer. This study was developed through a unique collaboration between the Clinical Genetics Branch of the National Cancer Institute's Intramural Research Program, the GOG CPC Committee, the Cancer Genetics Network (CGN), NCI's Cancer Treatment and Evaluation Program (CTEP) and NCI's Community Clinical Oncology Program (CCOP). This is a prospective, two-cohort, non-randomized observational epidemiologic study of women contemplating risk-reducing salpingo-oophorectomy (RRSO) in order to reduce their genetic risk of ovarian cancer. At-risk women made the decision

as to whether to undergo RRSO in consultation with their referring and primary physicians. All study participants completed a battery of demographic, epidemiologic and psychosocial instruments upon study enrollment, and provide blood samples for research-based genetic testing for germ line mutations in BRCA1/2, CA-125, serum and plasma storage. This biospecimen repository forms the resource upon which a series of laboratory-based translational research studies will be performed.

Women who choose to undergo RRSO had their surgical material collected under a standardized protocol that will governs tissue processing in the operating room and in the pathology laboratory. The presence of clinically occult primary cancers and histologic ovarian cancer precursor lesions are sought, and material was banked for subsequent molecular studies. Post-operatively, these participants were followed with twice yearly CA-125/Risk of Ovarian Cancer Algorithm (ROCA) evaluation every 6 months, health outcomes assessment, and quality of life assessment.

Women who declined RRSO enrolled in a novel study of ovarian cancer screening, using longitudinal changes in CA-125, as modeled by the ROCA algorithm, on a quarterly basis. Each CA-125 determination results in an estimate of the likelihood that the subject has ovarian cancer. For those in whom the suspicion is high, transvaginal ultrasound (TVUS) and gynecologic oncology consultation was arranged. For ROCA scores in the intermediate range, TVUS was performed; if abnormal, gynecologic oncology consultation was scheduled; if normal, the subject returned to the quarterly screening. TVUS and screening mammography were done, at a minimum, on an annual basis, as that represents the current standard care for high-risk women. Patients also periodically completed health outcome assessments and quality of life assessments.

Primary study outcomes include the development of ovarian, fallopian tube, breast and primary peritoneal carcinoma (PPC). Information on non-neoplastic events related to estrogen deficiency was also collected, although the study was not powered to detect significant differences in these parameters. This study includes a major focus on comparing the impact upon quality of life reported by surgical and screening subjects. Several of the secondary endpoint and ancillary analyses such as (1) modeling determinants of medical decision-making related to surgery and screening; and (2) cost-effectiveness analysis are in progress as current data analysis or projected to begin once the primary analysis is complete.

GOG-199 study closed to enrollment in November 2006 with a total of 2,605 women enrolled in the study. 1,030(40%) were enrolled in the surgical cohort and 1,575 (60%) into the screening cohort. The five years of prospective follow-up ended November 2011. This is the first large-scale, long-term prospective data ever collected from high-risk women, and will more precisely define the incidence of critical cancer endpoints and quality of life in

these patients. Rational and study design of GOG-199 as well as the baseline characteristics of the women enrolled in this study have been reported³³. Also as part of the baseline analysis and in fulfillment of a secondary endpoint, Skates et al published a manuscript defining CA-125 cut-point defined by marital status³⁴. Additional manuscripts will address the primary study endpoints of cancer rates between the two cohorts, prevalence of ovarian cancer and fallopian tube cancer in women undergoing RRSO and evidence for precursor lesions; quantify the positive predictive value and specificity of ROCA based on serial CA-125 measurements for ovarian cancer in the group that elected to not undergo RRSO; quality of life at baseline and with respect to changes over time in both cohorts. Thus far, 13 manuscripts have been published with the collaboration with the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)³⁵⁻⁴⁷.

In addition to the above aims, a series of ancillary analyses are ongoing. Current understanding of the pathogenesis of ovarian cancer holds that this malignancy has its origin in the single layer of cells which cover the surface of the ovary—human ovarian surface epithelial, or HOSE, cells. The performance of RRSO in the current study provides a unique opportunity to collect these cells for use in various molecular studies intended to shed further light on the pathophysiology of ovarian carcinogenesis in women at increased genetic risk. Since the harvest of these cells has not been previously accomplished in a clinical care setting, one of the research goals of this project is to obtain these materials, which we plan to use in proteomic and oligonucleotide array studies.

GOG-0199 serves as a foundation for the development of many additional studies in the GOG CPC Committee. GOG-215, a randomized phase II trial of zoledronic acid, an intravenous bisphosphonate, for the prevention of bone loss among women undergoing RRSO, was one such study. Each year, osteoporosis is responsible for 1.5 million fractures, including 700,000 vertebral fractures. The rate of bone loss experienced by untreated post-menopausal women causes a doubling in the risk of fracture every 10 years, on average. In addition, age-related factors other than bone loss also contribute, causing fracture risk to double approximately every 5 years overall⁴⁸. Premature menopause after oophorectomy is also associated with an increased risk of osteoporosis^{49, 50}. The bone loss begins immediately after RRSO, and accelerates in the first year post-oophorectomy, thus demonstrating the need for early intervention to prevent BMD loss in these women. Every premenopausal woman who undergoes this surgery will suffer from early menopause, and thus will be at risk of bone loss, osteoporosis and increased risk of fracture. Unfortunately, zoledronic acid proved too toxic for this vulnerable population of young women and the trial was terminated due to high invaluable rates.

Prevention of Endometrial Cancer

The prevention of low grade endometrioid adenocarcinoma should be able to be prevented with progestin. This is a disease of anovu-

lation, excess estrogen state, iatrogenic or secondary to excess adipose secretion of estrogens due to obesity. Progestin should prevent this transformation, except it has to be life-long. Progestins cause side effects that women consider intolerable including weight gain. The Mirena IUD is an ideal solution due to the internal bathing of the endometrium with levonorgestrel and minimal systemic absorption. The tradeoff is changing this device every five years and preventing the eventual need for hysterectomy, and is unlikely to reduce mortality. The more effective strategy is weight reduction, improved nutrition and exercise.

The mortality from endometrial cancer is mostly caused by high grade lesions including serous, clear cell, carcinosarcoma, and grade 3 endometrioid carcinoma. The epidemiologic analysis of GOG 210 was undertaken by Louise Brinton, Ph.D., and she compared these high risk lesions more lethal lesions compared to low grade endometrioid (grade 1 & 2). This analysis demonstrated that these high risk malignancies are more likely to be smokers, normal or underweight women, breast cancer patients and previously tamoxifen treated breast cancer patients. Gynecologic oncologists now understand that they need to prioritize staging in women with these risk factors, and we need to develop prevention interventions for women with these risk factors. The only current idea is to place a Mirena IUD in women with breast cancer, which is an ideal collaboration with NRG partners RTOG, NSABP and CCOPS.

GOG-137 (Estrogen)

The purpose of GOG 137 was to determine the effect of estrogen replacement therapy (ERT) on recurrence rate and survival in women who have undergone surgery for Stage I or II endometrial cancer. Eligible patients were provided randomly allocated therapy with ERT or placebo after undergoing surgery for early-stage endometrial cancer. The surgery consisted of hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic and aortic lymph node sampling. Planned duration of hormonal versus placebo treatment was three years, with an additional two years of follow-up. Between June 1997 and January 2003, 1,240 patients were provided randomly allocated therapy with ERT or placebo after undergoing surgery for early-stage endometrial cancer⁵¹. The median follow-up for all participants was 35.7 months (1st and 3rd quartiles: 23.0 and 48.8 months). Stage, grade, histological subtype, and percentage of participants receiving adjuvant therapy were similarly distributed between the groups. The median age at diagnosis for the 618 participants randomized to ERT was 57 years (range, 26-91 years). Two hundred and fifty-one (41.1%) participants were compliant with ERT for the entire treatment period. Disease recurrence was experienced in 14 patients (2.3%) and 8 (1.3%) developed a new malignancy, one was breast cancer. There were 21 deaths (3.4%), with five (0.8%) due to endometrial cancer.

The median age at diagnosis for the 618 participants in the placebo group was 57 years (range 30 to 88 years). There were 59 (9.7%) participants that began taking open-label estrogen while on study.

There were 12 participants (1.9%) who experienced disease recurrence, while 10 developed a new malignancy (1.6%), three of which were breast cancer (0.5%). There were 16 deaths (2.6%) in the placebo group, with 4 (0.6%) due to endometrial cancer.

Following the publication of the results of the Women's Health Initiative, enrollment fell and the study was closed prematurely after it became clear that the accrual goal of 2,108 could not be reached in a reasonable amount of time. Of the data from the 1,236 eligible and evaluable patients, the relative risk of recurrence (80% confidence interval) is 1.27 (0.916, 1.77) in the estrogen arm of this study as compared with placebo. Only twenty-six patients (2.1%) experienced disease recurrence. The relative risk confidence interval provides no indication that ERT is safe in terms of the risk of recurrence. Of note, was the very low risk of recurrence, as well as the incidence of new malignancy. In addition data from this study was used to determine whether there is a racial disparity in outcome between black patients and white patients with early-stage endometrial cancer treated similarly in a clinical trial setting. Findings of the study suggested that recurrence-free survival may be shorter among black women with stage I endometrial cancer, even in a clinical trials setting in which patients receive similar treatment and follow-up. This increased risk of recurrence appeared to be most evident in black women with endometrial cancer who maintained ERT after primary treatment⁵².

GOG-167A (Cancer risk)

GOG-167A involved the evaluation of the tissue by: the initial institutional (community) pathologist; centralized review by a GOG pathologist study panel; and a separate independent centralized review by the GOG Pathology Committee. These reviews were used to estimate the rate of concurrent carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia, to estimate rates of concurrence in making the diagnosis of AEH, and to develop descriptions of the issues involved in evaluating precancerous endometrial lesions. A translational objective of GOG167A was to use novel histomorphometric approaches to endometrial biopsy diagnosis to stratify those women who are very low risk of myoinvasive disease, and therefore candidates for surgery-sparing hormonal ablative therapy.

Subjective diagnosis of the intake "atypical hyperplasia" biopsies by pathologists was shown to be very poorly reproducible and poorly predictive in this regard. Moreover, the prevalence of concurrent carcinomas in this population was 42.6%, with a significant percentage of these being myoinvasive (30.9%). The community diagnosis of AEH was supported by the majority of the panel in only 39% of cases, and by all in 15% of cases (overall kappa value for the panel diagnosis of AEH of 0.29)^{53,54}. Unanimous agreement for any diagnosis was reached among each of the three members of the pathology review panel in 39% of cases. For the panel, pair-wise kappa values for any diagnosis ranged from 0.34 to 0.43, with an overall kappa value of 0.40. Diagnostic problems identi-

fied by the panel included those related to application of diagnostic criteria and those related to small quantity or fragmentation of tissue, poor fixation, cutting, or staining.

In contrast, computerized histomorphometric analysis is more reproducible, and has the additional advantage of weighing the outcome predictive value of component discrete variables. These classification systems were specifically developed using training sets independent of GOG167A, contrasting groups of women with and without myoinvasive endometrial adenocarcinoma⁵⁵⁻⁵⁸. In the 4-class rule parameters of gland outer surface density, volume percentage epithelium, epithelium thickness, and nuclear shape variation are combined to yield probability estimates of membership in one of four stratified classification groups: low grade hyperplasia (LGH), high grade hyperplasia (HGH), low grade adenocarcinoma (LGA), and high grade adenocarcinoma (HGA).

We tested the hypothesis that endometrial biopsies assigned by histomorphometry to one of the adenocarcinoma groups would capture the majority of deep myoinvasive carcinoma outcomes at hysterectomy. In GOG-167A, 233 women underwent successful endometrial biopsy and computerized morphometry using the 4-class rule to predict prospectively observed myoinvasive endometrial cancer outcomes⁵⁹. At hysterectomy, 5.1% (12/233) of women had deep myoinvasive adenocarcinoma extending beyond the outer half of the myometrium. Biopsy reclassification by the 4-Class rule into one of the carcinoma categories (LGA or HGA) was seen in 44% (102/233) of patients, and these encompassed 92% (sensitivity, 11/12) of the deep myoinvasive cancer outcomes. A 4-class biopsy diagnosis of any type of hyperplasia had excellent negative predictive value for deep myoinvasion, 99% (101/102). The algorithm may thus have value in identifying those low-risk patients who are candidates for nonsurgical therapy.

The contribution of 4-Class rule component variables to individually predict myoinvasive outcomes was measured by comparison of their distribution in the different outcome groups. Larger scale architectural parameters measuring epithelial abundance (volume percentage epithelium, outer surface density, epithelial thickness) were most associated with presence or absence of myoinvasion of any depth. Variation in nuclear size (anisokaryosis, measured as standard deviation of nuclear diameter) emerged as the single variable most associated with deep myoinvasion. These morphometric data confirm an observation from a previous GOG diagnostic study which showed that the presence of extreme nuclear pleomorphism (assessed by pathologists) worsens clinical outcome to that of one higher FIGO grade than would be assigned by architectural features alone⁶⁰.

Due to the need to develop an objective diagnostic approach to distinguish between endometrial precancer and cancerous lesions to improve the clinical management of these patients, high resolution digitized images of cell nuclei were recorded for karyometric

analysis⁶¹. Cases from GOG167A classified as AEH or superficially invasive endometrial cancer (SIEC) both compromise nuclei of two phenotypes: hyperplastic characteristics and premalignant/neoplastic characteristics. The main difference between the AEH and SIEC is the percentage of premalignant/neoplastic nuclei. When this percentage approaches 50-60% superficial invasion is likely. SIEC may develop already from lesions at the low end of the progression curve. AEH comprises cases which may constitute a low risk group involving <40% of AEH cases. These cases hold a percentage of <20% of nuclei of a preneoplastic phenotype. AEH cases from the central and high end of progression have >40% of nuclei of preneoplastic phenotype. Nuclei of the preneoplastic phenotype in AEH lesions are almost indistinguishable from nuclei in SIEC, where this percentage exceeds 60%. The percentage of nuclei of the preneoplastic phenotype in AEH lesions might serve as criterion for assessment of risk for the development of invasive disease.

Prevention of Cervical Cancer

In the United States, cervical cancer remains a commonly diagnosed malignancy in women, despite existing infrastructure and federally mandated funding to support screening for this disease. It is estimated that 12,340 new cases of invasive cervical cancer will be diagnosed in 2013 and an estimated 4,030 women will die in 2013 due to this cancer⁶². Older women and women of lower socioeconomic status comprise population subsets which are at disproportionate risk. Geographic regions with disproportionately high prevalence include along the U.S.-Mexican border, in Appalachia, and on the Delmarva Peninsula. Hispanic women have the highest incidence rate of cervical cancer⁶².

While research to identify factors presenting barriers to access to screening and care, both on the part of providers and patients, is ongoing, the GOG CPC cervix subcommittee is working on interventions targeting women with high-grade dysplastic disease. This patient population is at increased risk of developing invasive cervical cancer and can be cured.

The first step was the development of a multidisciplinary team of investigators with a primary interest in the prevention and early detection of cervical cancer. However, while high-grade dysplasia occurs only in the setting of persistent infection with an oncogenic strain of human papillomavirus (HPV), it is not a homogeneous disease. Therefore, in order to assess interventions in this population, it is critical to define parameters of outcomes. Interventions in this patient population must present minimal risk. The clinical trial cohorts must be very tightly defined and consistent.

This subcommittee developed a master protocol which will allow comparison of different types of interventions in this patient population. The eligibility criteria for the first set of protocols include histologically-confirmed diagnosis of cervical intraepithelial neoplasia (CIN)-3, HPV typing, and human leukocyte antigen (HLA)

phenotyping. All patients enrolled in these cancer prevention (CIN treatment) protocols will be followed for the same time intervals. Specimens collected longitudinally include serial colpographs, tissue at diagnosis and resection, with serial cervical swabs and peripheral blood lymphocytes being banked for the study of exploratory endpoints. Digital images of the histologic sections will also be scanned and banked. The primary endpoints of this series of studies include both histology and HPV viral load.

As a result of the coordinated efforts of this subcommittee, data collected across studies will be comparable and, in the aggregate, will create a sizable database for secondary research analyses. In addition, the subcommittee has developed a system of web-based collection of cervical images. This effort has established a digital database that serves as a complement to the previously-established tissue bank.

The careful study of interventions in this patient population will not only provide new therapies in a cohort at elevated risk of developing cervical cancer, but also provide a unique scientific opportunity to understand mechanisms of clearance versus persistence in a patient population that is poised to clear established disease.

GOG-207 (COX inhibitor)

One trial developed under the CIN master protocol was GOG-207. The trial is a therapeutic trial open to patients with cervical intraepithelial neoplasia 2/3 or 3. The objectives of this study are to determine the efficacy of Celecoxib to induce complete remission (or partial regression to CIN1) of CIN2/3 or CIN 3 as evaluated in the post treatment excisional biopsy and to determine the toxicity of Celecoxib as assessed by Common Toxicity Criteria (CTC). In addition exploratory objectives are to examine whether lesion size, as determined by colposcopic examination, changes in response to treatment with celecoxib, to determine the efficacy of celecoxib treatment in changing HPV viral load in cervical cells; to examine the association of histologic response; HPV viral load, lesion size, proliferation index, apoptosis index, angiogenesis and COX-2 in tissue. In addition cervical cytology karyometry will also be assessed as a potential marker for regression; as well as to determine the feasibility of digital imaging, web-based review of histopathology in a GOG study and to compare the diagnoses of the web-based review of histopathology with the diagnoses of GOG's standard procedure. This study completed accrual in April 2012 with 130 patients enrolled. Analysis is underway.

GOG-171 (MN expression)

This study incorporates an innovative biomarker approach to developing earlier detection methods for cervical cancer. GOG-171, which closed to accrual 2005, evaluated the utility of a novel tumor-associated antigen, designated "MN". This study enrolled patients with a cytologic diagnosis of atypical glandular cells of undetermined significance (AGUS), to evaluate the utility of MN

as a potential diagnostic marker. It was also designed to measure the frequency and type of cervical pathology associated with AGUS diagnosis. Final analysis was completed during the spring of 2007. The conclusion of this study was that both H-HPV and CA-IX testing are useful diagnostic markers for glandular lesions. However, H-HPV testing is a better diagnostic marker for the squamous lesions in women in the US. In the Japanese cohort, H-HPV had a sensitivity of 53% in CGLs and an overall specificity of 86%, whereas CA-IX had a sensitivity of 100% in CGLs and an overall specificity of 50%⁶³. P16 protein expression was observed in 11 out of 12 (92%) cases. None of the Lobular endocervical glandular hyperplasia (LEGHs), LEGHs with adenoma in situ (AIS) or adenoma with gastric phenotype (GA) were positive for H-HPV and only 8 out of 13 (62%) showed focal weak (1+) p16 expression. In contrast, all cases (100%) exhibited strong CA-IX protein expression⁶⁴. The discrepancy is in part due to different HPV testing methods used in this study as well as epidemiologic factors including diet, lifestyle, and environmental factors. Therefore, GOG 237 was made as a replacement protocol to improve on the diagnostic accuracy of the biomarkers evaluated in a ThinPrep cervical cell specimen by reduction of the false negative rates.

GOG- 237

Squamous cell carcinoma has been reduced through the process of cytology screening, identification of precursor lesions, and resection of those lesions. Most women afflicted with SCCA have not had a Pap in greater than three years. Adenocarcinoma patients may present bleeding and have perfect screening history. The precursor lesions for adenocarcinoma of the cervix are often missed on cytology alone. Biomarkers are likely to be helpful to cytopathologists to identify precursor lesions. The protocol for prevention and early identification of cervical lesions are to evaluate biomarkers in women with the AGC (atypical glandular cell) cytology test. The use of HPV testing, P16, CA-IX (MN) has been shown to be helpful in other studies. The analysis of GOG 171 has demonstrated potential genetic differences in Asian women when compared to U.S. women and further comparisons are being investigated. Women on GOG 237 undergo cervical colposcopy, endometrial and endocervical curettage and hysterectomy as indicated, and biomarker analysis is undertaken on cytology as well as histologic material. This data will help improve screening, potentially with the addition of P16 and MN staining on cervical cytology cases that are HPV positive or uncertain diagnosis. GOG -0237 is currently accruing patients.

Cancer Survivorship

GOG-225 (diet and exercise)

Cancer Survivorship research is in demand by the estimated, more than 13 million cancer survivors in the U.S. in 2013. This research focuses on active surveillance for the 16-18% who will develop a second cancer as well as management of long term treatment related toxicities.

