Chapter 12 |

The GOG Foundation, Inc. Trials Examining the Utility of Radiation Therapy




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Introduction

Radiation therapy (RT) has an important role in the treatment of gynecologic cancers in the primary, adjuvant, recurrent and palliative settings. The delivery of RT has evolved over the last several decades with advancements in technology through intensity modulated radiation therapy (IMRT), image guidance in external beam RT and brachytherapy. Evolution in beam intensity modulation with either a multileaf collimator or compensating filter have improved target delivery and avoidance of sensitive normal tissue leading to the adoption of Intensity-modulated radiation therapy (IMRT).[1] Additionally improvements in on-board kV imaging (OBI) and cone beam CTs (CBCTs) have allowed for more accurate confirmation that external beam RT is appropriately covering the targets of therapy, while avoiding normal tissue. Early favorable reports of clinical efficacy and decreased acute morbidity resulted in the adoption of IMRT in the treatment of gynecologic cancers.[2] There have been randomized and institutional trials comparing IMRT to traditional three-dimensional conformal radiation therapy (3D CRT) in gynecologic cancers, and The National Cancer Institute (NCI) has published guidelines for the use of IMRT in clinical trials.[3] As we will see in the clinical trials discussed below, both 3-D CRT and IMRT were allowed in treatment plans, though every IMRT plan required prospective review and adherence to published consensus contouring guidelines. Perhaps most importantly, the incorporation of specific RT guidelines with expert oversight, as part of contemporary trials, has helped ensure high quality radiation delivery on a broad scale.

Simultaneously, brachytherapy has undergone similar advances in the ability to image the pelvis and customize the dose delivered to an individual patient. Treatment planning with radiographic plain films has been gradually replaced with true 3D volumetric treatment planning with CT, ultrasound and MRI, allowing for improved target and normal tissue definition.[4] Low dose rate (LDR) brachytherapy with radium capsules initially, and subsequently Cesium 137 over the course of 40-80 hours, has been largely supplanted with high dose rate (HDR) treatment with Iridium 192 in the U.S., delivered over a few minutes in three to five fractions.[5] Lastly, the increased use of supplemental interstitial catheters in addition to traditional tandem and ovoid based treatments for locally advanced cervical cancer has enabled further customization of dose and radiation delivery.[6] The combination of these three factors have resulted in improved cervical cancer control rates of over 90% and decreased grade 3 toxicity rates under 10%, even in stage IIIB and IVA disease.[7]

Role of Radiation in Endometrial Cancer

Radiation therapy has been used in the adjuvant setting for treatment of all stages of endometrial cancer (EC). In the last decade, the Gynecologic Oncology Group (GOG) Foundation has conducted two trials evaluating the role of radiation alone and in combination with chemotherapy in the adjuvant treatment of high-risk early-stage EC and advanced stage EC. RT has also been used in the management of locally recurrent EC including recurrence at the vaginal cuff or nodal basins in patients that did not receive adjuvant therapy. Given prior trials showing a benefit to concurrent chemotherapy with definitive radiation in the treatment of cervical cancer, the GOG Foundation also evaluated the role of concurrent cisplatin with radiation in the treatment of locally recurrent EC.

Early-Stage Endometrial Cancer

Early stage (stage I-II) endometrial cancer patients have

historically been treated with surgical staging followed by consideration of adjuvant radiation in patients that are intermediate, high-intermediate or high-risk for recurrent disease. Relevant phase III trials looking at stage I-II patients and defining risk criteria included GOG-99, PORTEC-1 and PORTEC-2.[8-11] While radiation improved pelvic and vaginal recurrence rates in these studies, a survival benefit was not evident. The trial population in GOG-99 and PORTEC-1 was skewed towards a lower-risk patient group, likely due to the "no adjuvant treatment" arm. However, recurrence rates were significant in patients with high-risk criteria including older age, higher grade, lymphovascular space invasion (LVSI) and outer myometrial invasion. To study the benefit of chemotherapy in this higher risk population and patients with non-endometrioid histology, the GOG Foundation conducted GOG protocol 249, a phase III trial that randomized patients with high-intermediate- and high-risk early-stage EC to treatment with either whole pelvic external beam radiation therapy with or without vaginal cuff brachytherapy (WPRT) or a combination of vaginal cuff brachytherapy and chemotherapy (VCB+CT).

