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Historical Perspective

Twenty-first century cervical cancer management: A historical perspective of the gynecologic oncology group/NRG oncology over the past twenty years

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HIGHLIGHTS

- The Gynecologic Oncology Group (GOG) has been fundamental in advancing the science of cervical cancer management.
- Ongoing clinical trials will further define therapy in intermediate and high-risk cervical cancer after radical hysterectomy.
- Chemoradiation is the cornerstone to improved outcomes in locally advanced cervical cancer.

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ABSTRACT

Since 1970, the Gynecologic Oncology Group (GOG) has been at the forefront of evaluating and helping to implement ground breaking and paradigm changing research in the management of cervical cancer. While the most dramatic example of this impact was a series of clinical trials published in 1999 that evaluated chemoradiation therapy versus radiation therapy alone for patients with various clinical scenarios, including both locally advanced as well as post radical hysterectomy patients, investigation has continued to further refine and improve therapy. In 2014, based on the results of GOG protocol 240, bevacizumab became the first approved targeted therapy in a gynecologic cancer in the United States. Most recently, clinical trial work from the GOG is changing the standard of care for all clinical scenarios. Finally, an emphasis on survivorship and special populations are now top priorities.

1. Introduction

While screening has dramatically decreased the incidence of cervical cancer in developed countries, cervical cancer remains a significant public health challenge. Most recent estimates suggest that 13,240 women will be diagnosed with cervical cancer in the United States in 2018, while 4170 are expected to die in the same time period [1]. Although there is continued excitement about HPV vaccination and its potential ability to further decrease cancer precursors and ultimately the incidence of cervical cancer [2], higher vaccination rates as well as time to realize the full benefits of vaccination in countries like the United States are needed. Accordingly, investigations into the ideal management of cervical cancer will remain a critical part of gynecologic cancer care for several more decades at least.

The Gynecologic Oncology Group (GOG), and now NRG Oncology have been among if not the, principal participants among the cooperative groups focused on improving cervical cancer treatment and outcomes in the United States. Arguably, the most important contribution from GOG/NRG Oncology was a series of clinical trials that lead to the National Cancer Institute's landmark announcement in 1999 regarding the use of chemoradiation in patients receiving radiation as a therapeutic modality for different cervical cancer clinical scenarios [3–6]. Previously, reviews and meta-analyses have highlighted not only the use of chemoradiation [7–9], but both the development and use of various chemotherapeutic agents, primarily in a series of GOG sponsored clinical trials, in treating women with recurrent cervical cancer [10, 11].

Since this seminal work was published and incorporated into clinical practice, much of the subsequent evaluation in cervical cancer patient management has focused on ways to tailor surgical therapy in lower

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stage tumors, including attention to fertility preservation, evaluate the impact of therapy on overall quality of life in an attempt to limit future treatment related morbidities, evaluate the use of pre-therapy imaging, and to improve the effectiveness of both primary chemoradiation therapy and therapy for recurrent disease. This review will concentrate on both completed and ongoing clinical trials from the GOG/NRG Oncology from the last 2 decades including a review of common scenarios encountered in clinical practice.

2. Review

2.1. Preinvasive disease

Although pre-invasive disease is often out of the purview of cooperative group mandates, the GOG did perform a randomized placebo-controlled phase 2 trial (GOG 207) that utilized daily celecoxib in patients with high-grade cervical dysplasia that underwent both serial colposcopic examinations at pre-specified time points, as well as an end of therapy excisional procedure [12]. In this trial of 130 women with biopsy proven cervical intraepithelial neoplasia (CIN) 3, the use of 400 mg celecoxib daily, as compared to matching placebo for between 14 and 18 weeks, did not appear to increase HPV infection clearance, although serum vascular endothelial growth factor (VEGF) levels may predict a better likelihood of response to therapy.