When a woman with advanced ovarian cancer has completed chemo and biological therapy with or without maintenance treatment and is in a clinical complete remission, she is told to “come back in 3 months for a serum CA-125 determination and a pelvic exam.” Very little, other recommendations are made concerning lifestyle change because so little research has been funded or completed in this increasingly important area of oncology. The Women’s Health Initiative completed a trial of low fat dietary intervention versus standard diet in more than 48,000 healthy women over the age of 55 years and reported in a secondary, planned analysis, a 40% reduction in the risk of ovarian cancer after 4 years of the intervention⁶⁵. This unexpected result, plus those of multiple cohort and case control epidemiologic studies of the positive effects of regular physical activity on both risk and survival of advanced ovarian cancer, led Drs. David Alberts and Cynthia Thomson to design a 1,070 participants phase III trial of a combination low fat diet (less than 25% of calories from fat) plus the equivalent of 4,000 extra steps per day versus standard of care follow-up in patients with advanced ovarian cancer, in clinical complete remission after primary chemo and biological therapy with a without maintenance treatment. The primary endpoint of GOG-225 (the LIVES trial) is progression free survival with secondary endpoints being quality of life determinations and overall survival. In a unique arrangement with the GOG, Drs. Alberts and Thomson have taken on the responsibility of both the low fat diet/physical activity intervention and control group health education counseling from telephone and website technologies at the University of Arizona Cancer Center, with support of the GOG’s CCOP Research Base grant from the Division of Cancer Prevention, NCI, the National Ovarian Cancer Coalition (NOCC) and the Up the Volume Foundation, GOG-225 is accruing up to a dozen women weekly and should meet its accrual goal by mid-2015.

GOG-244 and GOG-269 (Lymphedema)

Lymphedema is being prospectively evaluated in GOG 244 and GOG 269. All women planning to undergo lymphadenectomy are tested preoperatively and post operatively and operative technique is being correlated with both objective evidence of lymphedema and patient reported outcomes of distress from leg swelling or discomfort. GOG-269 is evaluating the sensitivity, specificity, and feasibility of bioimpedance technology as compared to clinically derived measurements to include circumferential volumetric measurements to detect lower extremity lymphedema in patients who are undergoing an inguinal lymphadenectomy during the concurrent surgical management of a vulvar cancer. Intervention trials will be planned from this analysis and we expect alterations of surgical technique will help prevent this complication.

The CPC committee is committed to developing studies related to longer term effects of cancer and cancer treatments. Concepts investigating ways to reduce surgical morbidity for patients with cervical or vulvar cancer have been discussed. Studies of approaches to control chemotherapy side effects and improvement in post

chemotherapy symptoms are being conducted and developed. We are beginning to investigate whether there are disparities between duration and quality of life between groups of cancer survivors related to race or ethnicity, and have proposed a study to determine the effect of response on survival in patients with recurrent ovarian cancer. Three survivorship studies are described below.

GOG-0256 (cognitive function)

Many survivors report changes in cognitive function that occur following chemotherapy treatment. These issues affect the quality of life of patients. The Cancer Prevention and Control Committee initiated a study to quantify the incidence of change in cognitive function in newly diagnosed ovarian cancer patients throughout and following their primary therapy. GOG-0256, A Prospective Study of Cognitive Function during Chemotherapy for the Front Line Treatment of Advanced Ovarian Cancer, is a prospective study of cognitive function in woman with advanced ovarian cancer undergoing primary chemotherapy with carboplatin plus paclitaxel. Web-based and patient reported cognitive and patient quality of life assessments were conducted prior to chemotherapy, prior to cycle 4, after cycle 6 and 6 months after completion of primary therapy. A decline of 1.5 standard error of measurement per cognitive domain defines a cognitive impairment. This study closed in October 2012 when accrual was met with 249 participants. Final analysis of the data is ongoing.

GOG-195 (Fibrin Sealant)

Vulvar carcinoma is the fourth most common genital tract cancer in women. Radical vulvectomy and bilateral inguinal-femoral lymph node dissection is the standard method of therapy. Over the past 30 years, surgical modifications have been made that migrate toward a less radical approach for the treatment of vulvar cancer. The standard approach today is to perform a vulvectomy or hemivulvectomy for the primary lesion and to use separate skin incisions for the inguinal lymph node dissections. Despite these surgical modifications, the morbidity after an inguinal lymph node dissection (LND) remains quite significant. Some recent series have reported groin breakdown rates between 22 and 52%⁶⁶⁻⁶⁹. The risk of lymphocyst formation is also significant at 7 to 28%⁷⁰.

A recent review of 61 patients who received a LND was performed at the University of Oklahoma⁷¹. Of these patients, 88.5% underwent radical vulvar surgery and LND while 11.5% underwent LND alone. Patients were treated with either a unilateral (27.1%) or a bilateral (72.9%) LND. Adjuvant radiation was given in 24.1% of these patients. Postoperative cellulitis developed in 50.8% of the patients. Wound breakdown and lymphedema occurred in 27.3% and 47.3% respectively. When they occur, these wound complications usually delay postoperative inguinal radiation until they have healed. Radiation therapy after an inguinal dissection further contributes to lower extremity lymphedema.

GOG-195 is a randomized phase III trial that uses TISSEEL[®] VH fibrin sealant, a FDA-approved fibrin sealant, in the inguinal incisions in an attempt to reduce the morbidity associated with the surgical treatment of vulvar cancer. Fibrin sealant (glue) has been used successfully for reducing serous and lymphatic drainage after an axillary node dissection in breast cancer patients⁷². Cumulative drainage and day of drain removal was significantly less at a $p < 0.0003$ and $p < 0.0001$, respectively, in the fibrin sealant group versus controls⁷². In a similar study, besides decreasing the cumulative drainage and day of drain removal, the hospital stay in the fibrin sealant group was significantly reduced ($p = 0.006$)⁷³. In GOG-195, after completion of the inguinal lymphadenectomy and immediately prior to inguinal wound closure, commercially prepared TISSEEL[®] VH fibrin sealant will be applied to the wound of the treatment group. The control group will receive current standard of care comprised of a standard vulvectomy and inguinal lymphadenectomy without the application of TISSEEL[®] VH fibrin sealant. The incidence of lymphedema and complications will be then compared between the treatment and control groups. This study met its accrual goals and closed in the spring of 2005. Unfortunately, the fibrin sealant proved inactive in final analysis.

GOG-192 (Amifostine)

Neurotoxicity is increasingly recognized as a major symptomatic side effect of cisplatin-based chemotherapy. There is a body of literature on the incidence of cisplatin-induced neuropathy and there is general agreement that the most frequently abnormal parameters of the condition are vibratory sensation, deep tendon reflexes and sensory nerve conduction velocities. Peripheral neuropathy resulting from platinum-based chemotherapy, including single agent and combination regimens, generally improves over a period of several months following the discontinuation of chemotherapy. But in some patients, the symptoms of numbness, tingling and pain can persist many months, and may be permanent.

The establishment of cisplatin and paclitaxel as the standard treatment program for ovarian cancer heightened this concern, since paclitaxel is also a neurotoxic agent. Approximately 20% of patients treated with cisplatin (75 mg/m²) plus paclitaxel (175 mg/m²) delivered as a 3-hour infusion develop severe (grade 3) peripheral neuropathy^{74, 75}. Paclitaxel and cisplatin are used in treating other malignancies, as well, and neuropathy may occur in patients receiving platinum based chemotherapy for any of a variety of tumors. While the neurotoxic potential of carboplatin is less than that of cisplatin, when combined with 3-hour infusion paclitaxel, even this regimen will produce grade 2-3 neuropathy in a substantial percentage of individuals^{76, 77}.

GOG-192 was designed to investigate, prospectively, whether administration of amifostine can be used to treat platinum associated neurotoxicity. Anecdotal reports have suggested the agent may be able to reduce the severity of symptoms (and improve abnormalities documented in objective neurological testing) which have per-

sisted for at least several months. Ndubisi, et al.⁷⁸ reported five patients with chemotherapy-induced neuropathy treated with amifostine 500 mg/day as a five-minute infusion for five consecutive days repeated at 21 day intervals for a total of three courses. These investigators found three of the five patients showed improved vibratory sensation and modest improvements in quality of life score were seen in all five.

Evidence exists to support biologic activity of lower dose amifostine in other clinical circumstances. A dose of 200 mg/m² has been used with success in patients receiving radiation therapy^{79, 80} and has been approved by the U.S. Food and Drug Administration (FDA) for prevention of xerostomia in patients with cancers of the head and neck undergoing radiotherapy. This dose is also active in patients with myeloproliferative syndrome. Subcutaneous, as well as intravenous, administration of amifostine has been effective as a radioprotector and has been well tolerated in two published studies^{81, 82}. Plasma levels of the protein bound form of the active metabolite of Amifostine, WR-1065, are not statistically different whether the drug was given intravenously or subcutaneously⁸³.

It was the intent of this study to determine, in a preliminary manner, the rate of response of cisplatin-induced peripheral neuropathy to amifostine. The study employed a quality of life assessment of nerve status and function and an objective assessment of sensory threshold. The objective measure was a tailored version of the Weinstein Enhanced Sensory Test (the WEST-GOG), which was engineered specifically for this trial. The Weinstein monofilaments have been the subject of extensive prior validation research. GOG-192 accrued 29 patients of the planned 100 and the trial was closed by the GOG Operations Committee.

Quality of Life

Quality of life is a focus of the joint efforts of the CPC Committee and the Health Outcomes Research Committee (Quality of Life) in the GOG. Ovarian cancer, for example, is diagnosed in over 22,000 women in the U.S. every year. Approximately 30% of these women, including some with advanced-stage disease at diagnosis, will remain disease-free. We currently have fairly limited understanding about the quality of life and functional status of these women who have survived their cancers. The GOG is particularly well-positioned to conduct the important studies that will elucidate what special issues and challenges ovarian cancer survivors face, and what interventions can be made to meet those needs and improve ovarian cancer survivors' quality of life.

Previous ovarian cancer survivor quality of life research has focused on women with early stage disease, or on cohorts including other gynecologic cancers, or patients treated before the platinum-taxane first-line treatment era. These studies have reported that ovarian cancer survivors report physical (neuropathy, fatigue, poor sexual function, pain) and emotional (depression) difficulties. One

study included 200 women at least two years after diagnosis, evaluating, among other things, sexual functioning, pain, mental health, and fatigue⁸⁴. Sixteen percent (16%) of the women had not had any chemotherapy, but 22% had received radiotherapy. The study did not include details of treatment such as type or duration of chemotherapy. Fifty-three percent (53%) of the women in this study reported current pain or discomfort, while mental health and energy levels were reported to be similar or better than those in the general population. Fifty-seven percent (57%) reported that their sex lives had been negatively impacted by cancer and its treatment, although a specific sexual functioning assessment instrument was not used.

The next steps for the GOG in ovarian cancer survivorship research include an effort to determine whether progression-free and overall survival, quality of life, and late toxicity outcomes differ by race. Understanding whether ovarian cancer survivors have special needs (management of depression, persistent neurotoxicity, etc.) and whether non-white women have greater needs in these areas will lead to appropriate interventions to maximize the quality of life of all ovarian cancer survivors. These studies will also help determine what white and non-white survivors can expect in terms of overall quality of life and physical functioning, whether certain well-described short-to-moderate term toxicities, such as paclitaxel-related neuropathy persist among disease-free survivors, and whether they are more prominent among white or non-white women. Finally, this research will help us understand whether white women survive their ovarian cancer only to have their quality of life impaired by co-morbidities such as heart disease or depression.

Conclusions

Although gynecologic cancers represent very different diseases, there is a relatively well-identified pathway of carcinogenesis from the first initiated tumor cell to mild, moderate and severe dysplasia, ultimately leading to in situ carcinoma and invasive carcinoma that can be identified for cervical, endometrial and vulvar intraepithelial neoplasias, and potentially for ovarian cancer. The CPC Committee within the GOG has developed a coherent plan of attack on these intraepithelial neoplasias, focusing on epidemiologic, early detection, behavioral science, and especially chemoprevention research initiatives. The subcommittee structure allows this team of investigators to have expertise in all of the critical areas of cancer prevention and control, related to gynecologic cancer prevention and at the same time providing a continuous strategy for development of chemoprevention agents and supportive care interventions.

Although this brief chapter highlights only a few of the cancer prevention and control research initiatives within the GOG, there are additional research studies in various stages of development within the CPC Committee. Each of these studies is being developed within the subcommittee structure so that the multidisciplinary na-

ture of the field of cancer prevention and control can be applied to individual research trials within the GOG.

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Modality and Quality Control Committees



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Introduction

The modality committees represent Gynecologic Oncology, Medical Oncology, Nursing, Pathology and Radiation Therapy. In contrast to the site committee, the modality committees do not initiate new protocols. Members of the modality committees, however, have a direct input into new protocols as they are members on the numerous site committees. The main function of the modality committees are to review the area of protocols that require their special expertise, to make sure that adequate safe guards are in place and that the specific protocol manuals have adequate sections to cover specific therapies as prescribed by the protocols. The evaluation of the protocols by these committees prior to initiation of the protocols is extremely important in order to properly identify patients eligible for protocols but also to determine feasibility in regards to its objective.

Another important role of the modality committees is to perform quality control of the protocols while they are ongoing and also at the completion of the protocol in order to determine eligibility and compliance with the protocol.

The individual committees will be described separately although the general functions in regards to their specific modality are very similar.

Gynecologic Oncology Committee

This committee has as its responsibility the surgical quality control both prospective and retrospective. The committee is the repository for surgical expertise within the group. The core group maintains continuity and institutional memory with approximately 15% of the membership rotation on and off each year. This allows new investigators entering into the committee structure of the group. Not only do the members participate in the quality control in regards to surgical modality but that experience is also educational and improves the quality of data that they may submit from their

individual institutions.

All protocol entries that have a surgical requirement to them are reviewed by the Gyn Oncology Committee. All patient entries are reviewed and the review is a very consistent process. This review is carried out very early in the life of a given protocol so that if problems are detected early they can be corrected by altering the protocol or educating the investigators. The principal investigators are notified quickly and corrections can be made within their institutions so that errors will not be repeated, maximizing the sacrifice the patients make to participate in the GOG studies. Potential problems can be identified early in regards to protocol requirements and the study chair can correct these if necessary. Review of the surgery by the committee assures consistency across time and studies which is of particular value to study chairs if they are not surgeons. This early review can be very educational for the individual institutional PI in that eligibility requirements will be reviewed more stringently.

The review that the committee performs includes evaluation of GOG forms, dictated operative reports, pathology reports, and cytological reports, laboratory reports, imaging reports, and discharge summaries. This insures that any surgical procedure is in compliance with the surgical standard of the GOG. If after review it is determined that the patient is surgically ineligible, two additional reviewers and the chair must concur.

The GOG surgical standards are maintained in the surgical procedure manual. This manual is not a surgical text or atlas but rather is a statement of the minimum requirements for any given surgical procedure. This manual also lists the usual indications and contraindications for a given surgical procedure. It outlines extent of any given procedure, listing tissue to be removed, the extent of dissection, and the surgical boundaries. Also listed are the expected side effects and complications. Cases entered into GOG protocols

are measured against this standard. This insures consistency for all surgical procedures for all GOG protocols. The manual is reviewed at each semi-annual GOG business meeting and revised as necessary. If newer revised procedures are required for any given protocol, the gynecological committee provides the expertise to develop the same. Recent additions to the manual include the procedure for bilateral prophylactic salpingo-oophorectomy and pelvic lymphadenectomy and sentinel node biopsy for vulvar cancer. The applicable surgical procedure for a given protocol is included in the written protocol document as an appendix.

The Gynecologic Oncology Committee has its roots in the very beginning of the Group. Dr. Richard Boronow chaired an ad hoc committee dealing with surgical issues from the inception of the GOG until the formation of the Modality Committees.

In 1977, Dr. Frank Major became Chair of a standing committee, The Gynecologic Management Committee. This committee was charged with developing the GOG Surgical Procedures manual as a method of standardizing the surgery for patients on GOG protocols. The manual has been maintained and revised as necessary by the subsequent chairmen and members. The second function of the committee is to determine eligibility standards for GOG protocols. The committee also provides quality control for both surgery and eligibility.

Dr. Robert Park succeeded Dr. Major as chair. Dr. Major went on to chair the Sarcoma Committee. Dr. Park served as chair until 1983 when Dr. William Hoskins became chair. Dr. Park went to serve a long tenure as the group chairman.

In July 1984, Dr. Harrison Ball succeeded Dr. Hoskins who went to chair the Ovarian Committee. It was during Dr. Ball's tenure that the committee name was changed to the Gynecologic Oncology Committee. Also during this term, Dr. Ball oversaw the formation of the Laparoscopy Subcommittee chaired by Dr. John Shleearth. This subcommittee facilitated the incorporation of Laparoscopy into GOG protocols and the group as a whole.

Dr. Ball was appointed to the chair of the Corpus Committee in February 1995 and Dr. Charles Whitney became the chairman of the Gynecologic Oncology Committee. Dr. Nicola Spirto was named Co-Chair in January 2004 and Chair in 2010.

Other notable former members of the committee include Dr. William Creasman, Dr. Donald Gallup, Paul Morrow and many others.

Medical Oncology Committee

The Primary responsibility of this committee is to define the optimal use of commercially available chemotherapeutic agents and supportive care medications being employed in the conduct of GOG protocols. The committee is charged with defining optimal

standard management approaches involving the administration of chemotherapy in protocols in the GOG protocols. The committee also responds to issues regarding unique toxicities experienced by patients participating in clinical trials and defines how new commercially available chemotherapeutic and supportive medications should be employed in our study population. The committee in addition, formally evaluates all new protocol concepts that include chemotherapy for any issues or concerns regarding toxicity. These activities have resulted in several recommendations and implementations. The Committee has defined required frequency and renal function parameters for recalculating carboplatin AUC dosing. They have developed guidelines for the use of erythropoietin in GOG trials, developed suggested standard steroid prophylaxis for paclitaxel associated hypersensitivity reaction for weekly dosing schedules and evaluated complications associated with Bevacizumab. Dose reduction versus maintenance of dose intensity employing the use of bone marrow colony stimulating factors have been evaluated. These issues relate to the quality assurance activities of the committee.

The GOG chemotherapy manual as developed by the Medical Oncology Committee serves as the resource for dose frequency as well as toxicity issues involving chemotherapy and GOG trials. This establishes standard statements regarding the use of commercially available chemotherapeutic agents.

The Committee regularly includes presentations at the semi-annual meetings on GOG relevant protocol specific topics such as; standards for creatinine clearance determination; safety and monitoring of patients on anti-vascular agents; Carboplatin hypersensitivity reactions; IP Platinum agents and the inhibition of angiogenesis; and assessment of renal function in cancer patients receiving chemotherapy.

They Gynecologic Oncology Group (GOG) since its inception relied on developing a close relationship with the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI). Under prompting from external NCI advisors such as Paul Calabresi and John Ultmann, the first two directors of CTEP (Stephen K. Carter from 1970-1975, and Franco Muggia from 1975-1979) ensured close communication with the NCI and involvement of medical oncologists in generating protocols containing emerging chemotherapeutic drugs. Robert Slayton (with a strong interest in the chemosensitive germ cell tumors), Johannes Blom, H. James Wallace, George Omura and Tate Thigpen were among the first medical oncologists to participate in leading protocols containing chemotherapy. William McGuire, a member of CTEP with experience in the NCI intramural program, provided invaluable guidance to the GOG to structure phase I and I studies with new anticancer drugs. In 1977, the group chair, George Lewis and Tate Thigpen, with the biostatistical input of John Blessing launched master protocol #26. James Arseneau, who had emerged from the NCI intramural program, and Tate Thigpen were involved

in generating a steady stream of phase II studies with new drugs under the rubric of the Medical Oncology Committee. For example, in the 1989 launch of cisplatin by CTEP, Tate Thigpen prominently represented the GOG in describing the drug's key role in ovarian and cervical cancers, as well as in germ cell tumors. This became a traditional role in subsequent drug launches by NCI or industry.

