Chapter 5 |

The GOG Foundation, Inc. Uterine Cancer Trials



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Endometrial Cancer

Introduction

Until the early 1970's when the legacy Gynecologic Oncology Group was first launching a multi-center, multidisciplinary therapeutic approach for all gynecologic cancers, endometrial cancer therapy had, for decades, been based on institutional experiences rather than prospective, randomized trials. For the first time, a large collaborative group made it possible to conduct prospective trials in endometrial cancer while at the same time accumulating essential data 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, as well as other histopathologic features should be studied prospectively in many patients to provide a foundation for future trials to be developed.

Historically, carcinosarcomas were classified as uterine sarcomas. More recently, this has changed and carcinosarcomas are included under adenocarcinomas. They are treated the same way as poorly differentiated adenocarcinomas, and it is the epithelial component that are most likely the histology of the metastatic sites.
Currently, molecular subtyping of endometrial cancers serves to determine prognosis and treatment options for current patients, but also helps to define and initiate future practice changing trials within this classification.

Surgical Staging

GOG 33 was a large staging trial with nearly 1,200 patients with endometrial cancer accrued 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 surgical-pathologic data remains.[7] The continued relevance of these data in the era of molecular subtyping will need to evaluated.

In GOG 33, for patients without metastasis as 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, dimin-

ished 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 radiotherapy and/or chemotherapy. 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.

For carcinosarcoma, this usually consists of total abdominal hysterectomy and bilateral salpingooophorectomy 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%.[4]
Given lymphadenectomy has known complications of lymphedema, lymphocysts, vascular and nerve injury, blood loss, and prolonged operation time, many centers investigated the use of sentinel lymph dissection in endometrial cancer. This was developed largely by single institutional studies and has been adopted into the NCCN guidelines (2014) as a reasonable surrogate for fully lymph node assessment with apparent less complications.

Laparoscopy
Advances in laparoscopic technology emboldened a few surgeons to undertake cancer operations with this surgical modality. 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 improvement, and Homesley et al. reported the results of GOG 9206 describing the feasibility of laparoscopic staging of endometrial cancer.[8] Spirtos 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, where patients with clinical stage I to IIA uterine cancer were randomly assigned to laparoscopy (n = 1,696) or open laparotomy (n = 920), and 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. 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 sub-sets 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; increased risk of death as well as greater 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 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 several 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 not mandatory. Finally, this was the first group-wide study in which intensity-modulated radiation therapy (IMRT) could be employed. This study accrued quickly and was reported by Randall, Filiaci et al. 2019.[83] At 60 months, the Kaplan-Meier estimate of the percentage of patients alive and relapse-free was 59% (95% confidence interval [CI], 53 to 65) in the chemoradiotherapy group and 58% (95% CI, 53 to 64) in the chemotherapy-only group (hazard ratio, 0.90; 90% CI, 0.74 to 1.10). Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; hazard ratio, 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph-node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; hazard ratio, 1.36; 95% CI, 1.00 to 1.86). Pelvic or para-aortic nodal recurrences were more common in the chemotherapy arm, 9% vs 4%. Patients with serous cancer accounted for 15% of patients enrolled on GOG 249, and although the expectation was that chemotherapy may benefit patients with this high-risk histology, there was no significant difference in PFS or OS when chemotherapy was combined with VCB.

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, GOG184 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).

In the locally advanced population, the GOG conducted 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.

GOG 258 enrolled total of 813 patients with stage 3 or 4A endometrioid endometrial cancer, as well as stage 1 or 2 serous or clear cell carcinoma with positive washings. Pa-

tients were randomized to combined chemoradiation which consisted of cisplatin 50 mg/m2 on days 1 and 29 together with volume directed external beam radiation therapy, followed by carboplatin AUC of 5 to 6 plus paclitaxel at a dose of 175 mg/m2 every 21 days for four cycles, with GCSF support or a chemotherapy only regimen consisting of carboplatin AUC of 6 plus paclitaxel at a dose of 175 mg/m2 every 21 days for six cycles. In the chemoradiotherapy group, external beam radiation therapy was delivered to the pelvis with or without paraaortic fields. The planned total dose was 45 Gy in 25 fractions at 180 cGy per fraction. Intensity modulated radiotherapy and vaginal brachytherapy were allowed only in the chemoradiotherapy group. [84] Nearly all enrolled patients (98%) had no gross residual disease, and 94% underwent some degree of lymph node assessment. At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapsefree was 59% (95% CI, 53 - 65) in the chemoradiotherapy group and 58% (95% CI, 53 - 64) in the chemotherapy only group (HR 0.90; 90% CI, 0.74 - 1.10). Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%; HR 0.36; 95% CI, 0.16 to 0.82) and pelvic and paraaortic lymph node recurrence (11% vs. 20%; HR 0.43; 95% CI, 0.28 to 0.66) than chemotherapy alone, but distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; HR 1.36; 95% CI, 1.00 to 1.86). Furthermore, assessment of quality-of-life endpoints suggested both acute and long-term toxic effects of combination chemoradiation therapy, suggesting that chemotherapy alone was the most appropriate adjuvant regimen in this patient population.