2.2. Early stage tumors – Stage IA1–IB1

Patients with early stage cervical cancer are most commonly treated with one of several different surgical procedures, depending on both their fertility desires and the stage of disease [13]. For patients with Stage IA1 tumors, multiple fertility preserving and non-radical surgical options to include Loop Electrocautery Excisional Procedure (LEEP), Cold Knife Conization (CKC), and various approaches to simple hysterectomy are utilized. More recently, it has been recognized that fertility preservation may be an acceptable alternative in patients with Stage IA2 and IB1 tumors, that previously were managed with radical hysterectomy and lymphadenectomy. Following observations of the low rate of parametrial involvement, the increased use of minimally invasive surgical techniques and the observation of the relative effectiveness and safety of radical trachelectomy with lymphadenectomy, approaches to surgical management have focused on tailoring the procedure to the patients' tumor with a general approach of a less radical and fertility preserving surgery.

To further evaluate this approach in low stage tumors, GOG 278 (NCT 01649089) was developed to evaluate both physical function as well as quality of life in women with stage I squamous cell, adenocarcinoma or adenosquamous cervical cancer. Specifically, women with stage IA1 cervical cancer with lymphovascular space invasion (LVSI), Stage IA2 or Stage IB1 <2 cm in greatest dimension, that do not desire radical therapy and are undergoing either a simple non-radical hysterectomy or a CKC, both with pelvic lymphadenectomy are eligible. Patients are assessed for the impact of these procedures not only on the potential impact on bladder, bowel and sexual functioning, but in terms of the incidence and severity of lymphedema, recurrence and survival. At present, accrual is nearly 80% complete and patients undergo dedicated surveillance for at least 3 years after therapy.

2.3. Early stage tumors – intermediate recurrence risk following radical hysterectomy

Although radical hysterectomy with lymphadenectomy is definitive therapy and associated with an excellent prognosis for most patients undergoing surgery, the GOG performed a prospective evaluation of surgical pathology specimens and outcomes, GOG 49, in order to determine which pathologic findings were associated with a higher likelihood of nodal spread [14]. When specifically evaluating Stage IB patients that underwent a radical hysterectomy with pelvic and para-aortic lymphadenectomy, investigators identified depth of invasion, parametrial involvement, LVSI, tumor grade and gross versus occult primary tumor involvement as being associated with a higher risk of pelvic nodal involvement [15]. This pathologic data allowed the development of clinical trials in order to determine potential superior therapeutic options for patients with higher risk of cervical cancer recurrence.

To evaluate the clinical impact of pathologic risk factors in node negative and cervix confined disease, the GOG performed a trial, GOG 92, to determine the ideal treatment of patients deemed to have an intermediate risk of recurrence following a radical hysterectomy and lymphadenectomy. This trial evaluated women with a combination of LVSI, large tumor diameters and varying degrees of cervical stromal invasion with categories depicted in Table 1 [16]. Among 277 patients enrolled on the study, 137 received 46–50.4 Gy via external beam irradiation without vaginal brachytherapy. Preliminary results noted two-year superior recurrence free survival for patients receiving radiation, 88% versus 79%, at the expense of a nearly three-fold increase in grade 3/4 adverse events, 6% versus 2.1%. Subsequent analysis of longer term surveillance demonstrated a continued marked decrease in the risk of recurrence, HR 0.54 (90% CI 0.35–0.81, $p = 0.007$) without an improvement in overall survival (OS), HR 0.70 (90% CI 0.45–1.05, $p = 0.074$) [17]. Moreover, the protection against recurrence with radiation seemed more pronounced in those with adenocarcinomas or adenosquamous carcinomas, HR 0.23, (90% CI 0.07–0.74, $p = 0.019$).

While GOG 92 did not include chemotherapy, based on the cumulative data in both locally advanced disease as well as for high-risk early stage disease, many providers have recommended the addition of cisplatin chemotherapy to radiation in these patients even in the absence of clinical trial data. Accordingly, GOG 263 (NCT 01101451) was developed as a replacement or follow-up trial to GOG 92 to answer this exact question in a randomized study in women with Stage I-IIA cervical cancer. GOG 263 compares the use of external radiation therapy alone without brachytherapy or in combination with 6 cycles of weekly Cisplatin 40 mg/m^2 in women with intermediate risk pathologic findings following a radical hysterectomy with pelvic lymphadenectomy. Importantly, this trial will answer if the potential benefit in improved survival for patients with intermediate risk cervical cancer, is warranted or is outweighed by the potential added toxicity of cisplatin.

