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Chemoradiotherapy for cervical cancer

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Abstract

Cervical cancer remains a major health problem worldwide, despite advances in screening. For patients with locally advanced stage disease, failure to obtain local-regional control usually results in death. In an effort to improve local-regional tumour control, neoadjuvant and concurrent chemoradiation has been tested. Recently, five randomised trials performed by the Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG) and the SouthWest Oncology Group (SWOG) studying cisplatin-based chemoradiation have demonstrated a significant survival advantage. Three of the trials compared cisplatin-based concurrent chemotherapy and radiation to radiation alone and two trials compared cisplatin-based concurrent chemotherapy and radiation to radiation with hydroxyurea. In all of the trials, cisplatin-based chemotherapy administered concurrently with radiation therapy was more effective at reducing the risk of death by 30–50%. Acute toxicities, principally neutropenia and gastrointestinal, were more common with chemoradiation, but were transient and the rates of late complications (complications that persisted or occurred for more than 60 days after the treatment) were similar. Based on the results of these five randomised trials, the National Cancer Institute (NCI) released a Clinical Announcement stating that cisplatin-based chemotherapy, as used in these trials (i.e. concurrently with radiation therapy), as the new standard of therapy for cervical cancer. © 2002 Published by Elsevier Science Ltd.

Keywords: Cervix; Chemoradiotherapy; Cisplatin

1. Introduction

Cancer of the cervix, which has continually been decreasing in North America and Europe, remains the third most common cancer affecting women in the world [1]. The magnitude of this disease is probably much greater than recorded because most of the cases occur in under-developed countries which do not have complete and durable tumour registries. It has been estimated that perhaps as many as 750 000 cases occur annually, which would make it the most frequent female cancer in the world [2]. Additionally, because it effects younger women than other malignancies [3], an average of 26 years of life are lost for each patient affected [4]. Therefore, improvements in cure can profoundly affect longevity. The social consequences of the death of a woman who in turn may be the sole provider for her young children are tremendous. Even in developed countries such as the United States, there continue to be under-screened or high-risk populations such as the Asian, Hispanic, African American, American Indian and Appalachian whites [5]. Unscreened patients usually present with symptoms that are associated with advanced disease and poor survival.

Recently, large cooperative randomised clinical trials have shown superiority to the concurrent use of cisplatin-based chemotherapy with radiation therapy in a variety of advanced stage or high-risk settings. The term chemoradiotherapy is preferable to chemotherapy and radiotherapy because it implies a concurrent temporal relationship. The concurrent temporal relationship of chemotherapy and radiation therapy has shown more favourable results than when chemotherapy and radiation therapy were given at different times, i.e. either neoadjuvant or adjuvant. This study will review the use of chemotherapy with radiation therapy for cancer of the cervix.

Cervical cancer when untreated grows, invading adjacent anatomical structures and often metastasising to regional lymph nodes. As a result, patients often

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present with locally advanced disease. Locally advanced cervical cancer has been defined as a tumour whose size exceeds that which can be treated successfully (over 85% cure rate) with surgery alone [6]. Although radiation therapy has been used successfully for the treatment of locally advanced cervical cancer, radiocurability has been limited by tumour size. In their classic paper, Fletcher and colleagues reported the positive correlation between tumour size and radiation dose required for tumour control [7]. For large cervical lesions, the dose of radiation needed to achieve high rates of tumour control exceeds the dose tolerated by normal tissues in the pelvis. Although investigators have explored a number of technical innovations, including the use of hyperthermia [8], neutron beam irradiation [9], interstitial brachytherapy [10], and high dose-rate intracavitary therapy [11], none of these has had a major beneficial impact on treatment results. Some improvements in survival have come with greater emphasis with regard to the dose and proportion of intracavitary treatment and minimisation of total treatment duration [12,13]. However, local disease recurrence remains a significant problem for patients with locally advanced disease [14].