This trial included patients with stage I endometrioid histology if they had clinical and pathologic risk factors that defined them as high-intermediate, or high-risk, regardless of peritoneal cytology results, any stage II endometrioid cancer and stage I or II serous and clear-cell histology patients with negative peritoneal cytology. It was designed as a superiority trial to determine if VCB+CT improved recurrence-free survival (RFS) compared with WPRT. After a medial follow-up of 53 months, the 60-month RFS and OS were not significantly different between the groups.[12] The 60-month RFS was 76% in both the WPRT and VCB+CT groups, with estimated treatment hazard ratio (HR) for recurrence 0.92 [90% confidence interval (CI) 0.69 to 1.23] of VCB+CT related to WPRT. The 60-month OS was 85% for VCB+CT and 87% for WPRT, with estimated treatment HR for death being 1.04 [90% CI 0.71 to 1.52] of VCB+CT related to WPRT. Exploratory subgroup analyses of RFS and OS did not identify a cohort of patients who benefited more from VCB+CT when compared to WPRT. However, the cumulative incidence of para-aortic nodal or pelvic recurrences was significantly lower in the WPRT group with 4% compared to 9% in the VCB+CT group. The HR of para-aortic nodal or pelvic recurrences of RT relative to VCB+CT was 0.47, 95% CI 0.24-0.94. Acute toxicities were more frequent and severe in the VCB+CT group with increased neurotoxicity and worse patient-reported outcomes at four weeks, 11 weeks and eight months after treatment. Despite the results of non-superiority and a higher rate of adverse events (AEs) of VCB+CT over RT, there was an increase in the use of VCB+CT for the treatment of early-stage high risk EC.[13] These trends illustrate the problematic nature of early adoption of treatment strategies that were not prospectively confirmed to be superior to established treatments in well-designed trials.

Advanced Stage Endometrial Cancer

Historically, radiation therapy was used in the adjuvant treatment of stage III endometrial cancer.[14,15] RT was also the standard-of-care arm in multiple clinical trials studying the potential superiority of chemotherapy or sequential radiation and chemotherapy in patients with high-risk stage I-II disease and completely resected stage III EC.[16-19] The results of GOG Protocol 122 illustrated a survival advantage of eight cycles of chemotherapy over whole abdominal radiation (WAR) in patients with stage III-IV, optimally resected EC, establishing chemotherapy as a critical component to management of this disease.[20] Multiple clinical trials were then designed and completed to identify the most effective and tolerable chemotherapy regimen for advanced stage EC.[21-23] Ultimately, GOG Protocol 209 established combination carboplatin and paclitaxel as the preferred standard of care systemic chemotherapy regimen.[24]

In GOG Protocol 184, WPRT remained an important part of the standard of care treatment for optimally resected metastatic EC due to the known reduction in local recurrence seen in early-stage cancers.[25] While chemotherapy alone showed an improved five-year progression-free (PFS) and overall survival (OS) in GOG 122, the rate of local pelvic recurrence was 18% in the CT arm compared to 13% in the patients receiving WAR. Therefore, GOG 258 sought to evaluate whether adjuvant treatment with volume-directed RT with concurrent cisplatin followed by four cycles of carboplatin and paclitaxel (CRT group) improved relapse-free survival compared to six cycles of carboplatin and paclitaxel without radiation (CT group) in patients with optimally resected stage III and IVA endometrial cancer. Secondary endpoints included OS, acute and late toxicity and patient reported assessment of quality of life (QOL). At five years of follow-up, the RFS was 59% in the CRT group and 58% in the CT group (HR 0.9, 90% CI 0.74 to 1.10).[26] Exploratory subgroup analyses of RFS did not identify a subgroup of patients who may benefit more from CRT when compared to CT. The cumulative incidence of pelvic or para-aortic node recurrence and vaginal recurrence at 60 months was 11% and 2% respectively in the CRT group compared to 20% and 7% in the CT arm (HR0.36, 95% CI 0.16 to 0.82). The cumulative incidence of distant recurrence at 60 months was 27% in the CRT group and 21% in the CT group (HR 1.35, 95% CI 1.00 to 1.86). Completion of all prescribed therapy was

seen in 75% of the patients in the CRT group, compared to 85% of the CT group. While CRT showed a significant reduction in local pelvic/para-aortic and vaginal recurrence, the rate of distant recurrence was numerically higher than CT alone. Chemotherapy after RT was also associated with higher rates of hematologic toxicities, requiring granulocyte colony-stimulating factor (G-CSF) support, and a lower rate of completion of the prescribed cycles of chemotherapy compared to CT alone. These findings may have contributed to the higher rate of distant recurrence identified in the CRT arm of the study. Mature OS data for GOG 258 is pending, although given the perceived benefit of RT in reducing local and regional recurrence, CRT is still being prescribed nationally for advanced stage endometrial cancer in real-world practice.[27] In addition to the results outlined above, recent clinical trials have also improved our understanding of the association between molecular classification and prognosis, as well as the potential benefit from adjuvant therapy.[28,29] Molecular classification of EC is now incorporated into the definitions of EC risk categories and has informed the design and development of future clinical trials.[30, 31] NRG GY020 was designed to determine if the addition of immune checkpoint inhibition, with the anti-PD-1 drug pembrolizumab, to post-operative radiation would improve oncologic outcomes in mismatch repair deficient (dMMR) high intermediate risk endometrial cancer. This trial has completed accrual, with results pending at this time.