2.4. Early stage tumors – high recurrence risk following radical hysterectomy

Similarly, GOG 109 which was performed in conjunction with both the Southwest Oncology Group and Radiation Therapy Oncology Group, evaluated the role of chemotherapy added to post-operative external beam radiation therapy to the pelvis [4]. While GOG 49 was able to predict the impact of intermediate risk factors on recurrence and positive nodal status, much of the data available on higher risk features was retrospective [18, 19]. Nonetheless, based on the relatively consistent information that noted not only a higher risk of recurrence but also inferior survival, a prospective trial was developed which randomly assigned patients to either 49.3 Gy alone or in combination with cisplatin 70 mg/m^2 and 5-fluorouracil (5FU) 1000 mg/m^2/d over 96 h every 3 weeks. Of the 243 assessable patients on the two arms, the majority had positive pelvic nodes (207/243), with both positive

Table 1
Characteristics of intermediate risk factors for cervical cancer recurrence in patients undergoing radical hysterectomy with lymphadenectomy [16, 17].

Tumor size	Stromal invasion	LVSI
Any tumor size	Deep 1/3	Present
≥2 cm	Middle 1/3	Present
≥5 cm	Superficial 1/3	Present
≥4 cm	Deep or middle 1/3	Absent

parametrial involvement (83/243) and margins (12/243) much less common. At four years, patients on the combined chemoradiation arm had both superior PFS, 80% vs. 63%, and OS, 81% vs. 71%, with the hazard ratio point estimates for recurrence 2.01 ($p = 0.003$) and death 1.96 ($p = 0.007$) both inferior in the radiation only patients. Importantly based on study design, chemotherapy in this trial may have acted as a radiation sensitizer, in an adjunctive fashion after radiation of both with cycles 3 and 4 being administered following completion of external beam radiation therapy, or both.

Analogous to the treatment approach utilized where GOG 263 was developed as a replacement trial for GOG 92 in order to answer questions regarding chemoradiation for intermediate risk disease, the RTOG and GOG developed a trial, RTOG 0724/GOG0724 (NCT 00980954), which adds adjuvant chemotherapy to a standard post radical hysterectomy chemoradiation backbone. All patients in the trial will receive between 45 and 50.4 Gy of external beam radiation therapy administered either in a standard fashion or via Intensity Modulated Radiation Therapy (IMRT) with or without brachytherapy. Patients on the experimental arm with then commence adjuvant chemotherapy within four to six weeks from completion of chemoradiation which consists of four cycles of paclitaxel 135 mg/m^2 and carboplatin AUC 5 administered every three weeks. The primary objective of this trial is to determine if the experimental arm improves disease-free survival with OS being one of several secondary endpoints.

2.5. Quality of life/survivorship

While surgical excision is associated with generally favorable prognosis without the need for adjuvant therapy in many patients with Stage I cervical cancer, intermediate and high-risk patients notwithstanding, radical surgery can result in severe long-term sequelae. Consequently, the GOG developed GOG 244 (NCT 00956670) to prospectively evaluate the incidence of lower extremity lymphedema in a group of cervical, as well as endometrial and vulvar cancer patients, undergoing radical gynecologic surgery with concurrent lymphadenectomy. In addition to evaluating the incidence of lymphedema, various risk factors for the development of lymphedema as well as its potential impact on patient quality of life will be explored. Carlson recently presented the initial data for 138 cervical cancer patients with a median age of 44 (range 25–83) from the total study sample size of 1054 [20]. Study endpoints of a limb volume change (LVC) of >10% for any of the post-operatively visits between 6 weeks and 24 months were considered consistent with lymphedema, which was present in 48 or 35% of the cervical cancer patients. Moreover, LVC of a >15% change was present in 35 or 25%, with an LCV of >20% limited to 17 or 12% of these patients.