Over the last century, surgery and radiation and, more recently, chemotherapy have been individually used in various settings in an effort to improve survival rates of patients with cervical cancer. However, in the last decade, the role of multiple modality treatment including neodjuvant, concurrent and adjuvant chemotherapy with either surgery or radiation therapy as part of an initial treatment plan have been evaluated in randomised clinical trials. Recently, a number of cooperative clinical trials have demonstrated a benefit from the concurrent use of chemotherapy and radiation to treat cervical cancer [15–19]. These studies have provided the basis for a United States National Cancer recommendation for "...the use of cisplatin-based chemotherapy during radiation therapy for cervical cancer..." [20].

2. Biology of chemoradiation

The mechanisms of chemotherapy and radiation interactions are not completely known. Initially, when chemotherapy was combined with radiation therapy, it was believed that radiation controlled local disease, while chemotherapy controlled subclinical metastasis that lie outside the radiation field. However, increasing evidence suggest chemotherapy and radiation interact and increase the sensitivity of the local tumour to radiation therapy. As tumour cells progress through the cell cycle, they vary in their radiosensitivity. Sensitisation may occur because radiation therapy and chemotherapy compliment each other by affecting different phases of the cell cycle simultaneously. Chemotherapy may also increase tumour cell death by decreasing the shoulder or increasing the slope of the radiation dose–response curve by mechanisms that include direct tumour cytotoxicity, tumour cell cycle synchronisation, and inhibition of sublethal radiation repair [21].

Chemotherapy and radiation therapy have principally been studied in two primary schedules: (1) neoadjuvant and (2) concurrent. Neoadjuvant (preradiation) chemotherapy is delivered in an effort to reduce tumour volume before the radiation therapy. Since tumour volume before radiation therapy is the most important predictor of local disease control, this schedule makes intuitive sense. Furthermore, combined treatment may be less toxic when given sequentially rather than concurrently. However, an initial course of chemotherapy can lead to compromises in the intensity of the subsequent radiation therapy. Unfortunately, of the nine randomised trials of neoadjuvant chemotherapy and radiation versus radiation alone that have been published, seven showed no benefit from neoadjuvant therapy and two demonstrated a significantly better survival rate with radiation alone [22–30] (Table 1). In one of the two trials that demonstrated poorer survival, Souhami and colleagues reported patients treated with bleomycin,

Table 1
Randomised studies of new neoadjuvant chemotherapy followed by radiation therapy in cervical cancer

Reference	*n*	Regimen	Response		Survival		
			CT/RT (%)	RT (%)	CT/RT (%)	RT (%)	*P* value
[22]	138	MtxCVP	84.9	88.9	63	60	NS
[23]	66	BIP	75	56	–	–	NS
[24]	107	BOMP	47	32.5	23	39	0.02[a]
[25]	28	PECy	5	86	36	50	NS
[26]	177	BIP	70	69	38	43	NS
[27]	130	BOP	68	65	38	49	NS
[28]	260	EpP	72	92	47	70	0.02[a]
[29]	94	PF	53	57.5	38	40	NS
[30]	58	P	78	81	72	83	NS

B, bleomycin; C, chlorambucil; I, ifosfamide; M, mitomycin-C; Mtx, methotrexate; O, vincristine; P, cisplatin; V, vinblastine; Ep, epirubicin; F, 5-fluorouracil; CT, chemotherapy; RT, radiotherapy; NS, non-significant.

[a] Statistically poorer outcome with neoadjuvant chemotherapy and radiation.

vincristine, mitomycin-C, cisplatin (BOMP) chemotherapy followed by radiation had a significantly poorer survival rate than those treated with radiation alone [24]. Four patients died from bleomycin pulmonary toxicity which may have contributed to the poor survival rate of patients treated with neoadjuvant chemotherapy in this study. Furthermore, inappropriately, patients who failed to complete radiation therapy, which was more frequent in the neoadjuvant chemotherapy arm, were excluded from analysis. Another study published by Tatersall in 1995 utilised cisplatin and epirubicin as the neoadjuvant regimen. Despite the elimination of bleomycin, this study was discontinued early when an interim analysis revealed the detrimental effect of neoadjuvant chemotherapy on survival ($P = 0.02$) [28].