Recurrent Endometrial Cancer

Isolated vaginal or pelvic recurrences are commonly managed with external beam radiation therapy (EBRT) followed by intracavitary or interstitial brachytherapy (with or without boost to nodal basins). More recently, concurrent chemotherapy in conjunction with radiation was adopted by some in clinical practice after the results of Radiation Therapy Oncology Group (RTOG) Protocol 9708.[32] While retrospective series have shown that RT alone results in adequate local control for vaginal cuff recurrences, there continues to be a high rate of distant disease recurrence, particularly in patients with high grade disease, supporting the need for alternative treatment modalities in this group of patients.[33,34] GOG Protocol 238 was a randomized phase II study designed to investigate whether the addition of concurrent weekly cisplatin (40 mg/m2/week) to radiation therapy (Cis-RT) would improve progression-free survival (PFS) compared to RT alone in patients with locally recurrent EC.

Patients were eligible if they had a pelvic or vaginal recurrence without extra-pelvic disease. Prior adjuvant chemotherapy was permitted although patients could not receive neoadjuvant chemotherapy for treatment or disease recurrence or have received prior RT. Over 11 years, 165 patients were accrued with a median follow up of 60 months.[35] Five-year PFS was 68% in the RT alone group compared to 59.8% in Cis-RT group (HR=1.40, 95% CI: 0.82 to 2.39). Cis-RT was associated with an increase in gastro-intestinal (GI) and hematologic toxicity when compared to RT alone. Importantly, 81% of the patients enrolled in this study had grade 1 or 2 EC, suggesting that these findings may not be generalizable to high-grade EC patients. The low five-year PFS rate of 68% in the RT alone group speaks to the need for improved treatment strategies to achieve cure in locally recurrent EC.

Role of Radiation in Vulvar Cancer

Radiation therapy plays an important role in the treatment of vulvar cancer. Radiation is used as adjuvant therapy after surgery to decrease recurrence rates in patients with high-risk features including positive surgical margins and lymph node metastasis. Radiation is also used in the neoadjuvant setting to decrease the size of large primary tumors to make surgical resection more feasible and less morbid. Radiation can also be used as definitive therapy for tumors that are not amenable to primary resection. Lastly, RT is frequently used for palliative treatment of advanced or recurrent cancers to alleviate cancer-related symptoms in patients where cure cannot be achieved. Radiation dose is dependent on the purpose of treatment and can range from 45-70 Gy, and the radiation field can include the primary vulvar tumor with or without groin lymph nodes and lower pelvic lymph nodes.

The importance of surgical staging with inguino-femoral (IF) lymph node dissection (LND) was established by GOG protocol 88 which showed an improved 2-year disease-free survival (DFS) rate of 92% in patients with bilateral inguinal LND followed by EBRT compared to 70% in patient who underwent EBRT (50 Gy) alone.[36] Given the morbidity of complete IF LND, the technique of sentinel lymph node dissection (SLND) was studied in GROINSS-V, an observational study and GOG 173, a prospective validation study. GROINSS-V included patients with a <4cm squamous cell carcinoma (SCC) with >1mm invasion and clinically non-suspicious lymph nodes without pre-requisite of pre-operative imaging. Positive sentinel lymph nodes were identified in 31.5% of patients or 26.2% of groins, and the recurrence rate was 3% in patients with a negative SLN.[37] GOG 173 was a prospective, single-arm trial that enrolled a higher risk patient population with clinically non-suspicious nodes. All patients underwent SLND followed by a completion IF LND. The overall SLN detection rate was 92.5%, with a sensitivity of 91.7% and false negative rate (FNR) of 8.3%.[38] For tumors <4cm, the sensitivity was 94.4% with a FNR of 5.6%. The false nega-

tive predictive value (NPV) [1-negative predictive value] was 3.7% for all patients and this improved to 2% when looking at tumors that were < 4cm.