2.6. Pre-therapy imaging

Debate continues regarding the role of lymph node assessment in patients with locally advanced cervical cancer and the impact of the discovery and removal of occult nodal metastatic disease. In early locally advanced cervical cancer trials, patients generally underwent surgical assessment of their lymph nodes. However, with improving radiographic techniques and the development of Positron Emission Testing (PET) scanning capabilities, the role of pre-radiation surgical nodal assessment was questioned. Specifically, GOG 165 was the first chemoradiation trial that did not require a surgical assessment of the para-aortic lymph nodes [21]. A subsequent ancillary analysis of data from both GOG 165 and GOG 120 noted differences in outcomes based on clinical versus surgical staging of the para aortic nodes [22]. As noted in this analysis, although the radiation dose in GOG 165 was 5 Gy greater than that used in GOG 120 and administered over a shorter treatment course (10 versus 8 weeks), survival for patients with stage III or IV disease was worse in GOG 165, potentially suggesting a negative impact of imaging negative but pathologically positive para-aortic lymph nodes that were not surgically resected.

In order to determine if more modern imaging, such as PET imaging was sufficient to detect nodal metastatic disease in patients with locally advanced cervical cancer, the GOG partnered with the American College of Radiology Imaging Network (ACRIN) to answer this question [23]. Specifically, in GOG 233, 153 patients with locally advanced cervical cancer underwent pre-operative PET combined with contrast-enhanced diagnostic CT imaging followed by pelvic and abdominal lymphadenectomy. Surgical approach included either laparoscopic or an extraperitoneal approach with a goal of removing lymph nodes from 4 regions bilaterally: obturator, external iliac, common and para-aortic lymph node basins. In this trial, whose primary objective was to determine the accuracy of PET/CT to detect abdominal retroperitoneal lymph node metastasis, 43 of 153 (28.1%) patients with an adequate PET/CT and some pathology had pathologically proven abdominal lymph node metastasis; however, secondary to exclusion criteria including inadequate lymph node dissection, failure to perform pre-operative PET/CT, poor quality PET/CT or lack of pathologic submission, only 109 patients meet all criteria both from an imaging and surgical assessment standpoint. When comparing the combination of PET/CT versus CT alone, sensitivity was 0.50 versus 0.42 ($p = 0.052$) and specificity was 0.85 versus 0.89 ($p = 0.21$) respectively. These results suggest perhaps a modest improvement for PET/CT compared to CT alone.

2.7. Locally advanced disease

While chemoradiation with single agent cisplatin 40 mg/m^2 administered weekly remains the standard of care for patients with locally advanced cervical cancer, continued investigations have evaluated potential modifications or additions to this chemoradiation backbone in order to improve patient survival. As noted previously, the landmark clinical trials from 1999 radically altered the management of women with cervical cancer that was not amenable to a surgical resection [3–6]. Importantly, updated results have been published from several of these trials which note a continued and durable benefit for chemoradiation compared to radiation alone [24, 25]. In order to evaluate the impact of anemia on survival, the GOG commenced GOG trial 191 which utilized standard cisplatin based chemoradiation with or without recombinant human erythropoietin (EPO) [26]. Interestingly, in this trial where women were administered EPO to keep their hemoglobin >12.0 g/dL, the observation of more thromboembolic events in the experimental arm caused the trial to be closed early which limits interpretation. More recently, the GOG has compared both a prolonged venous infusion of 5-fluorouracil (5FU) versus weekly cisplatin as well as the addition of tirapazamine, a hypoxic cell sensitizer, to standard chemoradiation in two Phase 3 randomized controlled trials [21, 27]. Although 5FU had previously been evaluated in patients with locally advanced cervical cancer, this was in combination with other chemotherapy agents and had not been compared head-to-head with weekly cisplatin [6, 21]. Accordingly, GOG 165 evaluated a prolonged venous infusion of 5FU 225 mg/m^2/d for five days versus cisplatin 40 mg/m^2 weekly for up to 6 doses, where 5FU was predicted to decrease the risk of recurrence by one-third. During a planned interim data analysis, not only was 5FU not superior to cisplatin, it was inferior and was associated with a higher risk of both treatment failure, RR 1.29 (95% CI 0.91–1.80) and death, RR 1.35 (95% CI 0.96–1.97), which appropriately lead to the premature closure of the study. Although the trial was considered negative, it was the first trial which did allow the use of high dose rate brachytherapy in locally advanced cervical cancer patients.