The GOG became a major contributor in the clinical investigation of other emerging new drugs as attested by publications in Cancer Treatment Reports and other journals. Hy Muss joined the group in the early 1980s and became chair of the Committee-quality control of drug treatments had become a major responsibility and by 1989, when he left the group to work in breast cancer, he had completed work on the Chemotherapy manual that for years remained the backbone for protocol design, until adoption of protocol shells and web-based drug statements. By then, a number of medical oncologists had joined the group contributing expertise in key areas of therapeutics: Robert Young (staging and treatment of early state ovarian cancer), Stephen Williams (germ cell tumors), Bill McGuire (integration of paclitaxel in ovarian cancer), Franco Muggia (anthracycline cardiotoxicity, drug delivery), Gini Fleming (chemotherapy of endometrial cancer), David Spriggs (drug pharmacology), Robert Ozols (optimizing carboplatin in ovarian cancer), David Alberts (intraperitoneal therapy). In 1993, Developmental Therapeutics was placed under the leadership of Bill McGuire and Michael Bookman, whereas Medical Oncology – emphasizing treatment safety and quality control functions – continued under the leadership of Franco Muggia and James Arseneau. Maurie Markman became the chair of this committee in 1999, and contributed to help delineate carboplatin hypersensitivity reactions, appropriate use of cytokines, issues of dose-scheduling, and assessment and protection of neuropathy following taxanes and platinum. Franco Muggia and Paul Sabbatini are the current chair and co-chair respectively. In addition to reviewing pertinent items at each semi-annual meeting there is one or more CME presentations on relevant topics. Recently for instance considerable discussion concerning creatine clearance, weight and chemotherapy dosage has been thoroughly reviewed and recommendations made to the group.

In summary, Medical Oncology spurred the successful involvement of GOG in clinical drug development protocols – now carried forward under the Developmental Therapeutics Committee. Together with other modality committees, it tackles key issues concerning treatment safety, appropriateness of supportive care measures, and quality control.

Nursing Committee

The nursing Committee has been an active committee in the GOG since 1977. From the inception of an informal committee in 1977, under the leadership of Debby Smith, the committee has grown into a separate Modality Committee. Under the leadership of Terry

Chamorro, the Nursing Committee was authorized as a subcommittee of the Quality Control Committee. In 1994, the Nursing Committee was established as a separate Modality Committee under the leadership of Sharon Kelly. Leadership of the committee included four GOG nurses:

1977 – 1979	Debby Smith , UCLA Medical Center
1979 – 1983	Terry Chamorro , UCLA Medical Center
1983 – 1997	Sharon Kelly , Tufts-New England Medical Center
1997 – present	Susan Nolte , Abington Memorial Hospital

Initially, the Nursing Committee was a subcommittee of the Quality Control Committee, with a primary focus on quality control as related to the process of GOG study development and execution. Specifically, early efforts were directed at 1.) development of a nursing manual defining acceptable nursing procedures related to GOG protocols; 2.) participating as a review mechanism for the proper definition of the nursing role in each GOG study; 3.) reviewing all studies from a nursing perspective to ensure compliance with protocol requirements; 4.) educating GOG nurses on topics related to GOG protocols to ensure compliance with protocol requirements.

Currently, the Nursing Committee functions as a modality committee within the GOG. As nurses with expertise in the subspecialty of gynecologic oncology and actively involved in direct patient care and research activities, the members of the GOG Nursing Committee are in a unique position to facilitate quality nursing care. Members are included in protocol development from the concept phase through activation and implementation and are in an optimal position to provide nursing input to all GOG activities.

Committee membership has grown from the inception of the committee from ten nurses to twenty-five nurses. Nurses are represented from diverse geographic areas and clinical sites.

Efforts of the committee have included the development of a nursing conceptual framework, nursing manual, patient education materials, numerous educational presentations relevant to GOG protocols, nursing research related activities, and the development and assignment of a “nurse contact” to all GOG studies. Nurses are also active members on all site and modality committees.

Conceptual Framework

In 1990, following a presentation by Fran Lewis, RN, PhD, the committee developed a conceptual framework. The philosophy of the Nursing Committee, that prevails to this day is to “assist the woman and her family in the integration of the consequences and contingencies of the illness experience into their daily lives. This is accomplished by empowering the woman and her family with necessary skills and resources to maintain or improve quality of life. Empowerment includes instilling hope, reducing symptom

distress, enhancing knowledge and understanding, fostering communication skills, promoting sexual functioning and intimacy, social support and a self-care environment. Positive coping behaviors are enhanced by the rechanneling of negative emotions, misconceptions and cognitive beliefs.”

Nursing Manual

The Nursing Manual Subcommittee began work in 1989 for the purpose of developing nursing procedure guidelines related to GOG protocols. Early policies that were developed included guidelines for implantable right atrial catheters, nursing care of patients receiving intraperitoneal chromic phosphate, management of allergic and anaphylactic reactions, nursing care of patients receiving radiation implants, and intraperitoneal chemotherapy administration.

The Nursing Manual has been reviewed and revised on a regular basis. New policies have been added as relevant to GOG protocols. Patient education materials were added as a resource for GOG nurses to enhance patient education. In recent years, web based patient education materials were added.

Nursing Education

The Nursing Education Subcommittee has provided many educational sessions too numerous to list. A combined Nursing and Data Management educational session is conducted annually, also (Table).

In addition to educational presentations, several educational train-

ing sessions have been conducted related to GOG trials. For example, in the 1980's a workshop was conducted on the administration of BCG. In the 1990's a workshop on the use of the vaginal sound (an instrument designed to measure vaginal length), and the submission of tissue for the translational requirements of GOG trials were conducted. More recently, the Nursing Committee has been instrumental in the training requirements for a GOG trial evaluating lymphedema. Hands-on lymphedema training workshops are currently ongoing for this study. Protocol specific workshops and presentations are also conducted on a regular basis.

Research

As a modality committee, the Nursing Committee does not formally conduct research studies. However, in the 1980s, the committee developed a study to evaluate chemotherapy drug extravasation, and developed an instrument to record the degree and extent of extravasation. Other early research efforts were directed to the effect of alopecia on body image, management of nausea and vomiting, and evaluation and measurement of Cisplatin induced peripheral neuropathy. More recently the Nursing Committee supported a nurse scientist's implementation of a GOG study titled "GOG – 0259 Nurse-delivered Write symptoms vs self-directed Write symptoms vs care as usual for optimal symptom management for women with recurrent ovarian, fallopian tube, or primary peritoneal cancer". This study was a result of an ONS multi-site research training program that was conducted in 2006. A GOG team including Dr Heidi Donovan (nurse scientist) and GOG mentors participated in this program. Over the course of two years, Dr Donovan was successful in developing a GOG trial

Table. A representative list of some of the educational presentations.

DATE	TOPIC	PRESENTER
1990	<i>Development of Nursing Research</i>	Fran Lewis, RN, PhD
1990	<i>Peripheral Neuropathies Associated with Cisplatin</i>	Lois Almadrones, RN, MSN
1992	<i>Nursing Implications of Autologous Bone Marrow Transplant</i>	Constance Engleking, RN, MSN
1992	<i>Utilization of Nursing Research</i>	Deborah McGuire, RN, PhD
1994	<i>HIV and Cervical Cancer – Counseling and Testing</i>	Mitch Maimen, MD
1996	<i>Screening for Ovarian Cancer</i>	Susan Nolte, RN, PhD
1998	<i>Issues in Cancer Genetic Counseling and Testing</i>	Karen Johnson, MS
1999	<i>Quality of Life in Gynecological Cancer Survivors</i>	Lari Wenzel, PhD
2000	<i>Gene Therapy and Nursing Implications</i>	Jacalyn Gano, RN, MSN
2001	<i>Existential Aspects of Cancer Clinical Trials</i>	Karen Iseminger, RN, PhD
2003	<i>Overview of Complimentary Therapy</i>	Georgia Decker, RN
2004	<i>Update on HPV and Cervical Cancer Screening</i>	Mary Rubin, RN, PhD
2005	<i>Targeting VEGF and EGFR pathways in cancer</i>	Karen Oleszewski, RN, MSN
2006	<i>Intraperitoneal chemotherapy: rationale and nursing considerations</i>	Eliza Eldermire, RN, BSN
2008	<i>Systematic symptom assessment: implications for research and clinical practice</i>	Heidi Donovan, PhD RN
2009	<i>Venous thrombo-embolism prophylaxis, treatment and nursing management</i>	Sarah Bernstein, RN, MSN
2010	<i>Symptom experience of women with recurrent ovarian cancer</i>	Heidi Donovan, PhD RN
2012	<i>Biosafety issues for clinical trials</i>	Tony Reid, MD; Ronald Alvarez, MD; David Cohn, MD
2013	<i>The role of PARP inhibitors in the treatment of gynecologic malignancies</i>	Alice Chen, MD

and securing NIH funding to conduct the study through the GOG. The study exceeded the target enrollment timelines and was completed in 2012. This model was extremely successful in supporting the implementation of nursing research in the GOG and providing a mechanism to increase the participation of nurse scientists in GOG activities.

To facilitate the utilization of nursing research, the Committee presents research critiques. The purpose of research critiques is to assist nurses in critically evaluating nursing research on topics that have specific relevance to GOG trials and to promote evidence-based practice. Examples of research critiques include: survival in familial BRCA1/2 associated epithelial cancer; the experience of women receiving brachytherapy for gynecologic cancer; quality of life in patients coping with gynecologic cancer and their spouses; the trajectory of fatigue in adult patients with breast and ovarian cancer; and risks and benefits of estrogen plus progestin in health postmenopausal women; learning needs of nurses who care for persons with cancer; and neuropathy tools for measuring chemotherapy-induced neuropathy, psychological issues in ovarian cancer.

GOG Involvement

The Nursing Committee actively participates in quality control activities and protocol design through several mechanisms; nurse contact; review of concepts/protocols at GOG meetings; and membership on site and modality committees. The specific purpose of these activities is to provide important nursing input to all active and prospective GOG studies.

The nurse contact is responsible for prospectively reviewing the entire protocol and identifying, from a nursing perspective, any errors, omissions or inconsistencies that might affect patient eligibility, patient registration, safety protocol compliance and completion. After a study is activated, the nurse contact is available for nursing-related questions regarding study procedures. For especially complex studies, the nurse contact may give a formal presentation at GOG meetings to specifically address nursing issues. More recently, the nurse contact role has been expanded to include travel to international sites to promote protocol accrual and study consistency. For example, in 2008, HeeSun Kim-Suh (University of Oklahoma), nurse contact for GOG 218, and Jacalyn Gano (MD Anderson), nurse contact for GOG 213, traveled to Japan and Korea to give nursing presentation on these studies.

An important activity of the Nursing Committee is the responsibility to review concepts/protocols designated to require nursing input. On average, seventy concepts/protocols are reviewed annually. After discussion by the Nursing Committee, any suggestions are discussed at the Protocol Committee, and necessary action is taken based on nursing suggestions.

Nurses are also represented on all site and modality committees,

where as a voting member, they provide valuable nursing input to all committee activities. The nurse on these committees reports relevant nursing issues back to the Nursing Committee. In addition, in 2004, the GOG Board of Directors elected to have a permanent nurse position on the Board of Directors, resulting in the tenure of four nurses appointed to the Board of Directors.

Publications

Several efforts of the Nursing Committee have resulted in publications. Publications have included papers on the evaluation of functional status and peripheral neuropathy (Lois Almadrones); quality of life in ovarian cancer patients (Janet Walczak); the development and reliability of the vaginal sound (Deb Watkins-Bruner); alopecia and body image (Susan Nolte); and a survey of research priorities in gynecologic oncology nursing (Janet Walczak). In addition, nurses contribute as authors on GOG manuscripts (Nancy Fusco, Jennifer Loud). The completion of GOG 0259 will result in a significant number of publications that will include several GOG nurses.

Summary

The GOG Nursing Committee started in 1977 as an informal group of gynecology oncology nurses, and has grown into a strong and active modality committee. Members have input to all GOG activities, and are voting members on all site and modality committees, as well as the GOG Board of Directors. GOG nurses provide scientific input to the development of new protocols, and provide quality control to the implementation of all GOG trials.

Pathology Committee

The Committee's primary responsibility is quality control and quality assurance of the pathological diagnosis of specimens submitted to the GOG. Although the members of this committee do not design or manage protocols, they are involved as members of other committees in protocol design and management responsibility. This is particularly true in which the primary or secondary pathological or translational end point is an important objective of the protocol. The pathology committee also has responsibilities to select tissue specimens for the virtual tissue bank protocols, to maintain the pathology manual for the GOG, to advise the GOG tumor bank, to provide a forum for the training and continuing education of GOG pathologists who participate in the quality control review and to provide a pool of trained pathologists to serve as pathologists and co-investigators of GOG protocols.

The primary responsibility of the committee is quality control and quality assurance. Retrospective review of all pathology reports and representative tissue slides of surgical and cytological specimens are undertaken by the committee. Two pathologists from GOG member institutions work together at microscopes during semi-annual meetings to review the pathological diagnosis and staging to confirm eligibility. Cases lacking either complete documentation of submission of required materials are identified and

the PI notified with a request for additional information of tissue. Cases lacking consensus agreement of pathological diagnosis are referred to the referee pathologist for a final determination of eligibility.

The prospective quality assurance process has two components, the first being the participation of trained reviewing pathologists in the design and monitoring of the pathology component of the protocols. The second component is the ongoing review of the performance of pathology protocols that occurred during the semi-annual case review. Protocols yielding inconsistent pathology specimen submissions are quickly identified and protocols are modified or education material provided to member institutions to improve submission of protocol eligible pathology material. The many participating pathologists are also trained in the requirements of their pathology components of the GOG protocols during the case review and bring this knowledge and expertise back to their institutions.

The pathologists participating in the semi-annual case reviews also select cases for the virtual tissue bank. The virtual bank as it has been designated consists of a data file of individual tissue blocks that have been identified and characterized by pathologists during the quality control review as being the best example of submitted lesions. The patients enrolled on protocols that include the virtual tissue bank program provide informed consent for the use of these tissues. The tissue blocks are retained at the primary institution until request for specific research is used. This approach permits the prospective cataloguing of appropriately consented characterized tissue samples that can be retrieved for new translational research studies.

Members of the committee have also been instrumental in developing protocols to identify biomarkers or translational research. These have resulted in numerous publications. The Pathology committee has also been instrumental in revising standardizations for different pathological entities that have been accepted by national and international organizations. A good example of this is the grading for endometrial cancer and identification of the role of the squamous component of endometrial cancer.

In the early years when the GOG typically met in Buffalo, few pathologists attended the meetings. Four to six pathologists met outside of regular GOG meetings – usually at member institutions or on neutral territory (e.g. the O’Hara Hilton) - to review slides. Alexander Sedlis was the first Pathology Committee Chair and organizer of these reviews. Jason Norris was the first referee. These reviews took place on an ad hoc basis, sometimes after clinical trials were completed, and occasionally after a manuscript draft was written. One of the first reviews was of a trial of hormonal therapy in early state endometrial carcinoma. The poor agreements between the clinical and review diagnoses lead to the realization that all cases should be reviewed for the GOG to publish “clean” studies. “Review of all cases” remains the current GOG review model.

Until the mid 1980s, pathologists brought their own microscopes to reviews – frequently within strange wooden luggage or other contraptions, making them easily identifiable during registration. By the mid 1980s rental microscopes were provided for pathologists, and meeting moved from individual hotel rooms to larger and larger conference rooms.

Under the leadership of the Pathology Chairs (Alexander Miller, Richard Zaino) and the referees (Jason Norris, Stephen Silverberg) the scope of the pathology committee activities evolved during the late 70s and 80s from a review of pathologic diagnoses, to include a collegial forum of training of gynecologic pathologists. A Delphic system for slide review evolved where an experienced member would team up with a new member to review cases. Jason Norris or Stephen Silverberg (past and current referees), adjudicated disagreements. Besides reviewing thousands of GOG slides at a review, formal and informal presentations and discussions of gynecologic pathology always took place, often during dinner meetings. Once it became known that slides were being reviewed at meetings, the numbers of pathologists attending gradually increased to current numbers (approx. 40-70/meeting), keeping pace with the proliferation of GOG clinical trials in the 80s and 90s. This form of case review improved the diagnostic skills of all participants and provided an effective conduit for dissemination of GOG pathologic criteria to member laboratories. Discussion of problematic GOG protocol issues by this collegial and diverse group of gynecologic pathologists has influenced pathology practice worldwide – e.g. GOG definitions of primary peritoneal carcinoma have been adopted by the WHO, FIGO and ISGYP via dissemination of the GOG pathology manual and participation of GOG pathologists in these organizations.

As the scope of clinical activities of the GOG began to increasingly include, cancer prevention and control and translational research, in the 1990s, the pathology committee (Chairs, Richard Zaino, Jo Benda, William Rodgers) developed rapid and specialized pathologic review mechanisms and were key participants in the development of tissue banking, molecular diagnostic, and translational research protocols via their membership in the CPC, CEM, organ site and Tissue Utilization Subcommittees. As the number of studies and patients enrolled on GOG studies increased over time, the number of pathology reviews conducted at each GOG meeting has significantly increased. The number of pathology cases reviewed at recent meeting has exceeded 1,000 cases. Currently William Rodgers is the committee’s chair and Helen Michael is the co-chair. Six pathologists (G6) have and are reviewing a subject of GOG 210 specimens whose diagnoses have been associated with low reproducibility. This is extremely important as other prognostic factors for endometrial cancer must have an accurate diagnosis before data can be analyzed. In addition to path reviews the committee continues to evaluate topics of interest such as two grade designation for ovarian cancer with recommendations being made to the group.

Committee on Radiation Oncology

This committee pertains to all matters in regards to radiation oncology. The committee is charged with insuring consistency and appropriateness of radiation therapy to patients on GOG protocols as well as compliance with those protocols. The committee reviews radiation therapy treatment details including dose, time, volumes, ports, fraction size for all patients receiving radiation therapy on GOG protocols. This evaluation becomes part of the institution's data for assessment of its performance as a GOG group member. Each of these parameters are evaluated and scored as meeting protocol requirements, minor deviations or major deviations. This activity serves not only as a quality assurance function but also as an educational function. The committee also maintains and periodically updates a radiation oncology protocol procedure manual. The committee also has representation from the Radiological Physics Center (RPC) in Houston and interfaces with this organization as part of its QA role.

The committee is instrumental in evaluating and adopting new techniques in radiation therapy as they become available. Recently, for instance, is the introduction of high dose (HDR) intra cavitory technique in protocols involving cervical cancer. The committee working with the RPC developed a certification process in which institutions using HDR were required to demonstrate competency.

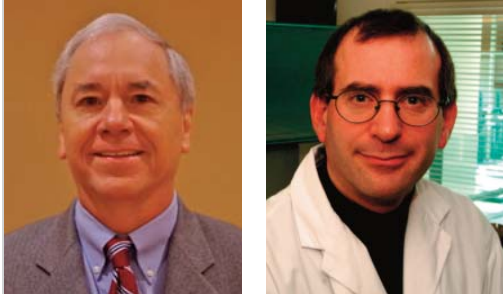
Quality control and compliance is a major activity of the committee. One important function of the committee is film and dosimetry review carried out on all cases entered into RT containing GOG protocols. Web-based review methodologies have been implemented to further enhance the timeliness and ease of the quality assurance activities.

Committee members participate in the deliberation of all multidisciplinary site committees. This allows radiation oncology members to propose concepts for consideration by the site committees and in many instances the committee members have served as study chair or co-chair for the studies involving RT particularly in study design, directing the ongoing evaluation of case entry material, assisting in analysis of study results, and participating in the publication of those results.

The Radiation Therapy Committee is responsible for the radiation therapy procedure manual which is used to assist in protocol compliance. New procedures are added to the manual as appropriate. These procedures include intensive, modulated RT (IMRT), brachytherapy techniques and imaging based brachytherapy.

Dr. Ivy Petersen serves as chair of Radiation Oncology committee. In addition to the radiologic oncology reviews educational sessions are also held during the committee's meetings.

Rare Tumor Committee



David M. Gershenson, MD, and Allan L. Covens, MD

Introduction

The GOG Rare Tumor Committee is among the newest committees of the cooperative group. It was initially established as a Working Group in 2005, facilitated by the advocacy of Dr. Ted Trimble, who was the Cancer Therapy Evaluation Program's (CTEP) GOG liaison at the time, and with the support of Dr. Philip DiSaia, GOG Group Chair. Subsequently, it became a full committee based on the group leadership's recognition of the increasing importance of rare gynecologic tumor research.