GOG 150 evaluated stage I-IV carcinosarcomas. 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.

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. Among patients getting cisplatin-based chemotherapy concurrent with radiation, 57.3% were alive and progression-free compared with 68% of patients who got definitive radiation alone -- a relative 50% worse outcome for the chemotherapy group over the study's median five years of follow-up, though this difference was not statistically significant (P=0.8). There were no differences in overall survival (OS) between the two cohorts, with 75.6% and 78.6% alive, respectively. Radiation therapy alone remains the standard of care for pelvic-only, vaginal cuff endometrial cancer recurrences.

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 practice was to initially treat all patients with hormonal therapy; however, 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 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, depot-provera were elucidated in GOG 211. In this study, Depot-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.

Other hormonal agents have been tested but do not appear to have superior efficacy to progestins. Anastrazole 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 eight weeks, and until evidence of progression. Although toxicity was limited, there was little evidence of anti-tumor activity.[22]

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. This completed study was the group's first randomized trial to evaluate the role of biologic therapy in endometrial cancer.[42]

In a single-arm, Phase 2 trial, Slomovitz and colleagues demonstrated that the mTOR inhibitor everolimus in combination with letrozole results in a high clinical benefit rate and high objective response rate in patients with recurrent endometrial cancer.[40] Subsequently, GOG 3007, a randomized phase II trial, evalauted everolimus in combination with letrozole compared to the alternating regimen of medroxyprogesterone acetate/tamoxifen. Chemotherapy naïve patients receiving everolimus/letrozole, demonstrated a 28-month median progression-free survival, while patients who received prior chemotherapy had a four-month median progression-free survival.38) Progression-free survival was also higher in chemotherapy naïve patients in the medroxyprogesterone acetate/tamoxifen group (five months versus three months). The results in chemotherapy naïve patients on everolimus/leterozole compares favorably to the chemotherapy trials,[24, 25] and warrants further investigation into hormonal therapy combined with molecularly targeted therapies as the standard of care in carefully selected patients (ie low grade, ER+) with anticipated benefits.

Three phase 2 trials demonstrated efficacy using CDK 4/6 inhibitors in combination with hormonal therapy in women with recurrent endometrial cancer. Based on these signals, GOG 3039 is currently accruing patients evaluating abemiciclib combined with letrozole for the management of recurrent disease. GOG 3075 is evaluating lerociclib, also a CDK 4/6 inhibitor, combined with letrozole versus letrozole alone in the first line management of advanced or recurrent disease.

The PI3K/PTEN/PIK3CA pathway is altered in 93% of endometrioid endometrial cancer with PIK3CA activing mutations in 53%. Recent data have shown promising responses in patients with ER positive endometrial cancer treated with endocrine therapy plus mTOR inhibitors or CDK4/6 inhibitors. The combination of alpelisib and fulvestrant was FDA approved for treatment of ER+ PIK3CA-mutated Breast Cancer on May 24, 2019, based on the SOLAR-1 study. GOG 3069 is evaluating the efficacy of alpelisib and fulvestrant for the treatment of ER+ PIK3CA-

mutated Endometrioid Endometrial Cancer.

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 several 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- fluourouracil to doxorubicin, cyclophosphamide and 5-fluourouracil.[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 intra- venously 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 re markable 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 like 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 cis- platin 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, GOG 0107, 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. Hematologic toxicities, response rates, PFS, and survival did not differ 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, GOG 9405, 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, GOG 0184 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 seven 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. GOG protocol 209 enrolled 1,381 women over approximately six years. TC as found to be noninferior to TAP with respect to OS (median, 37 vs. 41 months, respectively; HR 1.002, 90% CI 0.9-1.12) and PFS (median 13 vs 14 months; HR 1.032; 90% CI 0.93-1.15) (Miller, Filiaci et al. 2020). Neutropenic fever was similar between treatment arms, although sensory neuropathy, grade 3 or greater thrombocytopenia, emesis, diarrhea and metabolic toxicities were more frequent in the TAP arm. These findings established carboplatin and paclitaxel as the preferred systemic regimen for the treatment of metastatic or recurrent endometrial cancer, and as the backbone for future clinical trials.