Tirapazamine, which is thought to increase the cytotoxicity of cisplatin and had been evaluated both in recurrent and primary cervical cancer previously, was utilized with the standard cisplatin based chemoradiation backbone and compared to the standard chemoradiation backbone alone [27]. Similar to GOG 165, the experimental regimen was predicted to decrease the risk of recurrence by nearly one-third,

specifically 30% for GOG 219, when compared to standard therapy. Based on an interim safety analysis, the dose of tirapazamine was decreased which resulted in better tolerance of therapy. Unfortunately, during the study, the drug became unavailable which resulted in premature closure of the trial. At the time of study closure, 402 of 750 (53.6%) planned patients were accrued, and in the 387 evaluable patients, both the three-year PFS, 63.0% vs. 64.4%, and three-year OS, 70.5% vs. 70.6%, were similar in the cisplatin/tirapazamine arm and cisplatin alone arms respectively [27]. Unfortunately, these results add little to the current management of locally advanced cervical cancer. Pertinent and collated details from GOG chemoradiation trials for locally advanced cervical cancer are presented in Table 2.

While both GOG 165 and GOG 219 are considered negative studies in that no regimen was found to be superior to the standard cisplatin chemoradiation backbone, two additional trials have evaluated other novel approaches in a similar group of patients. The first, is a combined cooperative group trial, referred to as the OUTBACK trial (GOG274) and evaluates the use of 4 cycles of paclitaxel 155 mg/m^2 and carboplatin AUC5 administered every three weeks following chemoradiation therapy (NCT 01414608). GOG 274 has completed enrollment with >600 women enrolled by the GOG with results eagerly awaited. Triapine, a ribonucleotide reductase inhibitor, has been combined with standard chemoradiation therapy in patients with both cervical as well as vaginal cancer. Based on early encouraging preliminary results from Kunos and colleagues [28, 29], triapine was included in the replacement trial for GOG 274, GY006 (NCT02466971), a randomized phase 2 trial which will enroll nearly 200 women (Fig. 1). Results from both GOG 274 as well as GY006 will help inform whether modifications to the chemoradiation backbone warrant further evaluation.

2.8. Recurrent/metastatic disease

Bonomi and colleagues in an early GOG phase 3 clinical trial, presented milestone data when they demonstrated the optimal dose of cisplatin in the recurrent setting to be 50 mg/m^2 every 21 days, as comparted to other options of either Cisplatin 100 mg/m^2 every 21 days or cisplatin 20 mg/m^2 days 1–5 [30]. Building upon this historic finding, subsequent phase 3 trials evaluated various cisplatin-based combinations which unfortunately provided limited patient benefit, as although combination therapy was often associated with superior response rate (RR) and PFS, OS was not improved and this was at the expense of added toxicity [31, 32]. However, Moore and colleagues reported exciting results from GOG 169 when paclitaxel 135 mg/m^2/24 h was combined with cisplatin 50 mg/m^2, as compared to single agent cisplatin 50 mg/m^2 [33]. In addition to an improved RR of 35% vs. 19% and improved PFS of 4.8 vs. 2.8 months, quality of life was assessed for the first time in a metastatic cervical cancer randomized trial and demonstrated no apparent decrement with combination therapy.

With the widespread adoption of chemoradiation into primary therapy for locally advanced cervical cancer, response rates to both single agent platinum and platinum-based combination therapies were noted to decline as compared to historical controls [33, 34]. In GOG 179, the combination of 0.75 mg/m^2 topotecan on days 1–3 with cisplatin 50 mg/m^2 day 1 every 3 weeks as compared to single agent cisplatin 50 mg/m^2 lead to FDA approval, based on superior outcomes including an improvement in median OS of 9.4 months vs. 6.5 months ($p = 0.017$) for the combination arm. However, GOG 204, a four-arm trial that compared platinum doublets was subsequently performed and closed early for futility when none of the four combination arms: paclitaxel and cisplatin, topotecan and cisplatin, gemcitabine and cisplatin or vinorelbine were judged to be more effective than the others [35].