With the validation of the SLND technique, GROINSS-VII/GOG 270 sought to evaluate whether IF RT was a safe alternative to IF LND in vulvar cancer patients with a metastatic SLN. This large, prospective, observational study enrolled patients with early-stage vulvar squamous cell carcinoma (primary tumor diameter <4cm, clinically negative lymph nodes) who had undergone SLN staging. If the SLN examination was negative, patients underwent surveillance. If SLN showed metastasis, patients underwent 50Gy EBRT. Of the 1,552 patients enrolled in the trial, 1,222 (78.7%) had negative SLN, with a low groin recurrence rate of 2.6% concluding that it was safe to omit a completion LND and RT in patients with a negative SLN staging.[34] Sentinel lymph nodes were positive in 324 (21%) patients and these were further sub-classified into patients with SLN-micro-metastases (≤2mm) versus SLN-macro-metastases (>2mm).[39]

After 54 months, an interim analysis revealed that in patients with SLN-micromets (≤ 2mm) (n=160), the rate of isolated groin recurrence at two years was only 1.8% and therefore RT-alone to the groin was an effective treatment and complete IF LND could be omitted. However, the groin recurrence rate among patients with SLN-macromets (>2mm) or with extracapsular extension was 25%. This was in contrast to the 8.2% recurrence rate seen with IF LND +/- RT in GOG 173. In conclusion, RT alone to 50 Gy for patients with macro-metastatic SLN-positive groins was not a safe alternative to completion IFL and RT. As a result of these findings, the ongoing GROINSS-VIII study was designed to investigate whether a higher RT dose (56Gy) with concurrent weekly cisplatin was an effective alternative to completion LND in those with macro-metastases (>2mm), or more than one micro-metastases.

GOG Protocol 279 examined the efficacy and toxicity of adding gemcitabine (G) to weekly cisplatin (C), with concurrent technical advancements with intensity modulated radiation (IMRT) quality and dose escalation in patients (pts) with locally advanced vulvar cancer. Patients with locally advanced vulvar cancer (T2 or T3, N0-N3, M0) not amenable to surgery were enrolled in a single-arm, two-stage phase II study. Pretreatment inguinal-femoral lymphadenectomy or sentinel lymph node biopsy was performed if feasible. IMRT was prescribed with patients to receive 64 Gy IMRT to the vulva, 50 Gy or 64 Gy to the groins and low pelvis for positive nodes, and unresectable nodes, respectively. Csiplatin 40 mg/m2 and Gemcitabine 50 mg/m2 were administered weekly throughout radiation. Clinical and radiographic response was assessed 6-8 weeks after treatment. Complete clinical response (CCR) was confirmed to be a complete pathologic response (CPR) with biopsy. Resection or additional chemoradiation was performed for persistent disease. CCR, CPR, progression free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier and adverse events were assessed with the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v 4.0. It is anticipated that the trial results will be presented at an upcoming scientific congress.

Role of Radiation in Cervical Cancer

The primary treatment for large localized and regionally-spread cervical cancer (CC) is concurrent chemotherapy and radiation therapy (CRT). GOG Protocol 120 compared three different chemotherapy regimens given concurrently with radiation for the treatment of locally advanced CC. The improved PFS and OS, as well as tolerability of the cisplatin containing regimen established weekly cisplatin at 40mg/m2 as the standard of care chemotherapy in CRT for locally advanced CC.[40] The benefit of CRT compared to RT has not been evaluated prospectively in adjuvant treatment of CC patients with intermediate-risk factors after radical surgery. GOG Protocol 263 was designed to evaluate this and results of this trial are pending.

While the five-year relative survival of patients with localized CC is high at 92%, the five-year relative survival for patients with regional metastasis to pelvic and or para-aortic lymph nodes decreases to less than 60%.[41] Therefore, the identification of new and effective treatment strategies in this high-risk group is a priority. GOG Protocol 9929 was designed to examine immunotherapy in combination with CRT in locally advanced CC. All patients had node-positive disease. The phase I study reported on the safety, tolerability and efficacy of sequential ipilimumab (four cycles) after CRT for node-positive CC.[42] Secondary endpoints evaluated overall survival, as well as the potential effects of human papillomavirus (HPV) genotype, HLA allele status and programmed cell death 1 (PD-1) expression of peripheral blood before and after CRT and sequential ipilimumab. Of the 34 patients enrolled, 20 patients received ipilimumab and 19 were evaluable at the time of abstract publication. Ninety percent of patients completed all four cycles and 10% received two cycles of ipilimumab. The maximum tolerated dose of ipilimumab was 10mg/kg and three (16%) patients experienced an acute grade 3 toxicity (pancreatitis, neutropenia and rash), which self-resolved. Most of the acute toxicities were grade 1-2 gastrointestinal AE, rash

or endocrinopathies. With 12-month median follow-up, one-year DFS was 74% and 1-year OS was 90%. Tumor evaluations showed increased expression of PD-1 and inducible co-stimulatory molecule (ICOS) after CRT showing an increased immunogenic state after RT in these patients.