With the emergence of new information about the molecular profile and clinical behavior of various rare subtypes of ovarian cancer and other gynecologic malignancies over the past few years, it was appropriate to create a GOG committee focused on these neoplasms. By understanding the nuances of these tumors on the road to developing more effective therapies through hypothesis-driven research, it was considered quite possible that we would also gain a better grasp of the genes and pathways involved in the pathogenesis of more common tumor types. The GOG Rare Tumor Working Group held its inaugural meeting in July 2005. The committee was established to develop and conduct studies of rare gynecologic cancers (retrospective cohort, pilot, phase II, randomized phase II and III) that will enhance our knowledge base and improve patient outcomes.

Prior to the establishment of this committee, all ovarian cancer subtypes were treated on the same phase II and III clinical trials. To date, a number of phase II, randomized phase II, and randomized phase III trials have been activated specifically for women with rare ovarian cancer subtypes (see below). This research strategy has subsequently been endorsed by a Gynecologic Cancer InterGroup (GCIG) International Ovarian Cancer Consensus Conference in 2010 ¹ and a National Cancer Institute (NCI) Clinical Trials Planning Meeting in 2011 (not yet published).

At the committee's inaugural meeting in July 2005, 15 members were present. The meeting agenda focused on a brainstorming session to begin to formulate a consensus around rare gynecologic tumor research. Dr. Ted Trimble discussed the fact that CTEP was very supportive of the development of clinical trials of rare gynecologic cancers. However, he emphasized that the depth of CTEP's commitment to this field was unknown. The group was reminded that at a GOG site visit several years previously, one of the reviewers criticized the group for investing precious resources in the study of rare tumors. Dr. Trimble reassured the group that this perspective was no longer representative of CTEP's philosophy.

At the meeting, Dr. Nick Reed updated the group on the evolution of the GCIG Rare Tumor Working Group and the EORTC's studies of rare gynecologic cancers. In addition, the following issues were discussed: 1) There was a consensus that, to be successful in this area, GOG would need to commit leadership support and sufficient resources (pathology support, biostatistical support, translational science support, etc.) to conduct the mission; 2) It was likely that the establishment of a Rare Tumor Committee would meet with some resistance within the group as it advocated for additional resources, but those present were optimistic about the ultimate outcome; 3) The group consensus was that patient advocacy groups could be helpful in promoting rare gynecologic cancer research; 4) The group noted that partnering with industry would also be a key factor in the committee's success; 5) Much of the meeting was devoted to defining a "rare gynecologic cancer." There was a consensus that there is no perfect or universal definition. There was, however, a consensus that the group should initially focus on a relatively small number of specific types; 6) The group agreed that translational objectives should be included in virtually all of the committee's trials; and 7) The group agreed that there was an opportunity to partner with the GCIG and individual domestic and foreign groups to conduct intergroup and international studies to maximize patient accrual.

At its initial meeting, the group reviewed a comprehensive list of rare gynecologic malignancies and agreed to focus initially on the following tumor types:

- Ovarian sex cord-stromal tumors
- Malignant ovarian germ cell tumors
- Mucinous ovarian cancers
- Clear cell ovarian cancers
- Low-grade serous ovarian cancers
- Carcinosarcoma of the ovary
- Small cell carcinomas of the ovary and cervix
- Endometrial stromal sarcoma
- Uterine papillary serous carcinoma.

This list was subsequently modified.

Significant Accomplishments

Significant accomplishments of the GOG Rare Tumor Committee thus far include the following: 1) Establishment of a working group that then transitioned to becoming a full committee focused on rare gynecologic malignancies; 2) Initial focus on rare ovarian tumors, with emphasis on hypothesis-driven research with novel agents, innovative statistical design, and translational research components (*GOG 0239*, *GOG 0241*, *GOG 0251*, *GOG 0254*, *GOG 0264*, *GOG 0268*, *GOG 0281*); 3) Development of international collaborations to enhance patient accrual for rare tumor studies (*GOG 0241*, *GOG 0268*, *GOG 0281*, *RTM1205*); 4) Activation of the RFP mechanism for protocol concept submission in July 2008; 5) Addition of patient-advocates to the committee; and 6) Establishing protocols for rare tumors, which has resulted in an evolution of excluding them from eligibility for broad phase II and III trials that have historically included all tumor subtypes, thereby potentially eliminating exposure to ineffective therapy.

Mentorship

The Rare Tumor Committee includes a combination of both senior and junior investigators. On a number of trials, senior team members have or are mentoring junior members. Examples include *GOG 0239* (Drs. Gershenson/Birrer and Farley), *GOG 0241* (Drs. Gershenson and Frumovitz), *GOG 0251* (Drs. Gershenson and Brown), *GOG 0264* (Drs. Gershenson and Brown), *GOG 0268* (Drs. Birrer/Gershenson and Farley), *GOG 0281* (Drs. Gershenson and Gourley/Farley), and *GOG 0283* (Drs. Aghajanian and Hyman).

Clinical Trials of the Rare Tumor Committee

Since 2007, the Rare Tumor Committee has activated seven clinical trials of rare tumors. Another trial—*GOG 0187*—was inherited from the Ovarian Committee and recently completed accrual. In addition, 2 clinical trials are in the latter stages of development, and 2 have been approved by the Protocol Development Committee and are currently in the concept stage. The following is a brief summary of the GOG Rare Tumor Committee portfolio:

GOG 0187: “A phase II study of paclitaxel for ovarian stromal tumors as second-line therapy” (Van Le). At the time that this trial was conceived, information from both retrospective and prospective studies employing the most common chemotherapy regimens (cisplatin, doxorubicin, and cyclophosphamide; vinblastine, bleomycin, and cisplatin; or bleomycin, etoposide, and cisplatin) indicated substantial toxicity and limited durable activity²⁻⁵. Thus, in the search for novel agents with enhanced activity, the study of paclitaxel was a reasonable strategy. This trial was opened to patient entry in 2000 and closed to patient entry in 2013. The primary objective was to estimate the probability of clinical response and toxicity of paclitaxel as second-line chemotherapy in patients with measurable disease. Thirty-one patients were enrolled in this study. Analysis is ongoing.

GOG 0239: “A phase II trial of AZD6244 (NSC# 748727, IND# 77782) in women with recurrent low-grade serous carcinoma of the ovary or peritoneum” (Farley). Low-grade serous carcinoma of the ovary or peritoneum may arise de novo or following an original diagnosis of serous tumor of low malignant potential. Women with this subtype are diagnosed at a younger age on average and have a significantly longer overall survival than women with high-grade serous carcinoma⁶. It is relatively not as sensitive to chemotherapy as high-grade ovarian subtypes, and hormonal therapy has demonstrated activity in approximately 10% of patients with recurrent disease^{7,8}. However, with either chemotherapy or hormonal therapy, the stable disease rate is over 60%. Nevertheless, a continued search for novel agents is of great importance. Because the MAPK pathway appears to be prominent in the pathogenesis of low-grade serous carcinomas, with KRAS mutations in the range of 30-40% and BRAF mutations of about 5%, investigators have focused on trials using MEK inhibitors for this subtype^{9,10}. *GOG 0239* was opened to patient entry in 2007 and closed to new patient entry in 2009¹¹. The primary objective of this trial was objective tumor response and toxicity. Fifty-two patients were enrolled in this study and treated with selumetinib 50 mg twice daily, orally, until progression. Eight (15%) patients had an objective response to treatment, with one complete response and seven partial responses. 34 (65%) patients had stable disease. Grade 4 toxicities were cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient included gastrointestinal¹³, dermatological (nine), metabolic (seven), fatigue (six), anemia (four), pain (four), constitutional (three), and cardiac events (two). The median progression-free survival was 11.0 months, and median overall survival had not been reached at the time of the report. Formalin-fixed, paraffin-embedded tissue with sufficient DNA was available for mutational analyses for BRAF and KRAS in 34 patients. Two (6%) had BRAF mutations, and 14 (41%) had KRAS mutations. Unfortunately, there was no correlation between response and mutational status. The findings of this study have led to a replacement study—*GOG 0281* (see below).

GOG 0241: “A GCIG InterGroup multicenter phase III trial of open label carboplatin and paclitaxel +/- NCI-supplied agent: bevacizumab (NSC #704865, IND# 113912) compared with oxaliplatin and capecitabine +/- bevacizumab as first-line chemotherapy in patients with mucinous epithelial ovarian or fallopian tube cancer (mEOC)” (Gershenson). Women with advanced stage mucinous carcinomas of the ovary have a much shorter progression-free and overall survival than those with advanced stage serous carcinomas and are more likely to fail adjuvant platinum-based chemotherapy regimens^{12,13}. In addition to differences in clinical behavior, laboratory data support molecular differences between the different epithelial subtypes of ovarian cancer¹⁴. For this trial, the investigators hypothesized that a colorectal cancer-type therapy may offer a better outcome for patients with mucinous carcinomas of the ovary. Thus, this trial was designed to determine if oxaliplatin and capecitabine +/- bevacizumab improves progression-free and overall survival when compared to carboplatin and paclitaxel +/- bevacizumab in women with advanced stage mucinous ovarian cancer. This is an international trial led by investigators in the United Kingdom. It was opened to patient entry in 2010 in the United States, and to date 16 patients have been accrued in the United States. In the UK, accrual has been greater—in the range of 25 patients—but has still lagged behind projected targets. The primary objective of this trial is 1) to determine if capecitabine and oxaliplatin reduces the death rate compared to carboplatin and paclitaxel, and 2) to determine if bevacizumab reduces the death rate compared to no bevacizumab. Because the patient accrual in both the US and UK is significantly slower than predicted (which is principally related to the extreme rarity of this subtype), this trial is currently being considered for premature closure. In the US, CTEP is currently considering whether it is feasible to convert the trial to a phase II design, and that decision is pending.

GOG 0251: “A phase II trial of NCI-supplied agent: bevacizumab (NSC# 704865, IND# 7921) for recurrent sex cord-stromal tumors of the ovary” (Brown). Ovarian sex cord-stromal tumors are rare, accounting for only 5-7% of all ovarian malignancies. Surgery remains the cornerstone of initial treatment. However, effective systemic treatment remains relatively ineffective^{2-5,15}. Although both cytotoxic chemotherapy and hormonal therapy have modest activity, a search for more effective treatments is definitely warranted. Angiogenesis appears to be an important mechanism in the development of sex cord-stromal tumors of the ovary. Thus, this study proposed to evaluate bevacizumab as a biologic agent in patients with this rare subtype. The trial opened to patient entry in 2008 and closed to patient entry in 2011¹⁶. The primary objective was to estimate the frequency of objective response in patients with recurrent ovarian sex cord-stromal tumors. Thirty-six patients were enrolled in this study. Six patients (16.7%) had partial response, 28 patients (77.8%) had stable disease, and two (5.6%) had progressive disease. The median progression-free survival was 9.3 months. The authors thus concluded that bevacizumab has activity in the treatment of recurrent sex cord-stromal tumors of the ovary

with acceptable toxicity.

GOG 0254: “A phase II evaluation of SU11248 (Sunitinib Malate) in the treatment of persistent or recurrent clear cell ovarian carcinoma” (Chan). Patients with advanced stage or recurrent clear cell carcinoma appear to have a worse prognosis than those with serous carcinomas^{13,17,18}. Ovarian clear cell carcinomas have molecular similarities to renal cell carcinoma, with angiogenesis playing a central role in both tumor types^{19,20}. Thus, novel agents that are active in metastatic renal cell carcinoma may have activity in ovarian clear cell carcinoma. This trial was opened to patient entry in 2010 and closed to patient entry in 2013. The primary objective of this trial was to evaluate the response rate and toxicity of sunitinib malate, a highly potent, selective tyrosine kinase inhibitor, in patients with persistent or recurrent clear cell ovarian carcinoma. Thirty-five patients were enrolled in this trial. Analysis is ongoing.

GOG 0264: “A randomized phase II trial of paclitaxel and carboplatin vs. bleomycin, etoposide, and cisplatin for newly diagnosed advanced stage and recurrent chemo-naïve sex cord-stromal tumors of the ovary” (Brown). The optimal first-line chemotherapy regimen for ovarian sex cord-stromal tumors is unknown. Although BEP has been the most common regimen, it is associated with considerable toxicity and a significant risk of recurrence^{4,5}. More recently, taxane-based therapy has shown activity in this tumor type¹⁵. This trial was opened to patient entry in 2010. The primary objective is to assess the activity of paclitaxel and carboplatin with respect to progression-free survival (using bleomycin, etoposide, and cisplatin (BEP) as a reference) for newly diagnosed advanced or recurrent chemo-naïve ovarian sex cord-stromal tumors. To date, 17 patients have been enrolled in this trial.

GOG 0268: “A phase II evaluation of Temsirolimus (CCI-779) (NSC# 683864, IND# 61010) in combination with carboplatin and paclitaxel followed by Temsirolimus consolidation as first-line therapy in the treatment of clear cell carcinoma of the ovary” (Farley). Most studies have shown that patients with advanced stage clear cell carcinoma of the ovary have a worse prognosis than those with advanced stage serous carcinomas^{13,17,18}. It is widely thought that this difference is attributable to the lack of effectiveness of conventional chemotherapy. Over the past few years, multiple investigations have demonstrated that approximately 50% of ovarian clear cell carcinomas may have dysregulation of the PI3K/AKT/mTOR pathway²⁰. Thus, mTOR inhibitors may have activity in this particular subtype²¹. The mTOR inhibitor, Temsirolimus, is being employed in this trial concomitantly with chemotherapy and then as single-agent maintenance therapy. This study was opened to patient entry in 2010. To date, 86 patients have been enrolled. The target accrual is 90 patients. The primary objective of this trial is to assess the activity of the study regimen as measured by the proportion of patients who are alive and progression-free for at least 12 months after study entry. In addition,

this study will compare the outcome of patients from the US and Japan.

E2607: “A phase II trial of Dasatinib in KIT-positive patients with unresectable locally advanced or stage IV mucosal acral and vulvovaginal melanomas” (Leitao). This trial is an ECOG study with a GOG cohort of patients with vulvovaginal melanoma. To date, four of the planned 12 patients with vulvovaginal melanoma have been enrolled.

Clinical Trials in Development. Two clinical trials of the GOG Rare Tumor Committee are in the latter stages of development, and three further concepts have been approved and are awaiting further disposition. *GOG 0281*, “A randomized phase II/III study to assess the efficacy of Trametinib (GSK1120212) in patients with recurrent or progressive low-grade serous ovarian cancer or peritoneal cancer (Gershenson),” is a follow-up study to *GOG 0239* and randomizes patients between standard of care (which includes any of five choices—three chemotherapy agents and two hormonal agents) and Trametinib. In addition, patients on standard of care who progress are permitted to crossover to the investigational agent. This study is estimated to open to patient entry in late 2013. It is an international trial with colleagues in the UK, and the target accrual is 250 patients. The primary objective is progression-free survival, and the study includes several translational endpoints as well.

GOG 0283: “A phase II trial of DCTD-sponsored Dasatinib (NSC #73969) in recurrent/persistent ovary, fallopian tube, primary peritoneal, endometrial, or endometriosis-associated clear cell carcinoma characterized for the retention or loss of BAF250a expression (Hyman),” is also in the latter stages of development. This trial will replace *GOG 0254* as the first priority for women with recurrent clear cell carcinoma, and, as noted, includes multiple organ sites.

Three concepts have recently been approved by the Rare Tumor Committee and the GOG Protocol Development Committee and are awaiting further action. These include RTM1205, “A 3-cohort study (low-, intermediate-, and high risk) of patients with malignant germ cell tumors,” RTM1313, “A randomized phase II trial carboplatin/paclitaxel versus Trametinib monotherapy in patients with stage III and IV low-grade serous carcinoma of the ovary or peritoneum (Nickles Fader),” and RTM1303, “A randomized phase II study of XL-184 in women with recurrent clear cell carcinoma of the ovary, fallopian tube, or peritoneum (Farley).” RTM1205 is primarily being developed in collaboration with international investigators and will be led by the Children’s Oncology Group.

Future Directions

A number of the Rare Tumor Committee’s current and future trials have the real potential to be transformational and practice chang-

ing. For example, recurrent low-grade serous carcinoma of the ovary/peritoneum is a somewhat indolent disease but is relatively resistant to conventional systemic therapy (response rate to chemotherapy, <5%, and hormonal therapy, ~10%). The apparent improved response rate of 15% and PFS of 11 months in GOG 0239 is leading into a randomized phase II/III study comparing another MEK inhibitor with standard therapy. This trial definitely has the potential for a new standard. Similarly, GOG 0268 could represent a step toward establishing a new standard therapy for patients with advanced stage clear cell carcinoma of the ovary. And finally, an international trial currently under development, RTM1205, and led by the Children’s Oncology Group (COG) for patients with low-risk, intermediate-risk, and high-risk malignant germ cell tumors, has the potential to develop new standard management strategies (surveillance for early-stage disease, compressed BEP for intermediate-risk disease, and aggressive, alternating chemotherapy for high-risk disease).

Future plans of the Rare Tumor Committee include the following: 1). Continuing to build on the foundation of early studies by conducting a series of trials for the most relevant tumor types; 2). Continuing to enhance awareness of the nature of rare tumor types; 3). Capitalizing on new discoveries of the molecular biology and clinical behavior of rare tumor types to drive the research agenda; 4). Continuing to utilize the RFP mechanism to vet new rare tumor concepts; 5). Establishing a robust, well-annotated rare tumor bank within the GOG infrastructure; 6). Establishing a better framework for international collaborations through the Gynecologic Cancer InterGroup and other international organizations; 7). Continuing to explore innovative trial designs and statistical analyses that make evaluation of small studies possible; and 8). Optimizing the use of ancillary studies of rare gynecologic tumors. Thus, development of separate trials for patients with rare ovarian cancer subtypes has most certainly addressed unmet clinical needs.

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The Unique Role of the Statistical Component



John A. Blessing, PhD, and Mark F. Brady, PhD

Overview

When the Gynecologic Oncology Group (GOG) was formed and funded in 1970, Dr. Myron Hreshchyshyn, the first Chairman, established the Statistical Office at Roswell Park Memorial Institute due to its proximity to his office at Buffalo General Hospital. The office was located within the Department of Statistics and was headed by Dr. Nelson Slack. In May of 1974, Dr. George Lewis of Thomas Jefferson University was elected to serve as the second Group Chairman, effective July, 1975. In September, 1974, in anticipation of the relocation of the Statistical Office to Philadelphia upon Dr. Lewis' Chairmanship, Dr. Slack was assigned to different responsibilities and Dr. John Blessing was hired to "run out the clock" for the next nine months. Due to fortuitous circumstances, Dr. Blessing was successful in maintaining the Statistical Office at Roswell Park. The GOG, its Statistical Office (currently named the GOG Statistical and Data Center (SDC)), and Roswell Park (now named Roswell Park Cancer Institute (RPCI)) have undergone dramatic changes. In 2011, the GOG agreed to integrate with two other successful NCI sponsored Cooperative Groups, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG). The new entity, called NRG Oncology, will be a component of the NCI National Clinical Trials Network (NCTN). The current GOG SDC will likewise unite with the corresponding NSABP and RTOG statistical and data management centers to form the NRG Oncology Statistical and Data Management Center (SDMC). The SDMC will be fully integrated, yet distributed across three sites. The Roswell Park component will continue to focus on NRG Oncology gynecologic investigations, The dedicated and talented staff of the SDC now exceeds 50 and remains at RPCI. This chapter will attempt to describe the growth, function, and unique innovations of this office. A timeline that underscores significant GOG/SDC milestones of progress is presented at the end of this chapter.

The Early Years: 1970-1974

It is important to briefly review the status of the GOG Statistical Office in the early years of its existence, in order to have a baseline to measure its progress in scope, procedures, and responsibilities. In September, 1974, there had been 21 protocols activated. Data were being submitted, but there were no quality control measures in place. Patient entry was accomplished via sealed envelopes maintained in the individual member institutions. All protocols had what was referred to as "source data" coded on one IBM punch card per patient. Most submitted data were merely being filed, with very few protocols having any clinical data computerized for analysis. There were pathology and radiotherapy "repositories" maintained in the Group Chairman's office. However, no eligibility or evaluation measures were in place. There were no formal Statistical Reports prepared for semi-annual GOG Meetings; rather type-written summaries were distributed for selected studies. The staff consisted of Dr. Slack, one programmer, one secretary, one data entry clerk, and one clinical data coordinator.