Although not a prospective evaluation, Moore and colleagues retrospectively evaluated patient data from GOG protocols 110, 169 and 179 in an attempt to determine if prognostic factors exist which may predict response or lack of response to chemotherapy in the recurrent and metastatic setting [36]. Factors identified among 428 patients in these three phase 3 trials, that appeared to be associated with response to chemotherapy included: performance status >0, pelvic disease, receipt of prior radiosensitizer, time interval from diagnosis to first recurrence <1 year and African American race. Patients where then divided into three categories based on the number of risk factors present from Low Risk (0–1 factors) to High Risk (4–5 factors) and those with 2 or 3 factors being considered Mid Risk. This classification schema, often referred to as the Moore Criteria, was then applied to patients in another Phase 3 trial, GOG 149, to determine if indeed it accurately predicted differential outcomes. When the criteria were applied to the GOG 149 patients, response rate and survival did vary and appeared to correlate with the number of risk factors present. Specifically, median OS ranged from 11.93 months for those with Low Risk factors, to 5.58 months for those with High Risk factors. Moreover, in patients with High Risk factors, the overall response rate to additional chemotherapy was only 14.3% with a median progression free survival of a mere 3.38 months.

Table 2
Patient outcomes in GOG sponsored Phase 3 chemoradiation trials for locally advanced cervical cancer [3, 5, 6, 21, 26, 27].

Protocol	Stages	Chemotherapy	N	Proportion disease free	Proportion alive	RR/HR overall survival
GOG 85	II, III, IVA	HU	191	47%	43%	Referent
		5FU + CP	177	57%[a]	55%[a]	0.74 (90% CI 0.58–0.95)
				@8.7 yrs	@8.7 yrs	
GOG 120	IIB, III, IVA	HU	177	26%	34%	Referent
		CP	176	46%[a]	53%[a]	0.57 (95%CI 0.43–0.75)
		CP + 5FU + HU	173	43%[a]	53%[a]	0.51 (95%CI 0.38–0.67)
				@10 yrs	@10 yrs	
GOG 123	IB	None	186	60%	64%	Referent
		CP	183	71%[a]	78%[a]	0.63 (95%CI 0.43–0.91)
				@6 yrs	@6 yrs	
GOG 165	IIB, IIIB, IVA	CP	159	57%	64%	Referent
		5FU	157	40%	55%	1.37(95% CI 0.96–1.94)
				@4 yrs	@4 yrs	
GOG 191	IIB, IIIB, IVA	CP	52	65%	75%	NR
		CP + EPO	57	58%	61%	
				@3 yrs	@3 yrs	
GOG 219	IIB, IIIB, IVA	CP	194	63%	70.6%	Referent
		CP + TPZ	185	64.4%	70.5%	1.174 (95% CI 0.652–2.112)
				@3 yrs	@3 yrs	

N – number of evaluable patients per study arm; RR – relative risk; HR – hazard ratio; NR – not reported; GOG – Gynecologic Oncology Group; CP – cisplatin; HU – hydroxyurea; 5FU – 5-Flurouracil; EPO – recombinant human erythropoietin; TPZ – tirapazamine;
[a] Statistically significant differences.