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 mullerian tumors (MMMTs).[55,56] Ifosfamide also is active in the treatment of 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-angio-

genic 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. 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 three days every three weeks for eight cycles versus ifosfamide 1.6 g/M2/d for 3 days plus paclitaxel, 135 mg/M2 by three hour infusion on day 1 repeated every three weeks for eight 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 were 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 Phase III randomized study 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 pacli taxel (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. A total of 449 eligible patients were enrolled, with reported median OS of 37 months for patients treated with carboplatin plus paclitaxel compared to 29 months for the ifosfamide–paclitaxel with mesna arm (HR 0.87; 90% CI 0.70-1.075; p<0.01 for noninferiority). Median PFS additionally favored the carboplatin-paclitaxel arm (16 vs 12 months; HR 0.73; p < 0.01 for noninferiority). Both study arms experienced a similar decline in quality of life and increased neurotoxicity, although there was an increased in hematologic toxicity in the carboplatin-paclitaxel arm. The results of GOG 261 established carboplatin and paclitaxel as the preferred systemic regimen for patients with uterine carcinosarcoma.

GOG 150 evaluated stage I-IV carcinosarcomas 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.

Chemotherapy Plus Hormonal or Biologic 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 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 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.

The GOG conducted a phase II randomized 3 arm study incorporating different biologic agents (GOG 86P). This study randomized 349 patients to either: 1) carboplatin (C) + paclitaxel (P) + bevacizumab vs. 2) CP + temsirolimus vs. 3) C + ixabepilone + bevacizumab. The CP + bevacizumab triplet regimen compared favorably to the other treatment arms, with a 59.5% objective response rate (24.7% with complete response). In addition, when compared to a matched group from GOG protocol 209 (CP arm), the triplet regimen of CP + bevacizumab showed a significant improvement in OS (34 vs. 22.7 months; p<0.039). Grade ≥ 3 AEs occurring in >5% of patients on the CP + bevacizumab regimen were limited to hypertension and proteinuria (Aghajanian et al. *J Clin Oncol*).

Immunotherapy

Checkpoint inhibitors are approved in advanced and recurrent EC following prior treatment with systemic therapy, however ongoing studies are evaluating their use in other settings. For example, the first molecularly selected adjuvant therapy trial, NRG-GY020, has completed accrual and will shed light on the benefit of pembrolizumab in addition to radiation in newly diagnosed early-stage dMMR endometrioid EC (NCT0421406). ENGOT-en11/GOG-3053/KEYNOTE-B21 is a phase III study of pembrolizumab or placebo in combination with adjuvant chemotherapy with or without radiotherapy (NCT04634877). Data is pending maturity from ENGOT-EN6/GOG-3031/NSGO-RUBY, which evaluated the efficacy and safety of dostarlimab in combination with carboplatin-paclitaxel in recurrent or primary advanced EC compared with carboplatin-paclitaxel alone (NCT03981796). Recent findings from a planned interim analysis showed the combination produced a statistically significant improvement in PFS compared with chemotherapy alone in the dMMR/MSI-H cohort and in the overall population.[34] Likewise, data regarding the use of ICIs in combination with first-line chemotherapy in advanced and recurrent EC are pending: NRG-GY018 using pembrolizumab (NCT03914612). Finally, one study evaluating first-line ICI versus carboplatin-paclitaxel in advanced and recurrent dMMR EC: KEYNOTE-C93/GOG-3064/ENGOT-en15 using pembrolizumab (NCT05173987) is currently accruing.

Several studies are currently investigating combinations of checkpoint inhibitors with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors as they cause accumulation of DNA damage and may alter immune checkpoint receptor expression.[40-42] Platinum-based chemotherapy plus PARP inhibitors and CPIs as first-line treatment for advanced EC are being studied in both ENGOT-EN6/GOG-3031/NSGO-RUBY part 2 and DUO-E (NCT03981796, NCT04269200).

Both LAG-3 and TIM-3 are potential targets for immunotherapy as they participate in the immune escape of tumor cells. Expression of both markers is also stronger in dMMR EC than in other subtypes.[44-45] Research targeting these biomarkers is ongoing (GOG 3038).

Other targets

Selinexor is an oral selective inhibitor of nuclear export (SINE). In paired tumor samples it has been shown to inhibit nuclear export of the wild-type TP53 tumor suppressor. In the randomized phase III SIENDO trial, patients who were in response (CR/PR) to 1st line CP were randomized to selinexor maintenance or placebo as maintenance until progression. The trial showed a significant improvement in PFS, especially in the TP53 wild-type cohort, increasing median PFS from 3.7 months to 13.7 months. A confirmatory trial focusing only on TP53 wild-type tumors currently accruing.