The Lewis Years: 1975-1989

During this period the GOG Statistical Office began to evolve into a viable, interactive participant in all areas of GOG activity. A philosophy of collaboration was initiated which remains a cornerstone of its success. New initiatives included the creation of the GOG Statistical Report which has subsequently been prepared for each semi-annual GOG Meeting, participation in the formation of the GOG Protocol Committee and the development of the corresponding Protocol Procedures Manual. To further enhance scientific interaction, a system of Study Chair reviews was implemented which featured a team approach to study conduct involving the Study Chair, Statistician, and Clinical Data Coordinator. The Statistical Office enhanced their experience in the investigation of gynecologic malignancies and their ability to make contributions to study design correspondingly increased. As the Statistical Office staff expanded, noteworthy advances in data management,

quality control, and analytic techniques were evident. Moreover, Dr. Lewis' belief in involving the Statistical Office in all facets of GOG activity enabled its members to make contributions beyond the statistical arena. Finally, during this period a great emphasis was placed upon modality review and quality control, greatly improving institutional performance, which in turn resulted in dramatic improvement in the quality of submitted data. This section will chronicle these advances.

In May of 1974, Dr. Hreshchyshyn hired Ms. Frances Valvo to serve as the first administrative employee to work in the Group Chairman's office. She had previously served as the Group Administrator for the Acute Leukemia Group B (ALGB), the forerunner of today's CALGB, whose Statistical Office had been located at RPMI until May, 1974. Coincidentally, Dr. Blessing and the Data Entry Clerk had also worked at ALGB. These three individuals decided to attempt to create a GOG Statistical Report for the January, 1975 GOG Meeting, using a format modified from their prior experience. Thus, with collegial support from their former ALGB colleagues, the first GOG Statistical Report was prepared.

The next year, GOG Protocol 15, chaired by Dr. George Omura, was approaching maturity. Dr. Omura agreed to collaborate in an attempt to have the Study Chair review the analytical data for each case prior to analysis. A prototype form, called an EVL, to be used for Study Chair review of data as it existed in the computer was developed. Dr. Omura's review enabled questions to be posed to him by the Clinical Data Coordinator, enabled him to raise questions which required follow-up, and provided a record of his review in the patient chart. This review was considered highly successful and innovative. As a result, it was prospectively employed for the next series of studies developed (Protocols 22, 23, 24, and 25.) For these studies, a team consisting of the Study Chair, Statistician, and Clinical Data Coordinator collaborated to determine the "protocol-specific" data which should be prospectively captured and computerized. The success of this expanded use of the Study Chair review provided the rationale for its continued routine use. This process has been modified slightly over the years, but it remains the cornerstone of the GOG quality control review process. In addition to the critical interaction among the collaborating team, it provides an integral component of GOG quality control; it also gives the Study Chair confidence in the data which he or she must ultimately publish.

When Dr. George Lewis became Group Chairman in 1975, he took several steps which had a dramatic impact on the GOG Statistical Office and the entire Group. The first of these was reorganization of the process of study development. Prior to 1975, studies were developed during the semi-annual GOG Meeting in sessions which included all attendees. The discussions were long and the process was cumbersome. Dr. Lewis named Dr. Tate Thigpen as Chairman of a reorganized version of the GOG Protocol Commit-

tee. The committee composition was structured to include the Chairperson of both Site and Modality Committees to facilitate interaction among the various entities which contributed to sound study design. Of equal importance was the inclusion of Dr. Blessing as a voting member. Dr. Thigpen had developed a strong working relationship with the Statistical Office and had an appreciation of the importance of involving it in study development from inception of a concept.

In order to create a set of guidelines for Protocol conduct, Drs. Thigpen and Blessing drafted a Protocol Procedures Manual, which provided time-frames for study development, content, execution, and authorship. This document was then presented to the Protocol Committee, modified and adopted. Over the ensuing years, it has been further modified and adapted to correspond to the evolution of GOG. The important developments have been formalized and incorporated as part of GOG requirements. For example, early involvement by the Statistical Office to determine feasibility and design issues is mandated. Also, Study Chair review of cases is an expectation for Study Chairs of all prospective studies.

The intimate involvement in the protocol development process mandated by the Protocol Procedures Manual fostered the blending of medical and statistical considerations. Greater familiarity with the medical nuances enabled the Statistical Office to make innovative contributions. The first example involved development of Phase II trials procedures. In 1976, the GOG decided to conduct Phase II trials in six recurrent disease categories: epithelial ovarian carcinoma, squamous cell carcinoma of the cervix, non-squamous carcinoma of the cervix, adenocarcinoma of the endometrium, mixed mesodermal sarcomas of the uterus, and leiomyosarcoma of the uterus. Each of these disease entities had varying rates of accrual. Additionally, numerous agents were envisioned to be investigated in each category. There was concern that the process was about to become cumbersome to a Group with very limited resources.

Drs. Blessing and Thigpen collaborated to develop a Master Protocol (Protocol 26) that would contain all of the required components, other than drug-specific sections, in a standardized format. This would enable rapid development of a specific drug investigation by using the Master Protocol template and incorporating individualized supplementary drug sections. Protocol 26-A (the Master Protocol) contained the generic sections, while the specific drug section being investigated was detailed in a separate protocol. For example, the first drug studied (Piperazinedione) was assigned Protocol 26-B, the second (Cisplatinum) was Protocol 26-C, etc. An investigation into each of the six recurrent disease categories was initiated on Protocol 26-B simultaneously. Accrual was monitored within the Statistical Office for adherence to study design and attainment of targeted accrual goals. At the end of each month, the Statistical Office contacted the Chair of the Develop-

mental Therapeutics Committee to determine the appropriateness of continuing or ceasing accrual for each sub-study. If the decision was to cease accrual to a particular sub-study, a replacement investigation would be initiated in the next drug scheduled for study. During the tenure of Protocol 26, 116 studies were conducted involving a total of 34 agents, underscoring the dramatic efficiency of this innovative approach.

Subsequent development of Phase II studies further refined the process. In 1994, the single Master Protocol was replaced by individual disease specific protocol queues which facilitate the sequential study of various agents within each targeted disease. In 1996, two-stage sampling designs were incorporated to permit early cessation of accrual for ineffective regimens while protecting Type I and II error probabilities. Other advances included separate development of studies for cytotoxic or cytostatic agents, and also for studies with prior treatment or no prior treatment requirements. The underlying principles of successive development and conduct of Phase II trials within individual areas of investigation, close monitoring of accrual, and interaction with the Developmental Therapeutics Committee Chairman continue to this day.

A second example of contribution to design is seen in the area of squamous cell carcinoma of the cervix. An early Phase II trial of cisplatin (the aforementioned Protocol 26-C) in this population resulted in encouraging response rates. As a result, successive Phase III trials of this agent were undertaken (Protocols 43 and 64.) Although the response rates observed in these studies failed to reach expectations, most investigators felt that cisplatin should be the first chemotherapeutic attempt. At a semi-annual GOG Meeting, Dr. Blessing met with a group of investigators and suggested that, since cisplatin was not the panacea hoped for, perhaps a subgroup of investigators could be identified who would not feel ethically bound to utilize cisplatin and would participate in front-line Phase II investigations of new agents. As a result, Protocol 76 (a series of drug investigations in the treatment of squamous cell carcinoma of the cervix in patients who had not received prior chemotherapy) was developed. The participants were limited to a selected group of GOG members who would participate in this study, rather than the Phase III study in the same population. Of the first twenty investigations completed to date, seven yielded results that were utilized in the development of subsequent Phase III studies, emphasizing the importance of this contribution.

In concert with these progressive innovations, the staff of the GOG Statistical Office, under the direction of Dr. Blessing, began to gradually, but consistently grow. Ms. Valvo transferred to the Statistical Office in 1975 when Dr. Hreshchyn's term as Group Chairman ended. She focused on administrative aspects; initially she provided an overall sense of organization and prepared the expanding GOG Statistical Reports for each Group Meeting. However, she also assumed responsibility for manuscript development, one of the unique responsibilities assigned to the Statistical Office.

As early Protocols matured and the Phase II program was initiated, this aspect became of critical importance. Centralization of this process in the Statistical Office ensured that data were sufficiently mature to warrant analysis and that proper statistical input and interpretation would be inherent in all Group presentations. The Protocol Procedures Manual outlined the steps for manuscript development and the Statistical Office was charged with ensuring that they were implemented.

At the same time, Ms. Bette Stonebraker was employed part-time to participate in the development of a computer-based system for preparing randomization/patient entry systems. Phone randomization replaced the antiquated system of institutional envelopes. (Today, all patient entry is accomplished via the web.) In the course of this project, she became familiar with many aspects of GOG activity. In short order, she became a full-time employee, assumed the role of Clinical Data Coordinator for all ovarian protocols, helped form the GOG Data Management Subcommittee, and became a member of the Protocol Committee. (As will be seen later, she currently serves as Director of Data Management in the restructured GOG Statistical and Data Center.)

The evolving Statistical Office philosophy was one based upon scientific interaction involving the entire staff. Interaction between Statistician and Study Chair was essential in designing studies. However, the inclusion of the Clinical Data Coordinator in the team greatly enhanced this professional role within the Group, and the appreciation of this critical, yet often under-recognized role. Study Chair review in the Statistical Office served to enhance the perception of a dedicated staff, committed to GOG research.

It was during this period that several advances in data management occurred. As noted earlier, modality review was non-existent in the first years of the Group's existence. Resolving this deficiency was another of Dr. Lewis' priorities when he became Group Chairman. Due to the backlog of data facing the Statistical Office in 1975, Dr. Lewis placed the responsibility for modality review in the Group Chairman's office in Philadelphia to enable more resources to be quickly applied to these dual challenges. It was determined that all patients entered on GOG studies would have a central review of submitted slides by the GOG Pathology Committee. Likewise, the Gynecologic Oncology Committee would review the surgical aspects for all patients for whom such a review was applicable via submitted operation reports. The Radiation Oncology Committee was charged with reviewing the submitted films, reports, and materials for all patients receiving radiotherapy on GOG studies. Finally, the chemotherapeutic aspects, as well as overall case evaluation, would be accomplished via the evolving system of Study Chair EVL reviews. The individual modality reviews were conducted in the Group Chairman's office, while the Study Chair reviews were the responsibility of the Statistical Office. (In 1990, responsibility for all modality review shifted back to the Statistical Office. However, Dr. Lewis' vision in temporarily

locating this function in Philadelphia was critical in enabling the GOG to simultaneously address two enormous challenges.)

As the initial results of modality review became available, less than optimal eligibility rates in the 80% range were noted, prompting the need to develop measures to increase institutional compliance. To address this issue, the GOG created a Fast Fact Sheet for each protocol consisting of a series of eligibility questions tailored to that study's eligibility criteria. These questions are asked at entry (via phone or web) to screen prospective patient entries for eligibility. This step has had a pronounced effect; GOG eligibility rates now consistently exceed 95%.

Until 1978, Dr. Blessing constituted the sole statistical resource for GOG. In July 1978, Mr. Brian Bundy joined the Statistical Office as a Master's level statistician. Initially, he was assigned two ovarian studies (Protocol 25 and 52) begun by Dr. Blessing and several Phase II studies. As Mr. Bundy became familiar with GOG procedures and enhanced his statistical abilities, he was assigned responsibilities for most cervical studies and select ovarian and endometrial studies. He was added to the Cervix and Protocol Committees and became a key asset. In 1987, he obtained his Ph.D. degree. (Dr. Bundy continued to work with the GOG, until his departure in 2006.) Ms. Barbara Saczynski was hired as a Clinical Data Coordinator for cervical studies in 1978.

In 1982, statisticians at RPMI availed themselves of evolving computer technology and created a generalized database management system (Roswell Park Management Information System (RPMIS)). In order to verify its utility, it was essential that RPMIS be tested using actual data examples. The Statistical Office collaborated with RPMI in the conduct of a time study which compared the use of RPMIS versus traditional IBM punch cards in the data management of two simultaneous Phase II studies. The published results demonstrated the value of RPMIS, and led to the conversion of all GOG protocol databases to RPMIS on the Univac 90/80 mainframe computer. A subsequent paper in 1987 documented further successful experience with this system.

Another unique responsibility of the Statistical Office was initiated when the National Cancer Institute mandated a program of quality assurance audits to be enacted by each Cooperative Group in 1983. This program required each participating institution to be visited at least once every three years to: verify the accuracy and validity of submitted data via medical source documents; review compliance with regulatory aspects, including IRB processes and informed consent content; and examine drug accountability and security at those sites employing investigational agents. Unlike other Groups, GOG centralized this function within its Statistical Office, as this was the location of the submitted data that would be audited. (Many other Cooperative Groups have their data management component geographically separate from the statistical component.) This structure has provided many benefits. Of par-

ticular note, is that this arrangement provides a viable method of incorporating corrections noted during audits into the database. Additionally, the GOG strongly believes that the audit process provides a unique educational opportunity. The interchange has been a two-way proposition; by examining the most frequently-occurring errors and misconceptions, the Statistical Office has been able to provide education, protocol clarification, and dose calculation tools. This process enhanced the growing portfolio of quality control measures.

In 1986, Mr. Mark Brady joined the Statistical Office as a statistician. Mr. Brady had prior clinical trials experience and was quickly assigned to several ongoing studies. In a short period of time, he was able to assume responsibility for GOG studies in ovarian carcinoma and make valuable contributions. He obtained his Ph.D. in 1999. (As will be seen later, he currently serves as Director of Statistics in the restructured GOG Statistical and Data Center.)

Due to continuing growth in workload, acquisition of additional data management resources was essential. Accordingly, two individuals were promoted from within, based upon their demonstrated growth in entry level positions. In 1987, Ms. Angie Saxer was promoted to Clinical Data Coordinator for endometrial studies. In 1986, Ms. Patricia Brehm was promoted to Clinical Data Coordinator for Phase II studies, and subsequently in 2000 assumed that role for endometrial studies upon Ms. Saxer's departure. Each of these actions was based upon the ability of these individuals to accurately process a large volume of data, interact with investigators and representatives of member institutions, and represent the GOG in a professional manner. The ability of Statistical Office staff to understand the nuances of varied aspects of GOG activities and mechanisms has always fostered the ability to grow within the organization. This in turn, has tended to promote a high level of dedication and remarkable longevity of staff. In keeping with the Statistical Office philosophy of inclusion, the Clinical Data Coordinators became members of the relevant disease committees, which further enhanced their ability to participate in GOG science.

During this period, several analytic advances occurred. In 1984, procedures for designing studies with a time-to-failure endpoint were developed which estimated the time required for study maturity and completion. Also, experimentation with the use of personal desktop computers in study development and management was initiated. The following year RPMI statisticians developed the FRENED procedure for calculating Kaplan-Meier estimates and performing proportional hazards modeling in SPSS. Additionally, in 1989 the Statistical Office began using commercially developed software on PC's including SAS, SPSS and BMDP for statistical analyses. A Novell local area network (10 MB/sec) was established to permit intra-office file, printer and software sharing. Since an electronic infrastructure was not

available, establishing the intra-office network required the statistical office staff to physically run wires and modify their own computers.

From the outset, Dr. Lewis recognized the importance of involving the Statistical Office in all aspects of Group activity, both scientific and administrative. Accordingly, Dr. Blessing was named as a member of the Executive, Protocol, and Membership Committees. This policy has continued as the Statistical Office has expanded its staff and as the Group has broadened its scope. This has allowed Statistical Office staff to make significant contributions, and has enabled new initiatives to be fully incorporated into the GOG structure.

One example is the evaluation of member institutions by the GOG Membership Committee. Initially, the performance of member institutions was primarily gauged by their accrual. As quality control measures evolved, patient eligibility monitoring was incorporated. It was no longer sufficient to enroll cases, it was important that they be eligible as well. Accordingly, the Statistical Office was able to provide critical data to the GOG Membership Committee regarding institutional eligibility rates and timeliness of data submission for its use in evaluating member performance. Also, a program of Data Assistance Reviews was initiated to enhance the educational component of this evaluation. At the discretion of the Membership Committee, the GOG Statistical Office would organize and conduct an on site review of an institution to address problem areas. At least one representative of another institution with demonstrated proficiency in the problem area would participate in an effort to interact with investigators to develop procedures to avoid such problems in the future. This notion of an initial attempt to address and correct deficiencies before any punitive action was taken became an integral part of GOG philosophy.

A second example of the important Group-wide role of the Statistical Office was seen in the development of the GOG's innovative per capita reimbursement system in 1988. In this instance, the Statistical and Administrative Offices collaborated to poll all members for fiscal data which was then used to determine the average cost per patient across the entire Group. This simple, yet comprehensive formulation served as the rationale that supported the sole request made of NCI for all institutional funding. Therefore, it was of paramount importance that this presentation be supported by data, and be logically convincing. As a result of the adoption of per capita reimbursement, institutions were no longer required to prepare grant applications to participate, and the GOG was no longer burdened with review of these grant applications. The success of this mechanism of funding has led to its continued use for 25 years.

During Dr. Lewis' tenure as Group Chairman, the GOG Statistical Office staff grew in number, expertise, and responsibility. It developed an underlying philosophy of total involvement and com-

mitment, and it contributed greatly to the GOG's emergence from a Group with potential to one of the premier Cooperative Groups.

The Park Years: 1989-2002

By the time Dr. Robert Park became Group Chairman in 1989, the GOG Statistical Office had assembled a staff of talented individuals who possessed significant expertise and experience in clinical trials research in gynecologic cancer. The Statisticians and Clinical Data Coordinators had been involved for many years and were well-integrated into all facets of GOG activities. During Dr. Park's tenure, previous modality and quality control initiatives were enhanced, a formalized Quality Assurance Audit Committee was created, and a focus on medical ethics emerged. The GOG expanded its clinical trials emphasis to include basic science, quality of life, and cancer prevention and control research. To support these endeavors, the GOG Statistical Office expanded its expertise via a consulting component to address these areas. Based upon the growth and expansion of both staff and responsibilities, the GOG Statistical Office was formally reorganized. The resulting GOG Statistical and Data Center (SDC) featured continued excellence in statistics and data management and fostered the development of strong translational research and information technology components. The latter component emerged to provide state-of-the-art technologic advances not only to the SDC, but also to the entire GOG. This section expounds upon these significant accomplishments.

GOG quality control mechanisms continued to grow and, in 1990, further refinement of data timeliness was addressed. To this point, the Statistical Office had monitored this via a Delinquency List provided to member institutions. This list provided a catalog of all forms and materials that were overdue. While this was a valuable aid in the retrospective effort to retrieve missing data, it was not preventive. Accordingly, a Forms Due List was developed to supplement the Delinquency List. This led to an improvement in timeliness of data submission since proactively informing institutions of upcoming form submission deadlines enhanced their ability to avoid delinquencies. This is but one example of the philosophy of the Statistical Office to work with participants to determine their needs and be responsive to them.

As previously mentioned, responsibility for all modality review was transferred from the Group Chairman's office to the Statistical Office in 1990. Prior to that time, the responsibility for all modality review had been vested in one staff member in the Group Chairman's office. In order to expedite the processing of results and enhance the scientific involvement, the Statistical Office subdivided modality review responsibilities among three Clinical Data Coordinators. Each assumed the added responsibility for the modality review which was most relevant to her experience. Surgical review conducted by the Gynecologic Oncology Committee review was assigned to Ms. Stonebraker, who had been the Clinical Data Coordinator for several surgical staging protocols. Ms.

Saczynski, who was the Clinical Data Coordinator for all cervical studies, was assigned responsibility for review of radiotherapy due to its obvious connection in that disease site. Pathology review was ultimately assigned to Ms. Janis Barnes.

Important additions to the GOG Statistical Office staff continued to occur in the early 1990's. Based upon the growth in protocols investigating epithelial ovarian cancer, Ms. Suzanne Baskerville was added to the Data Management staff as a Clinical Research Coordinator. As a result of a dramatic increase in computer related activities, Mr. Joe Jelonek joined Ms. Karen Puehn to provide programming support. Ms. Laura Porter was hired to perform data entry functions due to an ever increasing volume of data. She later assumed the role of Forms Tracking Coordinator as GOG quality control measures were expanded. Ms. Amy Speaker was hired in a clerical role and subsequently was assigned responsibility for overseeing the randomization/patient registration process and assisting with quality of life data. (She later assisted Ms. Barnes and assumed the responsibility for GOG pathology review upon Ms. Barnes retirement in 2008.) Ms. Kathy Ker was employed to process radiotherapy materials. Subsequently, she assumed the role of Administrative Assistant upon Ms. Valvo's retirement. Her responsibilities included preparation of grants and semi-annual GOG Statistical Reports. She excelled in this capacity until her untimely death in 2002.