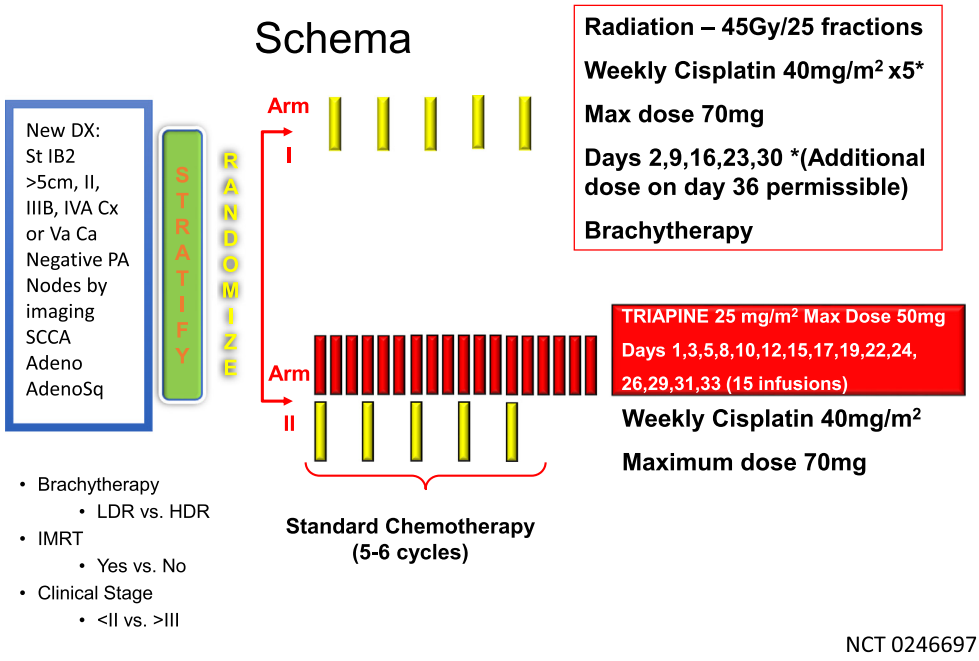

Fig. 1. Schema for GY006 evaluating the addition of the ribonucleotide reductase inhibitor, triapine (NSC#663249; IND#68338), to standard cisplatin based chemoradiation in locally advanced cervical and vaginal cancer.

While cytotoxic chemotherapy has been the mainstay of treatment for recurrent cervical cancer, the GOG has also evaluated non-cytotoxic therapy in a series of single arm trials in order to determine potential activity of these novel therapies. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth facto, was evaluated in patients with recurrent cervical cancer that had been treated with one or two prior lines of chemotherapy. GOG 227C was a trial of 46 patients, the majority of which (74%) had received only one line of chemotherapy and radiation (83%), of which 11 patients (23.9%) survived progression free for at least six months [37]. Last year, results from GOG 265, a single arm phase 2 trial, which evaluated the use of a *Listeria monocytogeneses* immunotherapy agent targeted in patients with 1–3 prior lines of therapy was presented at the Society of Gynecologic Oncology Annual meeting [38]. Of 50 evaluable patients, of which 52% had received 2 or 3 prior lines of therapy, 56% had received prior bevacizumab and 86% had undergone prior pelvic radiation, the 12-month OS rate was 38% with a median OS of 6.2 months (95% CI 4.4–12.3 months), including a patient with a confirmed complete response.

The encouraging single agent response to bevacizumab in GOG 227C, led to the development of the GOG 240 protocol, incorporating both bevacizumab and cytotoxic chemotherapy [39]. In addition, secondary to the decreased response to platinum seen in GOG 169 and 179, a decision was made to evaluate non-platinum-based therapy in addition to the standard chemotherapy control arm of paclitaxel and cisplatin. In GOG 240, 452 patients were randomly assigned in a 2 × 2 factorial designed phase 3 clinical trial to receive one of two chemotherapeutic backbones: paclitaxel 135 or 175 mg/m^2 with cisplatin 50 mg/m^2 or the non platinum doublet of paclitaxel 175 mg/m^2 on day 1 with topotecan 0.75 mg/m^2 days 1–3. In addition, a second randomization then assigned patients to either add or withhold

Table 3
Sentinel phase III GOG clinical trials in recurrent cervical cancer [30–35, 39, 40].

