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RTOG Gynecologic Oncology Working Group: Comprehensive Results

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Abstract

The purpose of this report is to comprehensively describe the activities of the Gynecologic Oncology Working Group within the RTOG. Clinical trials will be reviewed as well as translational science and ancillary activities. Over the past 40 years, a myriad of clinical trials have been performed within the RTOG with the aim of improving overall survival and decreasing morbidity in women with cervical or endometrial cancer. Major study questions have included hyperbaric oxygen, neutron radiotherapy, altered fractionation, hypoxic cell sensitization, chemosensitization, and volume directed radiotherapy.

RTOG 7920 demonstrated improvement in overall survival in patients with stages IB through IIB cervical carcinoma receiving prophylactic paraaortic irradiation compared to pelvic radiation alone. RTOG 9001 demonstrated that cisplatin and 5-FU chemoradiotherapy to the pelvis for advanced cervix cancer markedly improved overall survival compared to extended field radiotherapy alone. More recent trials have employed radioprotectors, molecular targeted therapy, and intensity modulated radiation therapy. Ancillary studies have developed CTV atlases for research protocols and routine clinical use. Worldwide practice patterns have been investigated in cervix, endometrial, and vulvar cancer thru the Gynecologic Cancer Intergroup (GCIG). Translational studies have focused on immunohistochemical markers, changes in gene expression, and miRNA patterns impacting prognosis.

The RTOG gynecologic working group has performed clinical trials that have defined the standard of care, improved survival, and added to our understanding of the biology of cervical and endometrial cancers.

Early Clinical Trials

RTOG gynecologic efforts are listed in chronologic order according to the following themes: early clinical trials, recent clinical trials, translational research and Gynecologic Cancer Intergroup efforts. In the late 1960's and early 1970's, there was substantial preclinical and clinical data available on the importance of hyperbaric oxygen, effects of fractionation, and utility of neutrons. Hyperbaric oxygen attempts to raise the partial pressure of oxygen in tissues to exploit the oxygen effect. Well oxygenated tissues are approximately 3 times more sensitive to radiation as anoxic tissues. Hyperfractionation theoretically may alter the therapeutic window by decreasing late effects while yielding similar tumoricidal effects. Neutrons are fundamentally different in that they are more heavily ionizing; that is, more destruction per track length. Consequently, the RTOG's first gynecologic trials were phase III questions addressing these issues. No benefit was identified with the experimental approach in these trials (table 1)¹⁻³. These early trials were underpowered to detect differences in the treatment arms: RTOG 7002 evaluating hyperbaric oxygen, RTOG 7105 testing standard fractionation versus split course, and RTOG 7608 comparing photons versus photons and neutrons had only 65, 287, and 156 patients each, respectively. These were ambitious efforts testing important, but technically challenging concepts such as hyperbaric oxygen and neutrons. Lessons in trial design were learned, and going forward greater statistical rigor has been adopted. Since the early 1980s, phase II efforts have been performed largely with the intent of advancing to phase III questions if an adequate signal is achieved.

Hypoxic cell sensitizers increase radiation induced free radical damage in hypoxic environments. After a phase I/II study was performed evaluating a nitroimidazole (misonidazole) as a radiation sensitizer, the RTOG embarked on a phase III study (80-05) in patients with stage IIIB and IVA cervix cancer (table 2)^{4,5}. This trial randomized 120 patients between RT and RT + misonidazole from 1980 to 1984, and showed no improvement in pelvic control, disease free survival (DFS), overall survival (OS), or toxicity.

The RTOG has a strong history of evaluating optimal palliative regimens as well. RTOG 8502 was a phase III protocol for advanced pelvic malignancies. In the pilot portion 151 patients were accrued to a regimen receiving 44.4 Gy in 12 fractions (3.7 Gy bid) with a variable rest interval of 3–6 weeks after each 2 day consecutive course of 14.8 Gy. The phase III portion randomized patients between a rest period of 2 or 4 weeks between fractions. There was no difference in late effects by length of rest period. Patients that received the full 44.4 Gy had a higher response rate. This fractionation scheme was found to produce good tumor regression, excellent palliation, and with a low incidence of complications⁶. This regimen is not widely used; however, it is effective and can be convenient for some patients.

The choice of the appropriate target volume has been a major theme in RTOG gynecologic studies. From 1979 thru 1986, RTOG 7920 randomized 367 patients to pelvic versus pelvic and paraaortic RT in patients with stage IB-IIIB cervical cancer⁷. The 10 yr OS rate was 44% in the pelvic arm and 55% in the extended field arm (p=0.02). The cumulative incidence of

grade 4–5 toxicities was doubled in the extended field arm (8% vs 4%, $p=0.06$). In this trial, there was no requirement for surgical staging and cross sectional imaging was not used in all patients.