To date, no study in cervical cancer has suggested a benefit for neoadjuvant chemoradiation versus radiation alone. These results are consistent with the findings of similar studies of neoadjuvant chemotherapy in patients with squamous cell cancer of the head and neck [31]. Investigators have suggested a number of reasons for the failure of neoadjuvant regimens to improve overall survival despite excellent chemotherapy response rates. Toxic deaths have negatively affected survival in some studies. Additionally, cervical cancer patients tend to have difficulty complying with treatment recommendations and several investigators have reported increased rates of non-compliance with radiation treatment among patients treated with neoadjuvant chemotherapy. It has also been suggested that initial chemotherapy causes accelerated repopulation of resistant clones, compromising the ability of radiation therapy to provide local disease control [32,33].

In the concurrent therapy schedule, radiation and chemotherapy are initiated simultaneously. This has the advantage of not delaying potentially curative radiation therapy. Additionally, this strategy minimises the risk of developing cross-resistant tumour cells, since there is no interval between the two techniques. However, the combination of therapies might increase side-effects, compromising the appropriate use of either therapy. An accepted tenet is that the adjunctive therapy should not compromise the chance of cure with radiation therapy alone.

In concurrent chemoradiation regimens, more attention must be given to the toxicity of the chemotherapy and to possible potentiation of radiation toxicity. The agents most commonly used with concurrent radiation in cervical cancer have included hydroxyurea, cisplatin, 5-fluorouracil (5-FU) and mitomycin-C.

Hydroxyurea is an inhibitor of ribonucleotide reductase, an enzyme necessary for DNA synthesis and repair. Hreshchyshyn first utilised hydroxyurea clinically concurrently with radiation therapy to treat patients with cervical carcinoma [34]. A series of studies performed at the Roswell Park Cancer Institute by Piver and colleagues further explored the use of concurrent hydroxyurea and radiation in locally advanced cervical cancer [35–38]. Simultaneously, hydroxyurea was evaluated in multi-institutional cooperative study performed by the Gynecologic Oncology Group (GOG) [39]. In this study of 97 evaluable patients with stage III-B and IV-A squamous cell carcinoma of the cervix, treatment with radiation and hydroxyurea showed a significantly increased complete response rate (68% versus 49%), progression-free interval (13.6 months versus 7.6 months) and survival (median 19.5 months versus 10.7 months) compared with radiation alone. These early trials of hydroxyurea as a radiation sensitiser suffered from statistical weakness related to the small sample size, frequent protocol violations and the large number of patient exclusions. While the use of radiation with hydroxyurea was accepted by the GOG as the new standard, this did not become accepted in common practice. Subsequently, the GOG conducted a randomised trial comparing hydroxyurea with misonidazole concurrent with radiation therapy and the hydroxyurea regimen was associated with a better survival rate ($P = 0.066$) and less neurotoxicity [40].

5-FU is believed to interfere with radiation repair and Byfield and colleagues showed that in order to achieve radiosensitisation, cells had to be exposed to 5-FU for at least 24 h after the radiation therapy was administered [41]. This is accomplished clinically with the use of a prolonged 5-FU infusion. Thomas and colleagues from the Princess Margaret Hospital investigated the combination of radiation, mitomycin-C and 5-FU infusion [42]. In a retrospective analysis comparing patients treated with radiation and 5-FU, the addition of mitomycin-C increased late toxicity [43]. Therefore, in a randomised trial, these investigators evaluated radiation given daily or twice daily with or without 5-FU infusion. A statistical benefit for 5-FU infusion was observed in patients with stage IB_2, IIA and IIB with unilateral parametrial involvement, but not with more extensive disease [44]. Furthermore, the benefit of 5-FU infusion was also observed only in patients who were treated with daily (as opposed to twice-daily) radiation [44].