Based upon its continued growth, the GOG Statistical Office, having grown from the initial five to 18 staff members, was formally recognized as an independent department within RPMI in 1991, with Dr. Blessing as its Department Chairman. This recognition by RPMI was indicative of the level of respect accorded to this group based upon their demonstrated accomplishments. Commensurate with the resulting increased administrative responsibilities, Ms. Mary Ann Kuczarski, Administrative Assistant, was hired to support these functions.

In 1992, Dr. Park requested that the Statistical Office form a Quality of Life (QoL) working group. Ms. Karen Iseminger was hired as a Cancer Research Scientist with a focus on QoL and quality assurance audits. She and Dr. Brady were original members of the GOG Quality of Life Committee when GOG formalized that area of research in 1993. Subsequently, she received a Ph.D. in Medical Ethics and was named to the GOG Protocol Committee as a medical ethicist. Her unique perspective has enabled her to participate in many areas of GOG activity such as the GOG Data Monitoring Committee, Data Safety Monitoring Board, and Human Research Committee. In 1994, Ms. Virginia Filiaci assumed the role of statistician for GOG studies in endometrial carcinoma and uterine sarcoma. She quickly adapted to that role and became a member of both the Corpus and Protocol Committees. (In 2010, she obtained her PhD and Dr. Filiaci was named Associate Director of the SDC Biostatistics and Science Division.)

Since the inception of the NCI mandated Quality Assurance Audit Program in 1983, all aspects of this function were centralized in the Statistical Office. In 1992, Dr. Park formalized this process by forming a Quality Assurance Audit Committee. In recognition of their inherent role in managing this process, three members of the Statistical Office were named to this four-person committee. Their participation in on-site reviews, coupled with their familiarity with GOG data management requirements, enhanced quality control, and simultaneously provided on-site educational opportunities for institutional staff. In 1994, Dr. Blessing collaborated with members of the newly formed NCI Clinical Trials Monitoring Branch (CTMB) in the development of Common Cooperative Group Guidelines for quality assurance audits and the Statistical Office helped pilot the interactive programs developed for scheduling and reporting. The uniformity of evaluation inherent in the Quality Assurance Audit Committee review of all audits enabled the GOG Membership Committee to incorporate the results of audits into its criteria for evaluating parent institutions. Due to the continued expansion of the GOG parent institutions, affiliates, and CCOP's, Ms. Carol Mullins was named Quality Assurance Audit Assistant within the Administrative Division of the Statistical Office with responsibility for the interactive scheduling of audits and preparation of reports. She served in that capacity until her departure in January, 2013. Additionally, the Statistical Office initiated periodic workshops to provide audit training, education, and improve performance.

The breadth of GOG science and the corresponding responsibilities of the GOG Statistical Office changed markedly in 1993. Quality of life research was added to the GOG research portfolio and a Tumor Biology and Applied Science Committee was formed to develop translational research studies. In 1995, the Cancer Prevention and Control Committee was created to undertake research in these emerging scientific areas. Each of these initiatives individually constituted a significant challenge. Moreover, the combined effect of the three endeavors was a monumental undertaking. Accordingly, the GOG Statistical Office initiated a program of obtaining the services of consultant statisticians to provide expertise in each area. Dr. Richard Kryscio, Chairman of the Biostatistics Consulting Lab at the University of Kentucky, agreed to participate in translational research, bringing noteworthy expertise in applying translational research to gynecologic oncology investigations. Dr. Howard Thaler, of Memorial Sloan-Kettering, joined as a researcher in quality of life; he too had considerable experience with the investigation of quality of life in gynecologic malignancies. Dr. Roger Priore, former Chairman of Biomathematics at Roswell Park and member of the Department of Social and Preventive Medicine at the University of Buffalo, agreed to participate in the epidemiologic studies being developed by the Cancer Prevention and Control Committee. Each of these talented professionals provided a significant time commitment to GOG, attended GOG meetings and served on relevant committees. They helped develop funding applications, participated in protocol de-

sign, and co-authored GOG manuscripts.

As the Group approached its 30th Anniversary in 1999, Drs. Park and Blessing discussed the nature of the GOG Statistical Office and reached two conclusions that have had significant positive implications. First, it was decided that the name of the office implied a much more limited scope of responsibility than the office actually bore. Unlike the statistical centers for most Cooperative Groups, the GOG Statistical Office also had responsibilities for all aspects of data collection and processing, information technology, quality control, publications, quality assurance audits, etc. Consequently, it was decided to rename the office as the GOG Statistical and Data Center (SDC) to better reflect these responsibilities. Secondly, the great increase in size of the staff, responsibilities, and complexity warranted a more formalized office structure which would continue under Dr. Blessing's overall leadership, but create three divisions (Statistics, Data Management, and Information Technology) with individual Directors and Associate Directors (where appropriate.) Initially, Dr. Eugene Sobel was named Director of Statistics and Dr. Brady served as Associate Director. Dr. Brady assumed the role of Director in 2003 upon Dr. Sobel's resignation. Ms. Bette Stonebraker was named Director of Data Management, formalizing a role she had played for many years. Mr. William Elgie was hired to serve as Director of Information Technology (IT) in 2000; he had considerable Cooperative Group experience that would prove vital in establishing an IT division.

Under this reorganization, Dr. Blessing continued to have overall responsibility for the SDC, but delegated individual leadership roles to the Directors. Moreover, Dr. Blessing and these individuals developed a series of meetings to enable all to have a voice in charting direction and focus. This format has fostered increased organization and provided a critical forum to allow joint decisions to be made on issues with implications for multiple divisions.

In 2000, Kathleen Darcy, Ph.D. accepted a position in the SDC and her expertise in translational research quickly led to her reclassification as a Translational Research Scientist, supporting the GOG increased effort in basic science research. Shortly thereafter, Dr. Zoe Miner joined Dr. Darcy in this effort. As a result, the expertise and resources dedicated to translational research available within the SDC increased substantially. Both Drs. Darcy and Miner became members of the GOG Committee on Experimental Medicine (CEM) and played integral roles in the incorporation of translational research components into clinical studies, as well as in enhancing the SDC interaction with the GOG Tissue Bank in the procurement and tracking of biologic specimen

The GOG continued to enjoy significant growth; during the period between 1999 and 2003, accrual grew by 43%, and Phase III accrual grew by 49%. Additionally, GOG protocols grew in complexity with the advent of translational research, quality of life,

and cancer prevention and control components. Accordingly, it became essential for the Statistics Division of the SDC to acquire new staff. Dr. Michael Sill brought his expertise to the growing portfolio of Phase II studies involving cytostatic agents. Ms. Marion Piedmonte and Mr. Jim Kauderer were hired to provide statistical support for studies funded by the Cancer Control grant. Ms. Helen Huang was employed to specialize in quality of life investigations while Mr. Chunqiao Tian, and later Mr. Jim Java, came on board to focus on ancillary data projects. Mr. Shamshad Ali has assumed responsibility for GOG cervical studies. All have become acclimated to GOG procedures in a remarkably short period of time and complement the longstanding experience of existing scientists.

Likewise, this period saw a comparable expansion in the Data Management Division. Corresponding to the growth in patient accrual, the volume of submitted case report forms grew by 68%. Coupled with the increased complexity of protocols, this created the need for hiring additional Clinical Data Coordinators. Ms. Sandra Dascomb was assigned responsibility for the management of Phase II study data, Ms. Linda Gedeon for a large scale Cancer Prevention and Control study, and Ms. Angela Vazquez for cervical studies. Case report form processing, data entry, clerical, and receptionist functions were performed by a talented group which included Ms. Rachele Dutka and Ms. Lois Newman.

The creation of the Information Technology division initiated a dramatic growth in technologic capabilities. Prior to 1999, the GOG had been well-served by two excellent programmers, Mr. Jelonek and Ms. Puehn. However, their primary responsibilities had been to accomplish the required programming needs of the Statistical Office. They spearheaded the progression from the original use of punch cards to the development of individual computer terminals, the incorporation of statistical packages, etc. In 1990, for example, Mr. Jelonek completed all required programming to allow the GOG to create a dedicated computer facility and become independent from the Roswell Park computer system. However, due to the limited staff, the programmers had been put in a position of reacting to requests that were based upon current needs.

Within six months of the inception of the IT division, its staff had grown to include Mr. Michael Calanan, a Systems Analyst, and Mr. Scott Gould, a Network and Systems Analyst, in addition to Mr. Elgie, Mr. Jelonek, and Ms. Puehn. The next year, Mr. Edward Kopek, a User Support Specialist and Ms. Florence Vecchione, a Technical Writer, were added. Shortly thereafter, Mr. Quang Le and Ms. Susan Klier came on board as Programmer/Analysts, after successfully completing IT internships within the SDC.

The IT staff was now positioned to fully participate in GOG activities, not merely respond to requests. Moreover, through their inclusion in SDC leadership, the IT division had the opportunity

to participate more fully in GOG activities and offer prospective suggestions for computer-related advances. In 2001, all SDC IT members were named to the Medical Informatics Committee and in 2003, Mr. Elgie was named Co-Chairman. A commitment was made to have IT staff attend GOG Meetings; this has enabled them to staff a Resource Room which offers wireless internet access in all meeting rooms, provide access to workstations, offer one-on-one technical advice and present training sessions on new GOG IT initiatives. Within a brief period of time, the dedicated GOG computer system was completely overhauled and expanded to foster future growth and an emergency back-up system was implemented.

Prior to 2001, the GOG had significant presence on the internet. Dr. Michael Bookman had secured industry support to establish a web-site for the Administrative Office. In 2001, the SDC in collaboration with Dr. Bookman, fostered electronic communication for the entire GOG via the establishment of a user-friendly, interactive web site. These endeavors resulted in the creation of the current SDC web site which offers a variety of reporting and data submission tools to assist staff at participating institutions in their day-to-day activities.

In 2001, with annual accrual exceeding 3,000 patients, the SDC began to replace the antiquated phone/fax based patient registration system with a web based patient registration/randomization system that is heavily utilized by the GOG to enroll patients. Initially, this was accomplished on selected studies, and has been continually expanded so that virtually all patients registered to GOG protocols are entered via the web.

These IT initiatives exemplified two key points. First, obviously, was the enhanced technologic ability of the SDC. Second, these projects illustrated the success of the restructured SDC in achieving its goals. Interaction among the Directors was essential in developing and achieving each plan of action. For example, both the Data Management and IT Divisions had to collaborate and coordinate to ensure that the critical eligibility screening component of phone-based patient entry was retained in the new web-based patient registration system. Subsequently, testing and then gradual conversion was achieved without disruption. Progress was monitored and discussed during routine Directors' Meetings.

Dr. Park's tenure as Group Chairman witnessed a dramatic growth into new areas of scientific investigation. In a similar fashion, the GOG Statistical and Data Center evolved to encompass new expertise, create an academic environment, and promote technologic advances.

The DiSaia Years: 2002 - Present

When Dr. Philip DiSaia assumed the Chairmanship of GOG in 2002, the restructured SDC was poised to take on many new initiatives due to both the stability and longstanding commitment of

SDC staff, as well as the infusion of additional expertise acquired via newly acquired members. Of particular note, a scientific liaison was established with the newly created Department of Biostatistics at the University at Buffalo. Moreover, as initial studies involving translational research and quality of life matured, procedures were developed to ensure the timely and efficient preparation of the increased number and more complex nature of manuscripts. In the current era of reduced federal support, the GOG embarked upon numerous collaborative ventures with industry resulting in the preparation an increasing number of grant applications and the need to efficiently manage resulting funding. These expanding responsibilities and a desire to enhance efficiency warranted the expansion of the SDC structure to include a formal Administrative Division. Web-based data entry was accomplished via the development of the SDC Electronic Data Entry System (SEDES) and the electronic management of biologic materials via the Bioinformatic And Specimen Tracking (BAST) system was initiated. More recently, NCI initiatives such as migration to the Oncology Patient Enrollment System (OPEN) and a common remote data entry system (Medidata Rave) have created new technologic challenges which have been successfully addressed. Finally, the decision to create NRG Oncology has initiated exciting new collaborative possibilities. The SDMC continues to be inherently involved in the planning, evaluation, and development of procedures in preparation for the inception of this venture. This section details these innovations.

In 1999, Dr. Blessing and Dr. Maurizio Trevisan, Chairman of the Department of Social and Preventative Medicine (SPM) at the University at Buffalo (UB), had initiated a formal relationship between the SDC and SPM. This constituted the onset of a formal academic relationship. In 2002, Dr. Alan Hutson was recruited to Chair a newly created Department of Biostatistics at UB. Subsequently, as a result of this fortuitous development, Drs. Hutson and Blessing initiated a symbiotic collaboration which has paid impressive dividends. Drs. Blessing, Brady, and Sill all have academic appointments at UB, while Dr. Hutson, Dr. Randy Carter, Associate Chairman of the Biostatistics Department, Dr. Jeff Miecznikowski, Dr. David Tritchler, and Dr. Lori Sheperd of the UB faculty became valuable GOG staff members. Dr. Hutson serves on the GOG Protocol Committee as well as the Committee on Experimental Medicine. Dr. Carter is a member of the Cancer Prevention and Control Committee and Drs. Miecznikowski, Tritchler, and Shepherd have further expanded the SDC expertise in translational research. As a result of this alliance, a program was initiated whereby UB students were able to do internships within GOG and/or have joint appointments. Mr. William Brady (2006), Mr. Austin Miller (2006), and Ms. Wei Deng (2010) became valued additions to the GOG Division of Biostatistics and Science while pursuing advanced degrees at UB. All three have successfully completed their PhD programs and have significant GOG responsibilities in Rare Tumors (Brady), Phase II trials (Deng), and Ancillary Data studies (Miller). Virginia Filiaci also

achieved her doctorate and has assumed the role of GOG Associate Director of Biostatistics and Science. She and Dr. Brady collaborate to provide outstanding statistical leadership and mentoring to a well-respected cadre of SDC biostatisticians and scientists who are fully integrated into GOG science. In 2009, James Java was hired to focus on ancillary data investigations. Dr. Heather Lankes was hired in 2008 as a Translational Research scientist and has interacted with the Committee on Experimental Medicine to greatly enhance the coordination of translational research investigations. Mr. Brandon Marzullo joined her in 2010 to round out the current TR staff upon the departure of Dr. Darcy. Both have contributed to the increased efficiency with the Committee on Experimental Medicine and the GOG Tissue Bank. The infusion of academia-based expertise and the careful recruitment of staff has enhanced the SDC's ability to meet the growing scientific diversity of the GOG and positions it to anticipate and proactively address future challenges.

Based upon the expanded administrative functions of the SDC, the Administration Division was formally created with Ms. Sally Bialy as Director, in 2003. This Division now encompasses fiscal management, manuscript preparation, all quality assurance audit functions, and the production of the semi-annual GOG Statistical Report, as well as administrative functions necessary for a department in excess of 50 staff members. The resulting constituency of the SDC Directors now represents every aspect of SDC activity and further enhances efficiency.

Substantial progress was also evident in the preparation of GOG manuscripts for publication. This process, which had been centralized in the GOG SDC and governed by the GOG Protocol Procedures Manual, requires timely development of a first draft by the primary Study Chair, collaborating Statistician, and Clinical Trials Editorial Associate. Subsequent steps involve review by Co-authors, the GOG Publications Subcommittee, and Journal reviewers. Manuscripts at each of these stages typically require revision and circulation. Following a GOG Retreat conducted by Dr. DiSaia in 2002, an increased emphasis was placed upon manuscript development. Accordingly the SDC hired Ms. Anne Reardon (2003) and Ms. Kim Blaser (2006) as Clinical Trials Editorial Associates to guide each manuscript through the various stages of manuscript development. Also, working closely with Dr. George Omura and Frederick Stehman, past and current Chairs of the Publications Subcommittee, and the GOG Operations Committee, Ms. Bialy developed a system to set, monitor, and enforce deadlines for each stage of manuscript development. The efficiency of this process was documented in an investigation¹ comparing the development time for phase II trials during 2003-006 vs 2007-10.

In recent years, the GOG received "flat" federal funding at best, and in some instances reduced levels of funding. As a result, NCI funding for the SDC grant was less in 2010 than it had been in 2000. This circumstance is compounded by the increased com-

plexity and commensurate workload mandated by current research studies. In order to ensure the continued high quality of GOG investigations, it has been necessary to explore avenues of supplementary funding. Under Dr. DiSaia's leadership, the GOG has recently embarked upon numerous liaisons with industry. Scientific development of protocols has become increasingly complex and labor intensive, as agreement among the GOG, the NCI, the corporate collaborator, and frequently the Food and Drug Administration must be negotiated. This impacts study design, content of data forms, toxicity reporting, etc. Additionally, the Administration Division of the SDC is now charged with the preparation and oversight of numerous contracts and/or applications for funding. As a result, the SDC has successfully assumed considerable additional fiscal responsibility to develop budgets, review contracts, manage funding, and ensure fulfillment of contractual obligations. In 2002, the SDC managed three modest sources of funding in addition to its primary NCI grant funding; by 2005, there were 47 additional awards, contracts, or applications for supplementary funding being managed.

In 2008, Ms. Jennifer Delair was hired as Grants, Fiscal, and Personnel Administrator to manage fiscal processes. With the advent of GOG Partners, the fiscal responsibilities multiplied as it is essential to disburse funds for NCI and non-NCI projects commensurate with effort required for each. Of particular note, an electronic mechanism was created to fine-tune budget requirements for each individual task associated with the development, conduct, data capture, quality control, analysis, and publication of any concept initiated through the Partners mechanism². This allows the SDC to function as a CRO in GOG collaborations with industry. The first such effort, Protocol 3003, was readily initiated using this process.

Between 1993 and 2003, the number of CRF's received annually in the SDC rose from approximately 40,000 to 70,000 forms. As a result, the SDC developed methodology for a web-based data entry system, SDC Electronic Data Entry System (SEDES), that allows for the intermediate submission of patient data over a highly secure internet connection. This project underscores the efficiency of the current office structure. The initial step in web-based data entry was the development of Case Report Forms (CRF's). This required collaboration involving statistical, data management, and IT staff to develop the design and content of each CRF and assure compliance with NCI Common Data Elements. Subsequent steps included range and logic testing for each question, form testing, and activation. Initially, web-based versions of individual forms were made available across all protocols. With the knowledge and feedback obtained from this process, the SDC initiated total web-based data entry for Phase III Protocols 197, 204, 209, and 210. Based upon the initial success and institutional feedback, the SDC convinced the GOG leadership to mandate web-based data entry for Protocol 212 prior to its activation in 2005. The database for this investigation, and that for Protocol

218 were used to collect data for regulatory review and possible drug approval. Upon receipt of the final database for the latter study in 2010, the sponsor remarked "...the database was inherently very clean ... very unusual and impressive for a cooperative group." This was a reflection of the thoughtfulness of the design, functionality of SEDES, and the thoroughness of the Clinical Data Coordinators.

In a similar fashion, this type of interaction was vital in the development of an electronic system to provide a bioinformatics platform that allows the efficient and accurate integration of clinical, patient consent, and specimen information with data generated from high through-put laboratory testing procedures. The Bioinformatics and Specimen Tracking (BAST) system consists of a series of interrelated databases and processes which facilitate the combination of clinical and translational data. It enables the tracking of the quality and utilization of GOG collected specimens and contains laboratory assay results and controls collected from approved testing labs. The creation of BAST was of paramount importance to efficiently accommodate the rapid expansion of translational research in GOG Protocols.

The Information Technology staff was augmented by the addition of Mr. Josh Killion (2005) and Mr. Kareem Kouis (2009) as programmer/analysts and Mr. Justin Dittmar (2007) as a technical writer/support specialist.

The NCI has mandated that all Cooperative Groups transition to a common electronic data entry system, Medidata RAVE in 2013. The SDC IT staff has been fully engaged in workshops, training sessions, webinars, etc. to be in the forefront of the RAVE adoption. The past Group-wide acceptance of and praise for the in-house accomplishments of SEDES and BAST provide every confidence that this hard-working group will make this transition as seamless as possible.