The RTOG has performed 2 trials evaluating twice daily RT in definitively treated cervix cancer patients: RTOG 8805 and RTOG 9210. The hypothesis was that higher biologic tumor doses can be delivered without increasing toxicity. RTOG 8805 was a phase II study in 81 patients delivering 1.2 Gy bid with a 4–6 hr interfraction interval⁸. A grade 3 and 4 late toxicity rate at 3 years of 6% was felt to be promising. Hence, this concept was applied in RTOG 9210. Patients eligible had positive paraaortic lymph nodes and were treated with extended field together with chemotherapy consisting of cisplatin and 5-FU. Only 69% of patients completed RT per protocol and the grade 4 GI toxicity rate was 31%⁹. This regimen was felt to be too toxic without benefit compared to standard chemotherapy and radiotherapy (CRT).

RTOG participated in both Intergroup trials that changed standard of care in women treated by hysterectomy for cervix cancer. In GOG 92 (RTOG 8706) 277 stage I patients were randomized to 46–50.4 Gy RT to the pelvis versus observation after radical hysterectomy¹⁰. Patients were eligible if they had two or more of the following factors: lymph vascular space invasion (LVSI), $>1/3$ stromal invasion, or tumor ≥ 4 cm. PFS was significantly increased with postoperative RT from 65% to 78%¹¹. For SWOG 8797 (RTOG 9112, GOG 109) patients with high risk disease after radical hysterectomy defined as positive lymph nodes, positive parametria, or positive margins were randomized to RT alone or RT plus 4 cycles of cisplatin and 5-FU. OS was significantly improved by 10% with CRT with a concomitant 30% decrease in distant metastases, and 50% decrease in local failure¹². In both these trials there was a particular benefit for patients with adenocarcinoma histology that received the experimental arm.

The addition of chemotherapy to radiotherapy in locally advanced disease was first found to be promising in RTOG 8515, and hence, this was tested in a phase III design in RTOG 9001¹³. Patients with bulky stage IB through stage IVA disease were randomized to pelvic and paraaortic irradiation versus pelvic radiation plus 3 cycles of 5-FU and cisplatin chemotherapy. A 16% improvement in OS at 8 years (67% versus 41%) was achieved in the concomitant CRT arm¹⁴. The hazard ratio for the reduction in death with the addition of chemotherapy was 0.51, and the rates of late complications were similar between the two arms. This landmark trial together with SWOG 8797 and 3 other GOG trials prompted an NCI alert in 1999 indicating a marked survival benefit for cisplatin-based RT in women with advanced cervix cancer, and promptly changed practice patterns worldwide.

More recent clinical trials

RTOG 9708 was RTOG's first trial performed exclusively in endometrial cancer. This phase II trial evaluated pelvic radiotherapy with concurrent cisplatin 50 mg/m² on day 1 and day 28 followed by 4 cycles of extended adjuvant or outback carboplatin and paclitaxel chemotherapy given at 4 week intervals. Eligible patients had high risk stage I through stage IIIC1 disease. This trial was deemed to be safe and effective with a 4 year OS of 81% and

no recurrences in patients with stage I–II disease¹⁵. This concept was advanced to a phase III trial; however, the trial had to be closed due to poor accrual (RTOG 9905). Currently, this CRT regimen is being tested in phase III trials in North America and Europe (GOG 0258 and PORTEC III, respectively). Additionally, this CRT regimen was used as the backbone for RTOG 0921. This phase II trial added Bevacizumab, an antibody directed against Vascular Endothelial Growth Factor (VEGF) given every 2 weeks for 3 times during the concomitant CRT for the same population as RTOG 9708. IMRT was used exclusively in this trial. RTOG 0921 completed accrual in December of 2011 after 34 patients were accrued¹⁶. There were 2 local failures and 5 distant failures, and two year OS and DFS were 97% and 79%, respectively.