Cisplatin is considered the most active cytotoxic agent for patients with metastatic and recurrent squamous carcinoma of the cervix [45]. Furthermore, randomised trials have failed to demonstrate a meaningful improvement in survival for multiagent regimens that include cisplatin when compared with single agent cisplatin [45,46]. In view of it's moderate bone marrow toxicity, cisplatin is an attractive agent to use with radiation therapy. *In-vitro* and *in-vivo* studies have demonstrated an increased cytotoxicity of cisplatin and radiation therapy. However, studies in cervical cancer cell lines have demonstrated a lack of synergy in most cell lines suggesting the principle mechanism is a decrease in tumour size and improved oxygenation as a direct effect

of the cytotoxicity of cisplatin [47]. Inhibition of the repair of sublethal radiation damage and hypoxic cell sensitisation have also been postulated as mechanisms of cisplatin activity [48]. The improved clinical response rate with concurrent in contrast to neoadjuvant cisplatin-based chemoradiation, suggests radiosensitisation is occurring. In animal studies, the effects of a variety of schedules of cisplatin in combination with radiation were studied [49] (Table 2). The schedule of cisplatin and radiation administration was critical to the radiosensitisation. Neither neoadjuvant or adjuvant schedules of chemotherapy resulted in increased therapeutic gain. Cisplatin administered as little as 6 h following radiation resulted in only a small benefit over radiation alone. The effects of equivalent doses of cisplatin administered on schedules every three weeks, weekly, and daily were also studied with more frequent administration either weekly or daily resulting in a greater therapeutic gain [49]. However, weekly cisplatin administration was as effective as daily administration and was a more convenient schedule. Lastly, the dose intensity of cisplatin also appeared important with the maximum effect seen with the greater cisplatin dose.

The combination of cisplatin and 5-FU has been utilised in advanced and recurrent cervical cancer. Neither agent results in significant myelosuppression making this an appropriate combination to utilise for radiosensitisation. The combination of cisplatin and 5-FU with concurrent radiation produced supra-additive cell killing in animal tumour models [50–52]. Numerous phase II and more recently randomised trials with this combination with radiation therapy have been performed.

Hydroxyurea inhibits ribonucleotide reductase decreasing the formation of deoxyuracil monophosphate (dUMP) which competes for thymidylate synthase with fluorodeoxyuridine monophosphate (FdUMP), the active form of 5-FU. The combination of hydroxyurea and 5-FU are synergistic for the inhibition of thymidylate synthase. The combination of cisplatin, hydroxyurea and 5-FU with radiation therapy has been studied in head and neck cancer, and cervical cancer [53,54].

Recently, the results of five large randomised trials comparing cisplatin-based chemoradiation with radiation alone or with radiation and hydroxyurea in patients with cervical cancer have become available (Table 3). These studies utilised concurrent cisplatin either alone or in combination with 5-FU or 5-FU and hydroxyurea. The GOG randomised 368 evaluable patients with stage IIB-IVA cervical cancer to receive radiation therapy with concurrent cisplatin and 5-FU infusion for 4 days versus hydroxyurea (GOG 85) [15]. Significantly less leucopenia occurred with cisplatin and 5-FU than with hydroxyurea. Patients on the cisplatin-containing treatment arm had a significantly better progression-free and overall survival. With a median follow-up of 8.7 years, this difference in survival is 55% versus 43% for the cisplatin/5-FU versus hydroxyurea regimens, respectively. In a subsequent trial, the Radiation Therapy Oncology Group (RTOG) randomised 388 evaluable stage IB-IVA patients to chemoradiation with cisplatin and 5-FU versus extended field radiation (RTOG 9001) [16]. This trial was based on a previous RTOG trial demonstrating superiority of extended field radiation in advanced cervical cancer [55]. Chemoradiation with cisplatin and 5-FU were again superior resulting in an overall survival of 73% compared with 58% for radiation alone. Chemoradiation decreased both the rate of local failure and the rate of distant failure. Acute toxicity was more common with chemoradiation, but the rates of late complications (complications that persisted or occurred more than 60 days after treatment) were similar. Lastly, in a trial by the SouthWest Oncology Group (SWOG) 243 evaluable patients with clinical stage IA_2, IB and IIA with high-risk factors such as nodal metastasis, parametrial extension

Table 2
Preclinical model (murine) of therapeutic gain factor for radiation utilising different cisplatin schedules[a]