The technologic advances, increased protocol complexity, volume of protocols, and exceptional Group-wide accrual prompted significant changes within the Data Management Division. In 2007, Angela Kuras was named Associate Director of Data Management. Her ability to interact closely with Information Technology staff was of great significance in fostering the continued evolution of GOG systems. In an effort to ensure the uninterrupted high level of expertise of the Senior Clinical Data Coordinators, the SDC instituted a program of having each one mentor new Clinical Data Coordinators. This resulted in the reassignment of Rachelle Dutka (2009) and Melissa Leventhal (2010) and the addition of Kristin Engel (2007), Randy Vogt (2009), Jill Evans (2010), and Jesslyn Reboy (2010). The foresight of this initiative was seen in 2009 when Patricia Brehm (Corpus) and Suzanne Baskerville (Ovary), two outstanding Senior Clinical Data Coordinators decided to retire. Ms. Engel and Ms. Dutka were then promoted to assume these responsibilities. (Typical of the long-term commitment that SDC

members have had to GOG, both Ms. Brehm and Ms. Baskerville have returned on a part-time basis). New additions to the Data Management staff include Sharon Desabrais (2007), Tracy Flick (2007), Mary Kaletta (2009), and Kristina Klausen (2009). Ms. Desabrais subsequently was switched to receptionist responsibilities in the Administration Division.

With the continual evolution of the SDC, innovative accomplishments were featured in peer reviewed manuscripts and abstracts involving all Divisions. This served to demonstrate their research prowess, present innovative initiatives, and underscore efficiency. Biostatistics and Science research includes: methodology for phase II trials with co-primary endpoints (Sill)³. The results of this research have been incorporated into the design of several Phase II GOG studies. drop-the-loser approach for designing multi-arm studies and proposed methods for reducing the bias in the estimated treatment effects and controlling type I error (Sill)^{4,5}; a biomarker based adaptive design two-stage randomized phase II study design (Filiaci)⁶; a permutation based approach to phase II historical control trials (Hutson)⁷; response as a surrogate endpoint for survival in endometrial cancer (Filiaci)⁸; and a comparison of weighted logrank procedures and a time-dependent Cox model (Brady)⁹;

Administrative Division efforts to enhance efficiency and education have been featured in both manuscripts and abstracts on topics which include: the value of the assignment, monitoring, and enforcement of deadlines in reducing the time to manuscript submission (Bialy)¹; initiatives for improvement resulting from an analysis of GOG Quality Assurance Audit results (Blessing)¹⁰; efficient management of diversified funding (Bialy)²; creation of a digital library for GOG manuscripts utilizing information technology infrastructure (Leventhal)¹¹. These results are of particular significance in a period marked by increased responsibility and limited funding.

Ms. Kuras presented Data Management Division innovations before the Society for Clinical Trials on the quality control of electronically captured data¹² and the ability to conduct remote, paper-less study chair reviews of data¹³. Information Technology presentations covered: on-line application for the tracking and implementing specimen consent choices (Elgie)¹⁴; electronic submission of paper based clinical reports, such as pathology and operative reports (Elgie)¹⁵; web-based management of phase I trials with multiple institution participation (Elgie)¹⁶; automated drug ordering in a Cooperative Group setting (Elgie)¹⁷; the secure exchange of electronic data (Gould)^{18,19}; and the creation of web-based teleforms (Puehn)²⁰.

The accomplishments achieved during this period relied heavily on the strong foundation built during the previous eras. Dr. DiSaia has continued the GOG tradition of including the SDC in all facets



GOG Statistical and Data Center (SDC) staff, Roswell Park Cancer Institute - Buffalo, NY

of GOG investigative activities. He has fully endorsed SDC initiatives and has developed innovative alternative funding mechanisms to ensure stability and growth in a difficult fiscal climate. His guidance and support have enabled the SDC to anticipate and meet the scientific, technologic, and financial challenges associated with GOG research.

NRG Oncology

With the alliance of the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and GOG to form NRG Oncology, the combined resources of the new entity are outstanding. This is particularly true of the NRG Oncology Statistical and Data Management Center (SDMC). As Co-Executive Directors, John Blessing, PhD (GOG), Joseph Costantino, DrPH (NSABP), and James Dignam, PhD (RTOG), will jointly govern this integrated entity which will be distributed among the three present locations (Buffalo, Pittsburgh, Philadelphia). Equal leadership representation from all three Legacy Groups ensures that the SDMC will be poised to take full advantage of the best practices that each individual group has to offer in order to integrate multiple systems and processes into a cohesive unit. The three Co-Executive Directors have a strong collegial relationship and friendship that precedes NRG Oncology. Likewise, the Division Directors from each Legacy Group have worked together on numerous NCI projects, inter-group studies, and scientific collaborations. The daunting process of developing the SDMC grant application required significant interaction: familiarization with one another's SOPs; discussion to identify areas of commonality and differences; development of NRG Oncology procedures, etc. The final written document represented a significant accomplishment. It presents a comprehensive, cohesive plan which retained the past expertise, yet would operate as one entity. Moreover, the reinforcement of the collaborative nature and willingness to compromise to achieve a common goal reflected

very positively on all participants. While the grant was submitted through Roswell Park with sub-contracts to the other locations, all three Co-Principal Investigators are equal. This is reflected in the grant submission, the governance plan, and all decision-making policies.

Since the decision to form this alliance, leaders of each Division of the SDC have been involved in numerous Working Groups to create the structure (Transition Steering, Administrative Transition, Communications, Grant Writing, Membership, Website) and develop Common Procedures (Audit, Publications, Biostatistics, Data Management, Modality, Outcomes, Scientific Agenda, Information Technology). Intense participation in meetings and/or conference calls continue to ensure that common procedures are in place upon the formal initiation of NRG Oncology targeted for 3/1/14. Indeed, many of the resulting SOPs are being utilized in the current Legacy Groups where possible.

The challenge to accomplish these tasks in such a short time has been formidable. Nonetheless, the GOG SDC members and their colleagues in NSABP and RTOG have accomplished a great deal in a very short time. The current GOG staff with its current leadership, structure, wealth of experience, expertise, academic affiliation, and collaborative arrangements (with UB, RPCI, NSABP, and RTOG) is uniquely poised to contribute to NRG Oncology's ability to maintain the highest standards of clinical trials development, execution, analysis, and dissemination of results.

GOG/SDC Milestones of Progress

1970 The "Cooperative Gynecology Oncology Group" involving ten institutions is founded and is later constituted as the "Gynecologic Oncology Group" (GOG). Dr. Myron

- Hreshchshyn is elected Group Chairman. The Group Chairman's Office is located at the Buffalo General Hospital and consists of a central endocrine laboratory and a pathology and radiation therapy repository. Drs. Irwin Bross and Nelson Slack establish the GOG Statistical Office at Roswell Park Memorial Institute (RPMI).
- 1971** Dr. Slack is appointed Group Statistician. Fifteen institutions participate in five GOG studies and enroll 49 patients.
- 1974** Dr. George Lewis is elected Group Chairman effective July 1975. Dr. John Blessing replaces Dr. Slack as Group Statistician. The Statistical Office consists of Dr. Blessing and four staff members.
- 1975** The Group Chairman's office is relocated to Philadelphia. The first formal GOG Statistical Report is prepared and distributed at the January GOG Meeting. The first Study Chair review is performed. The GOG Protocol Committee is established to coordinate protocol development and manage ongoing studies. The GOG Protocol Procedures Manual is created to regulate these processes. The 2,500th patient is registered onto a GOG study.
- 1976** Standardized Phase II study queues are implemented to facilitate protocol development and accelerate drug evaluation.
- 1977** The GOG Data Safety Monitoring Board (DSMB) is created to review treatment related deaths and unexpected toxicities.
- 1978** The Statistical Office utilizes Mag Card equipment to prepare documents electronically.
- 1981** GOG and RPMI statisticians begin to develop a library of in-house generalizable computer programs for designing clinical trials, generating graphical presentations and performing data analyses on a mainframe computer.
- 1983** The Statistical Office initiates a program of institutional quality assurance audits in accordance with NCI mandate. GOG clinical trials data are converted to a generalized database management system, called RPMIS, developed at Roswell Park to run on the Univac 90/80 mainframe computer. The ASCII terminals permit real-time data management through acoustic couplers over the phone line at 150 characters per second.
- 1984** Procedures for designing studies with a time-to-failure endpoint are developed which estimate the time required for study maturity and completion. Experimentation with the use of personal desktop computers in study development and management is initiated.
- 1985** RPMI statisticians develop the FRENED procedure for performing Kaplan-Meier and proportional hazards modeling in SPSS. The first treatment study incorporating a measure of each patient's self-assessed quality of life (Protocol 97) is initiated. The 10,000th patient is registered onto a GOG study.
- 1986** The Statistical Office joins RPMI's Corvus (1 Mbit/sec) PC local area network which permits file sharing and centralized backup/restore procedures. The Statistical Office creates the first electronic link with the Administrative Office via 1200 baud modems.
- 1987** Dr. Blessing purchases a PC-based graphics program in a discount computer store. This program is utilized to create study schemas that replace hand-drawn schemas in the semi-annual GOG Statistical Report. Lotus Inc. takes over development of this program and it later becomes known as Freelance.
- 1988** Dr. Robert Park is elected Group Chairman, effective July 1989.
- 1989** The Statistical Office begins using commercially developed software on PCs including SAS, SPSS and BMDP for statistical analyses. A Novell local area network (10 MB/sec) is established to permit intra-office file, printer and software sharing.
- 1990** The RPMIS data system is converted to a commercial relational data base management system, INGRES, running on a VAX minicomputer. A computerized Forms Tracking List is made available to all member institutions. All randomized Phase III studies are formally required to include planned interim analyses, unless there was a clear rationale to do otherwise.
- 1991** The GOG Statistical Office, formerly located within the Department of Biomathematics at RPMI, is formally named a separate Department with Dr. Blessing as Department Chairman. The Statistical Office assumes responsibility from the Administrative Office for modality reviews. The SDC collaborates with the CHTN to initiate the GOG Tissue Bank (Protocol 136). The 25,000th patient is registered.
- 1992** The Group Chairman requests the Statistical Office to form a Quality of Life (QoL) Working Group which is the precursor of the GOG QoL Committee (formed in 1993). The GOG Quality Assurance Audit Committee is formalized. At the request of the Nursing Committee, the Statistical Office designs the first GOG study (Protocol 9102) in which the primary endpoint is based on the patient's self-evaluated adverse effects of chemotherapy. The Statistical Office hops onto the electronic super highway.
- 1993** The GOG Tumor Biology and Applied Science Committee is formed which subsequently becomes the Committee on Experimental Medicine.
- 1994** A formal Data Monitoring Committee (DMC) is established which is charged with reviewing interim study results and monitoring the conduct of all GOG Phase III trials.
- 1995** The GOG Cancer Prevention and Control Committee is established.
- 1996** The designs for standard Phase II study queues are converted to multi-stage designs that permit early accrual termination when treatments are considered ineffective.

- 1997** The SDC collaborates with industry sponsors to provide data from Protocol 111 in order to obtain FDA approval for paclitaxel for the first-line treatment of women with advanced ovarian cancer.
- 1998** GOG data forms are completely redesigned to accommodate Common Toxicity Criteria (CTC) for reporting the adverse effects of treatment.
- 1999** The Statistical Office is restructured to create the GOG Statistical and Data Center (SDC) comprised of three Divisions: Biostatistics and Science, Data Management, and Information technology. The SDC collaborates with investigators from the US, Canada, Europe, Australia and New Zealand to develop the first multinational and largest GOG sponsored trial (Protocol 182). This study ultimately evaluates five study regimens and enrolls more than 4,000 women from all over the world.
- 2000** The SDC successfully re-competes for increased funding to enable it to grow commensurate with the Group's broadened research interests. The SDC expands to include statisticians with specialized experience in health outcome research, epidemiology and experimental medicine. The designs for Phase II study queues are converted to optimal and flexible two-stage designs, which eliminate the need to pre-specify fixed accrual sizes for each stage of the study. Web-based patient registration is initiated. The GOG adopts RECIST criteria for reporting tumor response evaluations. The 50,000th patient is registered.
- 2001** Dr. Philip DiSaia is elected Group Chairman, effective July 2002. Translational Research Scientists join the SDC to support the GOG basic science effort. The Medical Informatics Committee is formed. The SDC creates a user friendly, interactive web-site to foster electronic communication for the entire GOG. Annual accrual exceeds 3,000.
- 2002** The SDC collaborates with industry sponsors to develop the first GOG Phase III trial (Protocol 212) prospectively designed to seek FDA approval for a new agent.
- 2003** The SDC and the newly formed Biostatistics Department at UB form a symbiotic relationship. UB faculty members join the SDC staff and begin working on GOG studies, while SDC statisticians join the UB faculty. The first data forms for GOG trials are submitted via the web through the SDC Electronic Data Entry System (SEDES). Based upon the ever-increasing responsibilities of fiscal management, efficiency and organization, quality assurance audits, and manuscript development, the SDC formally adds an Administration Division to its structure.
- 2004** The SDC begins development of a Bioinformatics and Specimen Tracking system (BAST) to combine clinical and research databases and manage specimen collection.
- 2005** The first studies are initiated in which all study data are submitted electronically using SEDES (Protocols 212 and 218). The GOG's first prospective study is initiated in which its primary objective is the use of a high-throughput technology to diagnose gynecologic cancers (Protocol 220).
- 2010** The first GOG Protocol (261) using the Open Patient Enrollment System (OPEN) is initiated. SEDES database for Protocol 218 utilized for regulatory review and potential drug approval. 2011 Members of the SDC begin interaction with NSABP and RTOG colleagues to initiate planning for the NRG Oncology Statistical and Data Management Center (SDMC). Simultaneously SDC Leaders participate in Working Groups to develop all NRG Oncology committees, procedures, functions, etc.
- 2012** The first GOP Protocol (229-N) utilizing Medidata RAVE for electronic data capture is initiated.
- 2013** The NRG Oncology SDMC grant application is submitted in January. Anticipated start date is March, 2014.

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Uterine Corpus Publications

GOG 0020

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GOG 0021

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GOG 0028

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GOG 0033

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Zaino RJ, Kurman RJ, Diana K, Morrow CP. Pathologic Models to Predict Outcome for Women with Endometrial Adenocarcinoma: The Importance of the Distinction of Surgical Stage from Clinical Stage (A Gynecologic Oncology Group Study). *Cancer* 77: 1115-1117, 1996.

Zaino RJ, Kurman RJ, Brunetto VL, Morrow CP, Bentley RC, Cappellari JO, Bitterman P. Villoglandular adenocarcinoma of the endometrium: A clinicopathologic study of 61 cases. A Gynecologic Oncology Group study. *Am J Surg Pathol* 22(11): 1379-1385, 1998.

Creasman WT, DeGeest K, DiSaia PJ, Zaino R. Significance of true surgical pathologic staging: a Gynecologic Oncology Group study. *Am J Obstet Gynecol* 181(1): 31-34, 1999.

GOG 0034

Thigpen JT, Morrow CP, Blessing JA. Adjuvant Chemotherapy in High Risk Endometrial Carcinoma. *Endo Cancer*: 223-232, 1986.

Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hoenback ND, Kurman R, Thigpen JT. Doxorubicin as an Adjuvant Following Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma, Stage I and Occult Stage II (A Gynecologic

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GOG 0040

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GOG 0042

Muss HB, Bundy BN, DiSaia PJ, Homesley HD, Fowler WC, Creasman W, Yordan E. Treatment of Recurrent or Advanced Uterine Sarcoma: A Randomized Trial of Doxorubicin Versus Doxorubicin and Cyclophosphamide (A Phase III Trial of the Gynecologic Oncology Group). *Cancer* 55(8): 1648-1653, 1985.

GOG 0048

Thigpen T, Blessing J, DiSaia, P. Oral Medroxyprogesterone Acetate in Advanced or Recurrent Endometrial Carcinoma: Results of Therapy and Correlation with Estrogen and Progesterone Receptor Levels. The Gynecologic Oncology Group Experience. *Proc 1st Int Congress on Cancer and Hormones*: 1986.

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GOG 0055

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GOG 0057

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GOG 0069

Petrilli ES, Twiggs LB, Curry SL, Sikic B, Hatch K, Schlaerth JB, Blessing JA. Single Dose Actinomycin D Treatment for Non-metastatic Gestational Trophoblastic Disease. Presented SGO. *Gynecol Oncol* 23: 244 (#2), 1986.

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GOG 0079

Homesley HD, Blessing JA, Rettenmaier M, Capizzi RL, Major FJ, Twiggs LB. Weekly Intramuscular Methotrexate for Non-metastatic Gestational Trophoblastic Disease (A Gynecologic Oncology Group Study). *Obstet Gynecol* 72(3 I): 413-418, 1988.

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GOG 0081

Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, Soper J, Given FT. Oral Medroxyprogesterone Acetate in the Treatment of Advanced or Recurrent Endometrial Carcinoma: A Dose Response Study by the Gynecologic Oncology Group. *J Clin Oncol* 17:1736-1744, 1999.

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GOG 0083

Zaino RC, Whitney C, Brady MF, DeGeest K, Burger RA, Buller RE. Simultaneously detected endometrial and ovarian carcinomas: a prospective clinicopathologic study of 74 cases: a Gynecologic Oncology Group Study. *Gynecol Oncol* 83(2): 355-362, 2001.

GOG 0094

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Sutton G, Axelrod J, Bundy B, Roy T, Homesley H, Lee R, Gehrig P, Zaino R. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol* 100(2): 349-354, 2006.

GOG 0096

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GOG 0099

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GOG 0107

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GOG 0108

Sutton G, Brunetto VL, Kilgore L, Soper JT, Bell J, McGehee R. phase III trial of ifosfamide with or without cisplatin in carcinoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 79(2): 147-153, 2000.

GOG 0117

Olivier RI. The rationale for comprehensive surgical staging in endometrial carcinosarcoma: Letter to the editor. *Gynecol Oncol* 99(2): 521-522, 2005.

Sutton GP, Kauderer JT, Carson LF, Lentz SS, Whitney CW, Gallion H.. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 96(3):630-4, 2005.

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GOG 0119

Whitney CW, Brunetto VL, Zaino R, Lentz S, Sorosky J, Armstrong D, Lee R. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a GOG study. *Gynecol Oncol* 92(1): 4-9, 2004.

GOG 0121

Lentz S, Brady MF, Major FJ, Reid GC, Soper JT. High Dose Megestrol Acetate in Advanced or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study. *J Clin Oncol* 14(2): 357-361, 1996.

GOG 0122

Randall M, Filiaci V, Muss H, Spirtos N, Mannel R, Fowler J, Thigpen JT, Benda J. Randomized phase III trial of whole abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 24(1): 36-44, 2006.

GOG 0139

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GOG 0150

Wolfson AH, Brady MF, Rocereto T, Mannel RS, Lee Y, Futoran RJ, Cohn D, Ioffe OB. A phase III randomized study of whole abdominal radiotherapy versus combination ifosfamide mesma with cisplatin in optimally debulked stage I, II, III or IV carcinosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 107(1): 177-185, 2007.

GOG 0153

Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 92(1):10-14, 2004.

GOG 0159

Asbury RF, Brunetto VL, Lee RB, Reid G, Rocereto TF. Gosere-line acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Am J Clin Oncol*: CCT 25(6): 557-560, 2002.

GOG 0161

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GOG 0163

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GOG 0168

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GOG 0174

Osborne RJ, Filiaci V, Schink JC, Mannell RS, Alvarez Secord A, Kelley JL, Provencher D, Miller DS, Covens AL, Lage J. A phase III trial of weekly methotrexate and pulsed dactinomycin for low risk gestational trophoblastic neoplasia: a Gynecologic Oncology Group (GOG) study. *J Clin Oncol* 29(7):825 31,2011.

GOG 0176

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GOG 0177

Fleming GF, Brunetto VL, Cella D, Look KY, Reid G, Munkarah A, Kline R, Burger RA, Goodman A, Burks RT. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 22(11):2159 66,2004.

GOG 0180

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GOG 0184

Homesley H, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos N, Morris RT, DeGeest K, Lee R, Montag A. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin or with or without paclitaxel: A GOG study. *Gynecol Oncol* 112:543 52,2009.

GOG 0188

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GOG 0210

Brinton LA, Felix AS, McMeekin DS, Creasman WT, Sherman ME, Mutch D, Cohn DE, Walker JL, Moore RG, Downs, LS, Soslow RA, Zaino R. Etiologic heterogeneity in endometrial can-

cer: Evidence from a Gynecologic Oncology Group trial. *Gynecol Oncol* 129:277 84,2013.

GOG 9206

Homesley HD, Boike G, Spiegel G. Feasibility of laparoscopic management of presumed stage I endometrial carcinoma and assessment of accuracy of myoinvasion estimates by frozen section: a Gynecologic Oncology Group study. *Int J Gyn Cancer* 14(2):341 7,2004.

GOG 9402

Spirtos N, Eisenkop SC, Boike G, Schlaerth JB, Cappellari J. Laparoscopic staging in patients with incompletely staged cancers of the uterus, ovary, fallopian tube, and primary peritoneum: a Gynecology Oncology Group study. *Am J Obstet Gynecol* 193(5):1645 9,2005.