The treatment of advanced cervix cancer with CRT can be morbid. In attempts to ameliorate treatment related morbidity RTOG 0116 evaluated amifostine as a radiation protector in a two part trial for patients with high common iliac or paraaortic metastases. In the initial phase, patients were treated with CRT alone and in part II amifostine was added. The acute grade 3–4 toxicity rates were 81% and 87%, in parts I and II, respectively¹⁷. In RTOG 0128, celecoxib was evaluated as a radiation sensitizer in 84 patients with stage IB–IVA pelvic confined cervical cancer and, again, no increased benefit was observed for the study agent in this phase II trial¹⁸. RTOG 0417 evaluated radiotherapy and cisplatin together with bevacizumab in the identical population to RTOG 0128. This was found to be safe and effective with 76% and 94% of patients receiving chemotherapy and RT per protocol, respectively¹⁹. The 3 year OS rate in RTOG 0417 was 80% and appears promising; however, LRF continues to be problematic.

After hysterectomy small bowel frequently fills the pelvis complicating RT. To ameliorate acute and late toxicity RTOG 0418 evaluated IMRT in the postoperative setting. Prior to the initiation of RTOG 0418, a CTV atlas was described and published on the web to allow appropriate target delineation on protocol²⁰. Since this successful effort, many atlases have been developed throughout the RTOG for a variety of disease sites. Atlases used for CTV delineation are important tools in radiation oncology and this was one of the first developed, and currently is widely used. The primary endpoint in RTOG 0418 was to evaluate whether IMRT was transportable in a multi-institutional setting. This was felt achievable with 98% of cases having an acceptable IMRT plan²¹. It is of paramount importance to ensure that the local regional failure rate with IMRT does not exceed standard RT. Of 43 eligible women with endometrial cancer 4 patients had disease recurrence: regional in 2, suburethral in 1, and paraaortic in 1 for a local failure rate of 7%. This translated to a 3 year OS rate of 92%. Of 40 eligible patients with cervix cancer the 2 year rates for LRF, paraaortic failure, distant metastasis, and OS were 11%, 5%, 10%, and 95%, respectively. Thus, pelvic IMRT was found to be safe and effective and currently is used in a number of phase III trials.

Currently, the RTOG gynecologic oncology working group is participating in a number of phase III trials evaluating RT or CRT questions in endometrial or cervical cancer. RTOG 0724 is randomizing high risk cervix cancer patients after hysterectomy to standard CRT with weekly cisplatin versus the same plus 4 cycles of carboplatin and paclitaxel given in the extended adjuvant setting. The OUTBACK trial (RTOG 1174) has the exact same design for women with locally advanced intact cervix cancer (stages IB–IVA without positive para-

aortic nodes). In GOG 0238 (RTOG 0973), pelvic RT is being compared with cisplatin plus standard RT for women with pelvic recurrences of endometrial cancer. In women with stage I and II endometrial cancer GOG 0249 (RTOG 1070) evaluated pelvic RT versus vaginal brachytherapy and 3 cycles of carboplatin and paclitaxel. GOG 0249 completed accrual and results are eagerly anticipated. For women with stage III and IVA endometrial cancer GOG 0258 (RTOG 1073) is randomizing patients to CRT as delivered in RTOG 9708 with concurrent cisplatin and 4 cycles of extended adjuvant chemotherapy versus 6 cycles of carboplatin and paclitaxel chemotherapy alone. GOG 0263 (RTOG 1171) is evaluating pelvic RT versus CRT employing weekly cisplatin for patients with intermediate risk features after hysterectomy.

Translational Studies

The RTOG Gynecologic Oncology Working Group has also been involved in a number of translational science studies (Table 3). A secondary analysis of RTOG 0116 and RTOG 0128 evaluated the importance of brachytherapy quality in 103 patients. It was found that asymmetry of tandem to ovoids, displacement of the ovoids in relation to the cervix, and poor packing adversely impacted local control²². One of the potential benefits for IMRT is a reduction in hematologic toxicity. This may be particularly important for delivery of concomitant CRT in either cervical or endometrial cancer. A secondary analysis from RTOG 0418 evaluated whether DVH parameters correlated with hematologic toxicity. In 83 patients bone marrow doses were determined and patients with a median bone marrow dose of >34.2 Gy had higher rates of grade 2 hematologic toxicity²³. Also in RTOG 0418, we evaluated whether oral contrast changed the dose delivered via treatment planning systems. There was found to be a small but statistically significant reduction in dose with the administration of oral contrast.

The RTOG currently is producing an atlas for the use in vulvar cancer to aid clinicians worldwide in target delineation in vulvar carcinoma. Additionally, the RTOG has rigorously evaluated inter-physician MRI contouring abilities in cervical cancer. Using kappa statistics, there was found to be a good agreement with the GTV for various pelvic organs²⁴. Image guided brachytherapy with CT was compared with MRI. CT volumes were routinely larger; however, there was also slightly less variance between physicians with CT. CT was felt to be an acceptable replacement for MRI for image guided brachytherapy. The RTOG gynecologic cancer working group has also participated in standardizing pelvic organ contouring with the Genitourinary and Gastrointestinal Committees from the RTOG²⁵.