Schedule No.	Treatment day								Duodenum	Lung	
	0	1	2	3	4	5	6	7	Therapeutic gain	Early	Late
6			px	px	px	px	px		2.37±0.57	2.13±0.53	2.39±0.60
8			x6p	x6p	x6p	x6p	x6p		1.30±0.16	1.11±0.15	1.31±0.21
9			x	x	x	x	x	P	1.24±0.19	–	–
10		P	x	x	x	x	x		1.94±0.12	1.76±0.18	1.96±0.26
10′		P′	x	x	x	x	x			1.19±0.12	1.41±0.12
11			x	x	x	x	x		1.21±0.13	1.00±0.13	1.14±0.12
			p	p	p	p	p				
12			p	p	p	p	p		0.91±0.17	0.73±0.15	0.77±0.15
			x	x	x	x	x				

Drug doses: cis-DDP: p = 2.4 mg/kg; P = 12 mg/kg, except schedule 10′ where the single cis-DDP dose was 8 mg/kg. X = radiation therapy, 6 = 6-h delay. Schedules 11 and 12: the first five treatments were administered daily on Monday to Friday and the second five treatments started on the next Monday.

[a] From Ref. [49].

Table 3
Five randomised studies of concurrent chemoradiation in cervical carcinoma

Reference	Drugs	*n*	Survival		
			CT/RT	RT	*P* value
Chemoradiation versus radiation alone					
[16] RTOG 9001	CF	388	73	58	0.004
[19] GOG #123	C	369	83	74	0.008
[18] SWOG 8797	CF	243	80	63	0.01
Comparative trials of chemoradiation regimens					
[15] GOG #85	CF versus H	368	55 CF	43 H	0.018
[17] GOG #120	C versus H	526	64 C	39 H	0.002
[17] GOG #120	CHF versus H		66 CHF	39 H	0.002

C, cisplatin; F, 5-FU; H, hydroxyurea; RTOG, Radiation Therapy Oncology Group; GOG, Gynecologic Oncology Group; RT, radiotherapy; CT, chemotherapy; SWOG, SouthWest Oncology Group.

or involved margins of resection following radical hysterectomy were randomised between radiation therapy with cisplatin and 5-FU or radiation alone (SWOG 8797) [18]. This trial differed from the other four trials in that chemotherapy was given both concurrently during the radiation therapy for two cycles and for two cycles after radiation completion. The projected progression-free survival favoured the chemoradiation arm (80%) versus radiation alone (63%). The projected survival also favoured the chemoradiation arm.

To further study single agent cisplatin delivered weekly and the combination of cisplatin, 5-FU and hydroxyurea, the GOG performed a three-arm trial in 526 evaluable patients with stage IIB-IVA cervical cancer comparing weekly cisplatin versus cisplatin, 5-FU and hydroxyurea versus hydroxyurea alone concurrently with radiation therapy (GOG 120) [17]. This results demonstrated superior survival rates for both concurrent cisplatin regimens (66 and 64%, respectively) compared with concurrent hydroxyurea alone (39%). Again, local failure rates were significantly decreased in the cisplatin arms, suggesting the chemotherapy was acting as a radiation sensitiser. The toxicity of treatment was least with the single agent cisplatin regimen.

Tumour size has been recognised as a prognostic risk factor for stage IB cervical cancer [56]. However, the designation by the International Federation of Gynecology and Obstetrics (FIGO) of Stage IB_1 and IB_2 in 1994 established criteria that differentiated the clinical management of smaller from larger gross cervical tumours that are limited to the cervix. In a retrospective review, Finan and colleagues reported that patients treated with primary radical hysterectomy for stage IB_2 had a significantly poorer survival than patients with IB_1 tumours despite the more frequent use of postoperative radiation therapy [57]. The role of adjuvant hysterectomy for bulky stage IB cervical cancer has been evaluated by the GOG in a randomised trial of radiation versus radiation and adjuvant hysterectomy. Preliminary results suggested a lower relapse in the pelvis with immature survival results. Therefore, in the subsequent trial, radiation and adjuvant hysterectomy became the standard against which concurrent weekly cisplatin, radiation and adjuvant hysterectomy was compared (GOG 123) [19]. Among 369 evaluable patients, significant differences in progression-free survival and survival also favoured the chemoradiation arm. Estimated survivals at 36 months were 83 and 74%, respectively, for chemoradiation versus radiation therapy alone followed by hysterectomy. Pathological examination of the hysterectomy specimens demonstrated a significant decrease in persistent disease with chemoradiation. More leucopenia and gastrointestinal toxicity was seen with chemoradiation, but this was transient without serious sequelae.