GOG LAP2

Schlaerth JB, Mannel RS, Spiegel G, Barakat R, Pearl ML, Sharma SK. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study (LAP2). *J Clin Oncol* 27(32):5331 6,2009.

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GOG PILOT1

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GOG PILOT 11

Sall S, DiSaia P, Morrow CP, Mortel R, Prem K, Thigpen T, Creasman W. A comparison of medroxyprogesterone serum concentrations by the oral or intramuscular route in patients with persistent or recurrent endometrial carcinoma. *Am J Obstet Gynecol* 135(5): 647-650, 1979.

GOG PILOT 2

DiSaia PJ, Morrow CP, Boronow R, Creasman W, Mittelstaedt L. Endometrial sarcoma: lymphatic spread pattern. *Am J Obstet Gynecol* 130(1):104-105, 1978.

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Cervix/Vulva Publications

GOG 0004

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GOG 0005

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GOG 0019

Lagasse LD, Creasman WT, Shingleton HM, Ford JH, Blessing JA. Results and Complications of Operative Staging in Cervical Cancer: Experience of the Gynecologic Oncology Group. *Gynecol Oncol* 9(1): 90-98, 1980.

Berman ML, Keys H, Creasman WT, DiSaia PJ, Bundy BN, Blessing JA. Survival and Patterns of Recurrence in Cervical Cancer Metastatic to Para aortic Lymph Nodes. (Gynecologic Oncology Group Study). *Gynecol Oncol* 19(1):8-16, 1984.

GOG 0023

Wallace HJ Jr, Hreshchyshyn MM, Wilbanks GD, Boronow RC, Fowler WC Jr, Blessing JA. Comparison of the Therapeutic Effects of Adriamycin Alone Versus Adriamycin plus Vincristine Versus Adriamycin plus Cyclophosphamide in the Treatment of Advanced Carcinoma of the Cervix. *Cancer Treat Rep* 62(10): 1434-1441, 1978.

GOG 0024

DiSaia PJ, Gall S, Levy D, Bundy BN. A Preliminary Report on the Treatment of Women with Cervical Cancer, Stages IIB, IIIB, and IVA Confined to the Pelvis and/or Para aortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C parvum), Phase III. Presented at the NCI. *In Imm Human Cancer* 8: 331-335, 1982.

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Edition: 544-555, 1990.

Stehman FB, Bundy BN, DiSaia PJ, Heys HM, Larson JE, Fowler WC III. Carcinoma of the Cervix Treated with Irradiation Therapy I: A Multivariate Analysis of Prognostic Variables in the Gynecologic Oncology Group Presented at the 72 Annual Meeting of the American Radium Society. *Cancer* 67(11): 2776-2785, 1991.

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GOG 0031

DiSaia PJ, Blessing JA, Lewis Jr GC. Ongoing Clinical Trials in Clinical Intraepithelial Neoplasia by the Gynecologic Oncology Group, Part 2. *Gynecol Oncol* 12(2):S302-S305, 1981.

GOG 0036

Homesley HD. Carcinoma of the vulva. *Conns Current Therapy*: 888-893, 1986.

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Homesley HD, Bundy BN, Sedlis A, Yordan E, Berek JS, Jahshan A, Mortel R. Assessment of Current International Federation of Gynecology and Obstetrics Staging of Vulvar Carcinoma Relative to Prognostic Factors for Survival (A Gynecologic Oncology Group Study). *Am J Obstet Gynecol* 164(4): 997-1004, 1991.

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GOG 0037

Homesley HD, Bundy BN, Sedlis A, Adcock L. A Randomized Study of Radiation Therapy Versus Pelvic Node Resection for Patients with Invasive Squamous Cell Carcinoma of the Vulva Having Positive Groin Nodes (A Gynecologic Oncology Group Study). *Obstet Gynecol* 68(6): 733-740, 1986.

GOG 0043

Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized Trial of Three Cisplatin Dose Schedules in Squamous Cell Carcinoma of the Cervix (A Gynecologic Oncology Group Study). *J Clin Oncol* 3(8): 1079-1085, 1985.

GOG 0049

Delgado G, Bundy BN, Fowler WC, Stehman FB, Sevin B, Creasman WT, Major G, DiSaia P, Zaino R. A Prospective Surgical Pathological Study of Stage I Squamous Carcinoma of the Cervix: A Gynecologic Oncology Group Study. *Gynecol Oncol* 35:314-320, 1989.

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GOG 0123

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GOG 0141

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GOG 0204

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GOG 0205

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GOG 8903

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Rare Tumor Publications

GOG 0239

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Developmental Therapeutics Publications

GOG 0009

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GOG 0015

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GOG 0026B

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GOG 0026C

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GOG 0026D

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GOG 0026E

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GOG 0026F

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GOG 0026G

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GOG 0170J

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GOG 0170K

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GOG 0170L

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GOG 0170M

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GOG 0170N

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GOG 0181B

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GOG 0186C

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GOG 0186D

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GOG 0186F

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logic Oncology Group. *Gynecol Oncol* 120: 459-463, 2011.

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GOG 0227D

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GOG 0227E

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GOG 0229B

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GOG 0229C

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GOG 0229D

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GOG 0229E

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GOG 0230C

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GOG 0231B

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GOG 0231C

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GOG 8808

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GOG 9405

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GOG 9703

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GOG 9704

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GOG 9804

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GOG 9807

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GOG 9906

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GOG 9908

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GOG 9912

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GOG 9913

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GOG 9914

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Kunos C, Sill M, Buekers TE, Walker JL, Schilder JM, Yamada SD, Waggoner SE, Mohiuddin M, Fracasso P. Low dose abdominal radiation as a docetaxel chemosensitizer for recurrent epithelial ovarian cancer: a phase I study of the Gynecologic Oncology Group. *Gynecol Oncol* 120(2): 224-228, 2011.

GOG 9916

Gould N, Sill MW, Mannel RS, Thaker PH, DiSilvestro PA, Waggoner S, Yamada SD, Armstrong DK, Fracasso PM, Walker JL. A phase I study with an expanded cohort to assess feasibility of intravenous docetaxel, intraperitoneal carboplatin and intraperitoneal paclitaxel in patients with previously untreated ovarian, fallopian tube or primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 127(3): 506-510, 2012.

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GOG 9917

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GOG 9918

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GOG 9919

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I trial of dose dense (biweekly) carboplatin combined with paclitaxel and pegfilgrastim: a feasibility study in patients with untreated stage III and IV ovarian, tubal or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 118: 303-337, 2010.

GOG 9921

Dizon DS, Sill MW, Gould N, Rubin SC, Yamada SD, Debernardo RL, Mannel RS, Eisenhauer EL, Duska LR, Fracasso PM. Phase I feasibility study of intraperitoneal cisplatin and intravenous paclitaxel followed by intraperitoneal paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 123(2): 182-186, 2011.

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Experimental Medicine Publications

GOG 0114

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status, VEGF expression and progression free survival in previously untreated, advanced stage epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 115(3): 424-429, 2009.

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GOG 0119

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GOG 0136

Zorn KK, Jazaeri AA, Awtrey CS, Gardner GJ, Mok SC, Goyd J, Birrer MJ. Choice of normal ovarian control influences determination of differentially expressed genes in ovarian cancer expression profiling studies. *Clin Cancer Res* 9(13):4811 8,2003.

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GOG 0143

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GOG 0144

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GOG 0157

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GOG 0158

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GOG 0163

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GOG 0165

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GOG 0170D

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GOG 0172

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GOG 0177

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GOG 0210

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GOG 8004

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GOG 8810

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GOG 9404

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GOG 9911

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MISC

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Darcy KM, Mannel RS, Ramirez NC, Alberts DS, Jelonek J, Puehn K, Birrer MJ. Gynecologic Oncology Group ovarian treatment trials with specimen banking and translational research. *Clinical Ovarian Cancer* 3(2): 98-112, 2010.

In addition, 44 abstracts have been published.

Quality of Life Publications

GOG 0111

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GOG 0122

Bruner DW, Barsevick A, Tian C, Randall M, Mannel R, Cohn DE, Sorosky J, Spirtos NM. Randomized trial results of quality of life comparing whole abdominal irradiation and combination chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Qual Life Res* 16(1): 89-100, 2007.

GOG 0152

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GOG 0169

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GOG 0172

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GOG 0177

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GOG 0179

Monk BJ, Huang H, Cella D, Long HJ. Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 23(21): 4617-4625, 2005.

GOG 0184

Cella D, Huang H, Homesley HD, Montag A, Salani R, De Geest K, Lee R, Spirtos N. Patient reported peripheral neuropathy of doxorubicin and cisplatin with and without paclitaxel in the treatment of advanced endometrial cancer: Results from GOG 184. *Gynecol Oncol* 119: 538-542, 2010.

GOG 0204

Cella D, Huang H, Monk BJ, Wenzel L, Benda J, McMeekin DS, Cohn D, Ramondetta L, Boardman C. Health related quality of life outcomes associated with four cisplatin based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 119: 531-537, 2010.

GOG 0218

Monk BJ, Huang H, Burger RA, Mannel RS, Homesley HD, Fowler JA, Greer BE, Boente MP, Liang SX, Wenzel L. Patient reported outcomes of a randomized, placebo controlled trial of bevacizumab in the front line treatment of ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 128: 573-578, 2013.

GOG 8003

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GOG 9102

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GOG 9805

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GOG 9901

Swenson M, MacLeod J, Williams S, Miller A, Champion V. Quality of living among ovarian germ cell cancer survivors: a narrative analysis. *Oncol Nurs Forum* 30(3): 380, 2003.

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Gershenson DM, Miller AM, Champion VL, Monahan PO, Zhao Q, Cella D, Williams SD. Reproductive and sexual function after platinum based chemotherapy in long term ovarian germ cell tumor survivors: A Gynecologic Oncology Group study. *J Clin Oncol* 25(19): 2792-2797, 2007.

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27(25): 4142-4149, 2009.

GOG 9902

Wenzel LB, Donnelly JP, Fowler JM, Habbal R, Taylor TH, Aziz N, Cella A. Resilience, reflection, and residual stress in ovarian cancer survivorship: A Gynecologic Oncology Group study. *Psycho Oncol* 11(2): 142-153, 2002.

GOG LAP2

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MISC

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In addition, 25 abstracts have been published.

Cancer Prevention & Control Publications**GOG 0137**

Barakat R, Bundy B, Spirtos N, Bell J, Mannel RS. Randomized double blind trial of estrogen replacement therapy versus placebo in women with stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 24: 587-592, 2006.

GOG 0167

Trimble C, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke J II, Alberts D, Curtin JP. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 106(4): 812-819, 2006.

Zaino R, Kauderer J, Trimble C, Silverberg S, Curtin JP, Lim PC, Gallup D. Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 106(4): 804-811, 2006.

Bartels PH, Garcia FAR, Trimble CL, Kauderer J, Curtin J, Lim PC, Hess LM, Silverberg S, Zaino RJ, Yozwiak M, Bartels HG, Alberts DS. Karyometry in atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Gynecol Oncol* 125: 129-135, 2012.

GOG 0171

Liao SY, Rodgers WH, Kauderer J, Bonfiglio TA, Walker JL, Darcy KM, Carter R, Hatae M, Levine L, Spirtos NM, Stanbridge EJ. Carbonic anhydrase IX and human papillomavirus as diagnostic biomarkers of cervical dysplasia/neoplasia in women with a cytologic diagnosis of atypical glandular cells: a Gynecologic Oncology Group study in United States. *Int J Cancer* 125(10): 2434-2440, 2009.

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Kang L, Carter R, Darcy K, Kauderer J, Liao, SY. Monte Carlo EM algorithm for estimation in latent class model analysis with an application to assess accuracy of diagnostic accuracy for cervical neoplasia in women with AGC. *J Applied Stats* (IN PRESS)

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GOG 0195

Carlson JW, Kauderer J, Walker JL, Gold MA, O'Malley D, Tuller E, Clarke Pearson D. A randomized phase III trial of VH fibrin sealant to reduce lymphedema after inguinal lymph node dissection: a Gynecologic Oncology Group study. *Gynecol Oncol* 110: 76-82, 2008.

GOG 0199

Greene MH, Piedmonte M, Alberts D, Gail M, Hensley M, Miner Z, Mai PL, Loud J, Rodriguez G, Basil J, Boggess J, Schwartz PE,

Kelley JL, Wakeley KE, Minasian L, Skates S. A prospective study of risk reducing salpingo oophorectomy and longitudinal CA 125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: A Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev* 17(3): 594-604, 2008.

Antoniou AC, Sinilnikova O, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Schwartz PE, Blank SV, numerous coauthors from various groups. Common variants in LSP1,2q35 and 8q24 and breast cancer risk for BRCA1 and BRCA2 mutation carriers. *Hum Mol Genet* 18(22): 4442-4456, 2009.

Osorio A, Milne RL, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Schwartz PE, Blank SV, numerous coauthors from various groups. Evaluation of a candidate breast cancer associated SNP in ERCC4 as phenotypic modifier in BRCA1/2 mutation carriers. Results from the consortium of investigators of modifiers of BRCA1/BRCA2 (CIMBA). *Br J Cancer* 101: 2048-2054, 2009.

Antoniou AC, Beesly J, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Schwartz PE, Blank SV, numerous contributors from various groups. Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: Implications for risk prediction. *Cancer Res* 70(23): 9742-9754, 2010.

Antoniou AC, Wang X, Frederiksen ZS, McGuffog L, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Blank SV. A locus on 19p13 locus modifies the risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor negative breast cancer in the general population. *Nature Genetics* 42(10): 885-892, 2010.

Gaudet MM, Kirchoff T, Piedmonte M, Rubinstein W, Nerenstone S, Van Le L, Blank SV, Greene ML, Mai, PL, Offit K. Common genetic variants and modification of penetrance of BRCA2 associated breast cancer. *PLoS Genetics* 6(10): 1-9, 2010.

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Antoniou AC, Kartsonaki C, Sinilnikova O, Piedmonte M, Rodriguez G, Small L, Boggess J, Blank S, Basil J, Azodi, M. Common alleles at 6q25.1 and 1p11.2 are associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers. *Human Mol Genet* 20(16): 3304-3321, 2011.

Cox DG, Simard J, Sinnott D, Piedmonte M, Rodriguez GC, Basil JB, Blank S, Mazoyer S, Sinilnikova OM. Common variants of the BRCA1 wild type allele modify the risk of breast cancer in BRCA1 mutation carriers. *Hum Mol Genetics* 20(23): 4732-4747, 2011.

Im KM, McGee KM, Kirchhoff T, Green T, Greene M, Piedmonte M, Azodi M, Gold B. Haplotype structure in Ashkenazi Jewish BRCA1 and BRCA2 mutation carriers. *Hum Genet* 130: 685-699, 2011.

Skates SL, Piedmonte M, Rodriguez G, Van Le L, Cohn D, Azodi M, Nerenstone S, Kauff ND. Large prospective study of ovarian cancer screening in high risk women: CA125 cut point defined by menopausal status. *Cancer Prev Res* 4(9): 1401-1408, 2011.

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Ding YC, McGuffog L, Healey S, Piedmonte M, Andrews L, Cohn D, Rodriguez GC, DeMars LR, DiSilvestro PA, Neuhausen S. G972R in IRS1 modifies risk to develop ovarian cancer in BRCA1 and BRCA2 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 21(8): 1362-1370, 2012.

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M, Phillips KA, Cohn D, Rodriguez G, Van Le L, Hoffman JS. Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 carriers. *Human Mutation* 33(4): 690-702, 2012.

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Bojesen SE, Pooley, Piedmonte M, Salani R, Rodriguez G et al.. Multiple independent TERT variants associated with telomere length and breast cancer risk. *Nature Genetics* (IN PRESS)

Couch FJ, Wang X, Piedmonte M, Friedlander M, Cohn D, Rodriguez G, Bae Jump, VL, Small L, Blank S, et al. Genome wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genetics* (IN PRESS)

Gaudet MM, Kuchenbaecker KB, Piedmonte M, Greene M, Phuong M, et al.. Identification of a BRCA2 specific modifier locus at 6p24 related to breast cancer risk. *PLoS Genetics* (IN PRESS)

In addition, 12 abstracts have been published.

Ancillary Data Publications

GOG 0037

Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes: an update of a Gynecologic Oncology Group study. *Obstet Gynecol* 114(3): 537-546, 2009.

GOG 0056

Rose P, Ali S, Whitney C, Lanciano R, Stehman FB. Impact of hydronephrosis on outcome of stage IIIB cervical cancer patients with disease limited to the pelvis, treated with radiation therapy and concurrent chemotherapy: a Gynecologic Oncology Group study. *Gynecol Oncol* 117: 270-275, 2010.

GOG 0071

Kunos C, Ali S, Abdul Karim F, Stehman FB, Waggoner S. Post-

therapy residual disease associates with long term survival after chemoradiation for bulky stage 1B cervical carcinoma: a Gynecologic Oncology Group study. *Am J Obstet Gynecol* 203: 351-358, 2010.

GOG 0074

Stehman FB, Ali S, DiSaia PJ. Node count and groin recurrence in early vulvar cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 113: 52-56, 2009.

GOG 0085

Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical vs radiographic determination of para aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group study. *Cancer* 112(9): 1954-1963, 2008.

GOG 0099

von Gruenigen VE, Tian C, Waggoner S, Frasure H, Barakat R.. Treatment effects, disease recurrence and survival as related to obesity in women with early endometrial carcinoma: a Gynecologic Oncology Group study. *Cancer* 12: 2786-2791, 2006.

GOG 0102B

Markman M, Brady M, Hutson A, Berek J. Survival after second line intraperitoneal therapy for the treatment of epithelial ovarian cancer: The Gynecologic Oncology Group Experience. *Int J Gynecol Cancer* 19(2): 223-229, 2009.

GOG 0104

Alberts DS, Markman M, Muggia F, Ozols RF, Eldermire E, Bookman MA, Chen T, Curtin J, Hess LM, Liebes L, Markman M, Young RC, Trimble E. Proceedings of a GOG Workshop on Intraperitoneal Therapy for Ovarian Cancer. *Gynecol Oncol* 103: 783-792, 2006.

GOG 0107

Maxwell GL, Tian C, Risinger J, Brown C, Rose GS, Thigpen JT, Fleming G, Gallion H, Brewster W. Racial disparity in survival among patients with advanced/recurrent endometrial adenocarcinoma: a GOG study. *Cancer* 107(9): 2197-2205, 2006.

Modesitt SC, Tian C, Kryscio R, Thigpen JT, Randall M, Gallion HH, Fleming GF. Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and

cisplatin: a Gynecologic Oncology Group study. *Gynecol Oncol* 105: 59-65, 2007.

Farley JH, Tian C, Rose GS, Brown CL, Birrer M, Risinger JJ, Thigpen JT, Fleming GF, Gallion HH, Maxwell GL. Chemotherapy intensity and toxicity among black and white women with advanced and recurrent endometrial cancer: A Gynecologic Oncology Group study. *Cancer* 116(2): 355-361, 2010.

GOG 0111

Winter W, Maxwell GL, Tian C, Sundborg M, Rose GS, Rose PG, Rubin SC, Muggia F, McGuire W. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 26(1): 83-89, 2008.

Zorn KK, Tian C, McGuire WP, Hoskins WJ, Markman M, Muggia FM, Rose PG, Ozols RF, Spriggs D, Armstrong DK. Prognostic value of pretreatment CA 125 in advanced ovarian carcinoma: A Gynecologic Oncology Group study. *Cancer* 112:1028-1035, 2009.

GOG 0114

Hamilton CA, Miller A, Miller C, Farley JH, Chernofsky MR, Krivak TC, Stany MP, Rose GS, Markman M, Ozols RF, Armstrong DK, Maxwell GL. The impact of disease distribution on survival in patients with stage III epithelial ovarian cancer cytoreduced to microscopic residual: a Gynecologic Oncology Group study. *Gynecol Oncol* 122(3): 521-526, 2011.

Gardner GJ, Baser RE, Brady MF, Bristow RE, Markman M, Spriggs D, Thaler HT. CA125 Regression in ovarian cancer patients treated with intravenous versus intraperitoneal platinum based chemotherapy: A Gynecologic Oncology Group study. *Gynecol Oncol* 124(2): 216-220, 2012.

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GOG 0119

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Young Investigator Awards Publications**GOG 0095**

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