Amplification of the ERBB2 oncogene resulting in overexpression of protein HER2 is considered a negative prognostic indicator and is associated with serous ECs and the p53abn/CNH subtype.[48-50] A recent phase II trial found chemotherapy plus trastuzumab (anti-HER2 monoclonal antibody) versus chemotherapy alone for advanced and recurrent HER2-positive serous EC significantly improved PFS (12.6 vs 8.0 months, HR=0.44, 90% CI 0.26-0.76) and OS (29.6 vs 24.4 months, HR=0.58; 90% CI, 0.34-0.99)51. NCCN guidelines now include trastuzumab in addition to chemotherapy for this patient group5. There is ongoing investigation of dual HER2 inhibition with NRG-GY026, which will compare chemotherapy plus trastuzumab versus trastuzumab/pertuzumab in HER2-positive serous EC (NCT05256225). Additionally, dual therapy with trastuzumab and tucatinib, a HER2 small molecule inhibitor, is being evaluated in solid tumors with HER2 alterations, including EC (NCT03835819).

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 re current 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 biologic 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 en-

dometrial 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 database, with over 42 presentations and publications having been generated .[44]

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. Multi-modality 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 may recur. However, in patients with localized disease, the optimal adjuvant postoperative therapy has been, and continues to be, under active investigation.

Chemotherapy
A GOG study, #20, evaluated adjuvant doxorubicin vs no further therapy for patients with uterine sarcoma. There was 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] 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]

An early phase II trial of bolus etoposide in advanced and recurrent LMS showed approximately a 11% response rate,[66] and a subsequent study of prolonged oral etoposide showed minimal activity.[67] Similar minimal response rates were observed with pa clitaxel[68] 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.

All this work has informed the design of two phase III trials in the GOG. GOG 250 accrues patients with measurable recurrent or advanced LMS between two regimens. Arm I: gemcitabine followed by placebo on day 1 plus gemcitabine and docetaxel on day 8 of each three-week cycle. Arm II consists of the same regimen, except that instead of placebo in arm I, bevacizumab is given. Treatment continued until progression or adverse effects prohibit further therapy. GOG 250 enrolled 107 patients and the addition of bevacizumab failed to improve PFS, overall survival, or ORR, and the trial was terminated early for futility.[85]

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 four cycles, with GCSF. Unfortunately, only 38 of the target 216 patents were enrolled on

study, despite international collaboration, and the study was closed due to accrual futility. Importantly, however, restricted mean survival time for OS was estimated as 34.3 months (95% CI, 25.3 to 43.3 months) in the chemotherapy arm and as 4772.4 months (95% CI, 43.6 to 49.1 months) in the observation arm and the restricted mean survival time for recurrence-free survival was estimated as 18.1 (95% CI, 14.2 to 22.0) months in the chemotherapy arm and as 14.6 months (95% CI, 10.3 to 19.0 months) in the observation arm. These findings called into question the benefit of adjuvant therapy in patients with disease confined to the uterus, although it is notable that the small sample size precluded robust statistical comparison.[86]

Thus far both chemotherapy and radiotherapy has not shown to be beneficial in the adjuvant setting. GOG 3088 is a randomized phase II trial evaluating letrozole versus observation for LMS that express the estrogen receptor.

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 could achieve 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]

Into this fray entered the GOG 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 GOG 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 five-day methotrexate IM or IV, methotrexate with folinic acid rescue, and five-day dactinomycin. While effective, these regimens were inconvenient for patients and labor intensive for providers. The GOG conducted two phase II trials, which showed that a single dose of dactionmycin 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 intramuscular 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/m^2 is statistically superior to weekly parenteral methotrexate at 30 mg/m^2 as initial management for low-risk GTN.[80]

Following 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", was 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. Sixty-four women were enrolled with 40% (lower 95% confidence limit 27.6%) were cured after second curettage. An additional two patients (3%) achieved a complete response but did not complete follow-up. Overall, 26 of 60 patients were able to avoid chemotherapy. Surgical failure was observed in 34 women (59%) and was more common in women 19 years old or younger or 40 years old or older. One case of grade 1 uterine perforation was successfully managed by observation. Four grade 1 and one grade 3 uterine

hemorrhages were reported. New metastatic disease (lung) was identified in one of these women after second curettage. In three patients (surgical failures), the second curettage pathology was placental site trophoblastic tumor, and it was placental nodule in one additional patient. Thus, second curettage appeared to be an appropriate approach for these patients.

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 titled, A Phase III Randomized Trial of Pulse Actinomcyin-D versus Multi-day Methotrexate for the Management of Low-Risk Gestational Trophoblastic Neoplasia has reported. The complete response rates for multi-day methotrexate and pulse actinomycin-D were 88% (23/26 patients) and 79% (22/28 patients) (p = NS) respectively, there were two recurrences in each arm, and 100% of patients survived. The multi-day MTX regimens though more efficacious were associated with significantly more mucositis and were significantly less convenient.

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 actionomycin-D is an active regimen.[81]

Conclusion

For over thirty years the GOG has driven the progress in treating uterine corpus malignancies. With the continued leadership of the GOG. evidence-based progress to treat endometrial cancer are promising and will hopefully improve the rising incidence and mortality of this disease in the United States.

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