The importance of total treatment time has been identified as an important prognostic factor in radiation therapy for cervical cancer [58,59]. A total dose of 85 Gy to point A delivered in less than 8 weeks has been accepted as the optimal schedule. Two of the cisplatin-based chemoradiation trials delivered 81 Gy to point A allowing up to 10 weeks for treatment [15,17]. Both of these trials had median treatment times of 9 weeks. The total treatment times within the arms of these trials were nearly identical suggesting that any survival benefit seen was the result of an intervention, in this case cisplatin-based chemoradiation, and not due to a difference in the treatment time.

Collectively, all five trials comparing cisplatin-based chemoradiation to radiation alone showed a significant reduction in the risk of recurrence and death with chemoradiation [15–19]. The five randomised cervical cancer trials involved a total of 1894 women with a wide variety of disease stages of cervical cancer in which radiation therapy would be used. There is remarkable symmetry in the reduction of relative risk of relapse or death by 30–50%. This consistency of results presents compelling evidence for the inclusion of cisplatin-based chemotherapy with radiation in the treatment of

patients with cervical cancer who require radiation. Based on the results of these five trials, the National Cancer Institute (NCI) released a Clinical Announcement stating "strong consideration" should be given to the incorporation of concurrent chemotherapy with radiation for patients who require radiation therapy for the management of cervical cancer [20].

Since the Clinical Announcement by the NCI, the Canadian NCI reported a trial with conflicting results [60]. In this multi-institutional trial, 253 patients with stage IB >5 cm-IVA received radiation with weekly cisplatin at a dose of 40 mg/m^2/week versus radiation therapy alone. The 1-, 3- and 5-year survivals were not significantly different although all slightly favoured the cisplatin chemoradiation 83% versus 78%, 69% versus 66%, and 59% versus 56%, respectively. For unexplained reasons, the complications were greater following radiation alone, 12% versus 6%, $P=0.08$. Why did the results of this trial vary from the previous trials? The Canadian trial was randomised, multi-institutional, and used appropriate doses and schedules of cisplatin and radiation therapy. While radiation therapy delivery was more optimal in the Canadian NCI trial, an optimal radiation schedule was also utilised in RTOG 9001 where chemoradiation was statistically better [16]. A major difference between the treatment arms in the Canadian trial was anaemia, which was more common among the cisplatin-treated patients. The failure to correct this anaemia in the chemoradiation therapy arm may have accounted for an up to 25% decrement in survival [61]. Additionally, the patients in this trial were only staged by computerised tomography. Surgical staging with paraaortic lymphadenectomy. Further analysis of the data demonstrates that the confidence intervals of this trial overlap with the five published American randomised trials and their pooled data continues to show a statistical benefit to chemoradiation (data not shown).

3. Controversies

A number of questions regarding chemoradiation remain unanswered by the current randomised trials. For example, what is the ideal chemoradiation agent? In reviewing the most successful arms of these trials, while all included cisplatin, some included 5-FU or 5-FU and hydroxyurea, while others did not. This questions the role of 5-FU or 5-FU and hydroxyurea. The role of 5-FU was evaluated in a randomised trial by Thomas and colleagues which demonstrated a benefit in survival with the addition of 5-FU alone to radiation for patients with stage IB_2-IIB with unilateral parametrial involvement, but not for patients with more advanced disease [44]. For unknown reasons, this benefit was seen for patients who received daily radiation therapy, but not twice-daily radiation therapy. The GOG initiated a trial comparing radiation with weekly cisplatin versus radiation with continuous 5-FU infusion. However, this trial was closed when an interim analysis demonstrated that the continuous 5-FU infusion could not be superior. The addition of hydroxyurea with cisplatin and 5-FU as utilised in GOG 120 increases toxicity with no improvement in survival.