Aneuploidy and percent S phase fraction from RTOG 9001 and the University of Miami were evaluated by flow cytometry on fresh tissue in 57 patients, and found to have no prognostic value²⁶. RTOG 0128 had a number of scientific secondary endpoints. Tumor tissue biopsies were obtained prior to treatment and at the time of the first brachytherapy implant. RNA collection was feasible in a cooperative group study, and gene expression was found to correlate with clinical features such as histology, but not stage^{27, 28}. Additionally, using the differential gene expression signatures between the original biopsy and the biopsy at the initial implant, a 7 gene signature panel was identified that could predict outcome in advanced cervical cancer patients from 0128²⁹.

Immunohistochemistry (IHC) is a powerful technique for measuring protein expression and correlating clinical endpoints for well annotated samples in RTOG studies. In 51 patients from RTOG 0116 and 0128, subunit expression of ribonucleotide reductase by IHC was prognostic in node positive patients³⁰. From RTOG 0128, chromovision was compared with aqua technology for evaluating IHC. It was concluded that these technologies provided different results. Additionally, COX-2 was found to be inversely correlated with survival in this study³¹. A collaboration with Canadian investigators determined that ERCC1 expression is a negative prognostic factor in the advanced cervical cancer population³².

Fewer projects have been performed in endometrial cancer in the RTOG. However, one project used paraffin embedded tissues to evaluate microRNA expression as a prognostic factor, as well as the role of an inherited mutation in a microRNA binding site (the KRAS-variant) as a genetic marker of risk. This study found that microRNAs may be predictive of certain clinical features, and that the KRAS-variant may be a genetic marker of risk of type II endometrial cancer. Follow on studies have evaluated microRNA signatures in cervical cancer tissues and results are being analyzed.

Gynecologic Cancer Intergroup radiotherapy analyses

The RTOG has also participated in secondary studies of the Gynecologic Cancer Intergroup (GCIG) (Table 4). The GCIG comprises over 20 cooperative groups worldwide. Four of these projects involved surveying members of these groups regarding practice patterns in cervix, endometrial, vulvar cancer, and the use of brachytherapy. The cervix cancer study identified that radiation dose and use of chemotherapy was similar worldwide, and hence, these should not be barriers to trial participation between groups³³. The endometrial cancer survey demonstrated that the radiation dose was similar worldwide; however, there was no standardization of vaginal brachytherapy prescription³⁴. In some countries it was customary to prescribe radiation to a set fraction of the vaginal length, and in others it was more common to prescribe to a precise length to the vaginal apex. In vulvar cancer, the radiation dose was similar worldwide; however, chemotherapy was not standardized³⁵. A more recent survey evaluating practice patterns in brachytherapy demonstrated that cooperative groups in Asia used a lower dose compared to non-Asian cooperative groups³⁶. For example, the external beam and brachytherapy equivalent doses for Asia and Europe were 71.2 Gy and 83.2 Gy, respectively. Other GCIG projects have included recommendations for staging and the importance of performing cervical cancer trials within the developing world where the greatest burden of disease exists^{37, 38}.

Conclusions

The RTOG Gynecologic Oncology Working Group has a rich history of performing informative phase II and phase III trials as well as ancillary studies. With the merger of NSABP, RTOG, and GOG to form NRG, the quality of gynecologic trials and the ancillary science will improve. Various expertise from the groups are complimentary. In the future, we will continue to evaluate the potential for personalized treatment. Advanced radiotherapeutic technologies such as IMRT, IGRT, and IGBT will be rigorously tested in defined patient subsets to discern if they improve the therapeutic window for gynecologic

patients. Imaging biomarkers such as MRI or PET modalities may be important as early response indicators permitting dose escalation or de-escalation in advanced cervix cancer. We will also continue to evaluate protein expression, mRNA and micro-RNA gene signatures and genomic technologies to potentially exploit chemotherapy or radiation sensitivity. It will be important to continue to refine appropriate treatment populations to achieve better overall survival, a reduction in morbidity, an improvement in quality of life, and to promote cost effectiveness.