Protocol	Chemotherapy	N	RR	CR	PR	PFS (mos)	OS (mos)
GOG 43	CP 50 mg/m^2 D1	150	20.7%	10%	10.7%	3.7	7.1
	CP 100 mg/m^2 D1	166	31.4%*	12.7%	18.7%	4.6	7.0
	CP 20 mg/m^2 D1–5	128	25%	8.6%	16.4%	3.9	6.1
GOG 110	CP	140	17.8%	6.4%	11.4%	3.2	8.0
	CP + I	151	31.1%*	12.6%	18.5%	4.6*	8.3
	CP + M	147	21.1%	9.5%	11.6%	3.3	7.3
GOG 149	CP + I	146	32.0%	NR	NR	4.6	8.5
	CP + I + B	141	31.2%	NR	NR	5.1	8.4
GOG 169	CP	134	19%	6%	13%	2.8	8.8
	CP + P	130	35%*	15%	21%	4.8*	9.7
GOG 179	CP	146	13%	2.9%	10.1%	2.9	6.5
	CP + T	147	26.7%*	10.4%	16.3%	4.6*	9.4*
GOG 204	CP + P	103	29.1%	2.9%	26.2%	5.8	12.9
	CP + T	111	23.4%	1.8%	21.6%	4.6	10.3
	CP + G	112	22.3%	0.9%	21.4%	4.7	10.3
	CP + V	108	25.9%	7.4%	18.5%	4.0	10.0
GOG 240	CP + P + Bev	115	50%	16%	35%	8.2*	17.5*
	CP + P	114	46%	10%	36%	6.0	15.0
	T + P + Bev	112	48%	12%	37%		16.2
	T + P	111	25%	5%	20%		12.0

N – number of evaluable patients per study arm; OS – overall survival; PFS – progression-free survival; RR – response rate; CR – complete response; PR – partial response; GOG – Gynecologic Oncology Group; D – day of the cycle; NR – not reported; CP – cisplatin; I – ifosfamide; M – mitolactol; B – bleomycin; P – paclitaxel; T – topotecan; G – gemcitabine; V – vinorelbine; BEV – bevacizumab; C – carboplatin.

bevacizumab 15 mg/kg every 3 weeks. In addition to a greater response rate, 48% vs. 36% ($p = 0.008$), OS was improved with the addition of bevacizumab to chemotherapy, 17.0 months vs. 13.3 months with a HR for death of 0.71 (98% CI 0.54–0.95, $p = 0.004$). This improvement in OS was confirmed in the final analysis, 16.8 vs. 13.3 months (HR 0.77, 95% CI 0.62–0.95, $p = 0.007$) which was recently published [40]. Comparisons of the key phase 3 trials from the GOG are presented in Table 3. Moreover, the Moore Criteria were evaluated in a prospective fashion by collection at patient enrollment, which confirmed the earlier discriminatory ability of the criteria to predict outcome [36, 41]. In GOG 240, patients with High Risk factor Moore Criteria had an observed RR of 18.5% ($p < 0.0001$) with a median PFS of 4.7 months ($p = 0.005$) and OS of 8.2 months ($p < 0.001$) with all of these outcomes inferior when compared to patients with either Mid Risk or Low Risk factors [41]. Specifically, RR in Low and Mid Risk patients were 57.1% and 43.2% respectively, while PFS 9.2 vs. 6.9 months and OS 21.8 vs. 14.7 months, both respectively, were much improved when compared to High Risk factor patients. Nonetheless, patients with Low Risk factors did not appear to benefit from the addition of bevacizumab to chemotherapy in survival outcomes, although patients with Mid or High Risk disease had statistically superior PFS and OS when stratified for the use or lack of use of bevacizumab, with a 5.8 month improvement in OS seen in both these groups.

3. Conclusion

The GOG/NRG Oncology has had a very successful history in not only evaluating management strategies in women with cervical cancer, but in advancing the science for the care of women with this disease. While results from chemoradiation therapy trials are considered seminal, current investigations will continue to define and alter the treatment paradigms for these patients. Forthcoming studies will further guide fertility preserving surgery and likely limit patient morbidity, refine and further optimize chemoradiation for locally advanced disease and build upon the chemotherapy and bevacizumab backbone from GOG 240, which although the most active regimen in metastatic disease, is still not curative.

Conflict of interests

The authors affirm they have no conflict of interests for the current manuscript.

Author contribution section

Conception and Design – Monk
Collection/Assembly of Data – Leath
Analysis/Interpretation – Leath, Monk
Manuscript Writing – Leath, Monk
Final Approval of Manuscript – Leath, Monk
Accountable for All Aspects – Leath, Monk

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