What dose of cisplatin is important? The dose of cisplatin in four of the trials was approximately 200–240 mg/m^2 [16–19]. Regimens utilising lower doses of cisplatin have included other agents to achieve equal efficacy. In GOG 120, the three-drug regimen clearly had more toxicity.

What is the role, if any, of post-radiation adjuvant chemotherapy? Recently, Wong and colleagues reported the use epirubicin-based chemoradiation followed by adjuvant epirubicin for five cycles versus radiation alone [62]. The arm which included chemoradiation and adjuvant chemotherapy had superior survival. However, whether this survival benefit is due to chemoradiation or adjuvant chemotherapy or both is unknown. When utilised for patients with known metastatic disease, concurrent chemotherapy and pelvic radiation followed by adjuvant chemotherapy has not resulted in prolonged survival [63]. This is consistent with the lack of efficacy of systemic chemotherapy for metastatic cervical cancer. However, in SWOG 8797, the continuation of chemotherapy for 3–4 cycles (two cycles beyond completion of radiation therapy) resulted in an improved survival compared with patients who received only one or two courses of chemotherapy [18]. However, the patients who completed the prescribed four courses of chemotherapy may have had a better performance status or been more compliant with both chemotherapy and radiation therapy.

Lastly, a recent review of chemoradiation therapy for cervical cancer questioned the efficacy of combined therapy in patients with advanced stage disease (stage IIB with bilateral parametrial involvement or stage III) [64]. In response to this, a subgroup analysis of stage II and III patients was performed for the most recent three-arm GOG trial. In contrast to this recent review, this subgroup analysis demonstrated statistical benefit for both stage II and III patients (data not shown).

4. Extended field radiation

Para-aortic nodal metastasis is the most significant prognostic factor in patients with locally advanced cervical cancer [65]. Survival rates depend on the extent of pelvic disease, but range between 25 and 50% for patients treated with extended field radiation therapy alone [66]. Efforts to increase the radiation dose to the

Table 4
Phase I trials of concurrent chemoradiation

Weekly cisplatin + weekly paclitaxel
Weekly cisplatin + weekly tirapazamine
Weekly cisplatin + daily oral topotecan
Weekly cisplatin + weekly gemcitabine

para-aortic region have been associated with excessive normal tissue toxicity [67]. Chemoradiation with cisplatin and 5-FU infusion with extended field radiation was evaluated with daily or twice-daily radiation in phase II studies by the GOG and RTOG [68,69]. While not a randomised comparison, the twice-daily radiation was associated with a higher incidence of gastrointestinal toxicity (31% versus 14%). The combination of weekly cisplatin with extended field radiation therapy has also been reported in a group of patients without clinical evidence of paraaortic nodal involvement. Weekly cisplatin was well tolerated and the rate of complete response was high [70]. In summary, cisplatin-based chemotherapy can be delivered with extended field radiation, but whether it will improve survival with acceptable toxicity requires evaluation in a randomised trial.

5. Potential chemoradiation agents

A number of newer chemotherapy agents including carboplatin, paclitaxel, gemcitabine, oral 5-FU, tirapazamine and camptothecin analogues are candidates for study with radiation therapy in cervical cancer [71–76]. Cisplatin and carboplatin are often used interchangeably for systemic treatment. However, because of the increased myelosuppression, carboplatin should not be used interchangeably with cisplatin in concurrent chemoradiation treatment of cervical cancer. The combination of weekly cisplatin with weekly paclitaxel, weekly tirapazamine, weekly gemcitabine, and daily topotecan will be studied in upcoming GOG phase I trials with pelvic radiation and pelvic plus extended field radiation therapy for cervical cancer (Table 4).

In conclusion, proper delivery of radiation with attention to the total and intracavitary dose, treatment time and anaemia is essential in the optimal management of locally advanced cervical cancer. Based on the current trials, cisplatin-based concurrent chemoradiation remains 'strongly advised' for patients requiring radiation therapy for the management of cervical cancer. Studies of new agents in combination with cisplatin are ongoing.

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