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Table 1

RTOG phase III gynecologic clinical trials

Study #	Years	Study Design	Result
7002	1972–1975	RT vs. RT + hyperbaric oxygen	Survival same
7105	1965–1980	Standard fractionation vs. split-course	Survival same
7608	1976–1984	Photons vs. photons + neutrons (external)	Survival same
7920	1979–1986	Pelvic RT vs. Pelvic + Paraaortic RT	Improved survival for paraaortic RT
8005	1980–1984	RT vs. RT + misonidazole	Survival same
8502	1985–1989	Palliative RT (short vs long rest interval)	Similar
8514	1977–1980	Photons vs. photons + neutrons (Cf-252)	Terminated due to poor accrual
8706*	1988–1989	RT vs Observation after hysterectomy	Improved PFS with RT
9001	1990–1997	RT vs. chemoradiotherapy (CRT)	Improved survival for RT + chemo
9112*	1991–1996	RT vs CRT for post op cervix	Improved survival for CRT
9905*	2000–2003	RT vs CRT + carbo/taxol	Closed for poor accrual
0724*	2009—	CRT vs CRT + carbo/taxol	On going
0238*^	2007—	RT vs CRT for rec. uterine ca.	On going
0249*^	2008—	Pelvic RT vs VCB in stage I/II uterine ca.	On going
0258*^	2009—	CRT vs Chemo in stage III/IV uterine ca.	On going
0263*^	2010—	RT vs CRT post op intermed. risk cervix	On going
1174*	2012—	CRT vs CRT + carbo/taxol	On going

* Intergroup trials;

^ GOG number

Abbreviations: RT radiotherapy, CRT chemoradiotherapy, PFS progression free survival, VCB vaginal cuff Brachytherapy, Carbo carboplatin, op operative

Table 2

RTOG phase II gynecologic clinical trials

Study #	Years	Study Design	Result
7905	1979–1982	10 Gy × 3 + misonidazole	Too toxic
8515	1985–1988	Chemo + RT in adv. cervix	Promising
8805	1988–1989	Bid RT in adv. cervix	Safe and effective
9210	1992–1995	Bid CRT in adv. cervix	Too toxic
9708	1997–1999	CRT + outback carbo/taxol in endo	Safe and effective
0116	2001–2007	CRT + amifostine in PA node + cervix	No benefit for amifostine
0128	2001–2004	CRT + Celebrex in adv. cervix	No benefit for Celebrex
0417	2006–2009	CRT + Bevacizumab in adv. cervix	Safe and effective
0418	2006–2008	IMRT for post op cervix/endo	Transportable, safe, effective
0921	2009–2011	IMRT/Bevacizumab + outback carbo/taxol	Safe

Table 3

RTOG translation science from gynecologic working group

Study #	Hypothesis/Question	Result
9001	Does aneuploidy or S phase fraction predict outcome?	No
0116/0128	Is brachytherapy quality important?	Asymmetry, displacement and poor packing decreased outcome
0128	Is RNA collection feasible in a cooperative group study?	Yes
0128	Does gene expression correlate with clinical features?	Gene expression correlates with histology
0128	Does a gene signature predict outcome? (Weidhaas)	7 gene signature panel predicts outcome
0418	What is the appropriate target post hysterectomy? (Small)	CTV Template generated for international use
0418	Do DVH parameters correlate with Heme toxicity? (AK)	Decreased Heme toxicity with less dose to bone marrow
0418	Does contrast change dose?	Bowel contrast reduces dose to target
0116/0128	Ribonucleotide reductase as a prognostic factor?	Reduce OS in cohorts with increased expression by IHC
9905/9708	Does the KRAS-variant miRNA predict outcome?	Yes
0128	Chromavision vs AQUA for CD34 and COX2?	COX2 inversely correlated with survival
0128	P53/ERCC1/Ki67 as prognostic factors?	ERCC1 is an adverse prognostic factor
Other	Practice patterns in vulvar cancer? (King)	Low utilization rate of IMRT
Other	Consensus guidelines in intact cervix? (lim)	GTV agreement high with MRI
Other	Normal tissue contouring? (Gay)	Pelvic organ contouring standardized
Other	CT vs MR for image guided brachytherapy?	Both CT and MR are acceptable

Table 4

RTOG participation in secondary studies of the Gynecologic Cancer Intergroup

Year	Hypothesis/Question	Results
2007	Global practice patterns in cervix cancer	RT dose and use of chemo similar worldwide
2009	Global practice patterns in endometrial cancer	RT dose similar. Vaginal brachytherapy not standardized
2009	Global practice patterns in vulvar cancer	RT dose similar, use of chemo not standardized
2009	Proposal for changes in Staging of Gyn cancers	Multiple changes suggested
2010	Priority of cervix cancer trials	Need for trials in developing world
2012	Global practice patterns in brachytherapy	Asia uses a lower dose