Building upon GOG 9929, NRG GY017 was a phase I randomized trial, where immunotherapy was added to standard chemoradiation (CRT) in an effort to improve outcomes for patients with node-positive cervical cancer. Optimal sequencing of CRT with immunotherapy is unknown. NRG GY017 (NCT03738228) is a randomized phase I/Ib trial of the anti PD-L1 antibody, atezolizumab, before and concurrent (Arm A) or concurrent with CRT (Arm B) to determine the best sequence of therapy to result in immune activation, as determined by clonal expansion of T Cell Receptor Beta (TCRbeta) repertoires and tumor-associated TCR clones in peripheral blood. Secondary objectives include toxicity, and the predictive value of T-cell repertoire parameters for clinical outcomes.

Forty patients were randomized; 36 patients with locally advanced cervical cancer with positive lymph nodes were randomized to three doses of atezolizumab (1200mg) on day -21, 0, 21 (Arm A) vs. day 0, 21, 42 (Arm B). All eligible and evaluable patients received CRT and ≥1 dose of atezolizumab. Tumor biopsies were obtained pre- and during therapy, and peripheral blood was collected. TCR metrics were evaluated by Adaptive immunoSEQ assay. Dose limiting toxicities were assessed during and up to 30 days post CRT. Comparison of arms, and pre- to post-treatment comparisons were performed using Wilcoxon rank sum or signed rank test. Correlations of TCR clonality and diversity with clinical outcomes and biopsy results were explored.

Of the 40 patients, 4 patients were not assigned study treatment and excluded from the analysis. For the 36 eligible and treated patients, the median follow-up time was 20 months. Median age was 48 years; the majority of the patients were white non-Hispanic, white race, performance status of 0, squamous cell carcinoma, and FIGO stage IIB. Seventy-five percent of all patients completed all protocol therapy, 86% received >4 cycles of cisplatin with RT. Of the 36 patients, 30 were DLT evaluable according to the protocol: Arm A: 16 patients with no DLTs; Arm B: 14 patients with 3 patients reported to have a DLT (8%) : one immune related event reported as colitis (3%), non immune related colitis, and thrombocytopenia with cisplatin delay greater than two weeks. Overall, three patients in Arm A and seven patients in Arm B experienced a grade 3 or higher treatment-related adverse event; with the exception of one, all of the grade 3 events were deemed to be not immune-related. Thirty-one patients had on-treatment tumor biopsy at the first brachytherapy; 10 patients (28%) showed no residual tumor on biopsy. There was an increase in peripheral blood TCR clonal expansion and expansion of tumor-associated T-cell clones between baseline and day 21 in Arm A ($p=0.0001$) and Arm B ($p=0.001$). There was no statistically significant difference between the two treatment arms for either T-cell clonal expansion or expansion of tumor-associated T-Cell clones. Patients with higher pre-treatment TCR diversity had increased likelihood of complete pathologic response in on-treatment biopsy ($p= 0.049$). Overall, at 12 months, the DFS for the entire cohort is 72%. Our data indicate that atezolizumab as a primer and concurrent with CRT is safe and shows immune modulating activity in women with locally advanced cervical cancer. There was no difference in change in T-Cell clonality between the arms. Favorable DFS was observed in both arms at 12 months for this high-risk patient population. Correlation between the treatment schedule, T-cell repertoire parameters, and clinical outcomes will be performed as the follow-up becomes more mature.

Understandably, the interplay between immunotherapy, radiation therapy and the underlying malignancy, inclusive of the tumor microenvironment, are complex and multifactorial. As we look to develop and design future trials, it will be critical to not only identify potentially therapeutic novel drugs, but also consider appropriate sequence of treatment to best potentiate immunologic effects and identify molecular biomarkers to aid in characterizing patients most likely to benefit from immunotherapy.

Conclusion

Radiation therapy continues to play an important role in the management of gynecologic cancers. Through an evolution of RT techniques, there has been meaningful progress in reducing adverse effects and complications via optimization of on target dosing. Furthermore, RT is being explored in combination with systemic treatment strategies including chemotherapy, immunotherapy, and targeted agents. While we strive to discover more effective treatment combinations, it will be important to balance efficacy with potential treatment related adverse events. The GOG Foundation continues to lead the development and completion of clinical trials that will inform the utility of radiation with a goal of cure, while in parallel educating providers internationally on appropriate radiation delivery in the gynecologic cancer space.

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