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Original Article

Long-term Survival and Late Toxicity after Chemoradiotherapy for Cervical Cancer — The Addenbrooke's Experience

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ABSTRACT:
Aim: **To evaluate the long term cause-specific survival and late toxicity of chemoradiotherapy for carcinoma of the cervix treated outside research settings.**
Materials and methods: **Between May 1999 and April 2003, 74 patients with carcinoma of the cervix were treated with radical radiotherapy given concurrently with weekly cisplatin chemotherapy. Three patients died during treatment, leaving 71 patients available for analysis of long-term survival and late toxicity of treatment. In total, 56 patients (78.9%) received chemoradiotherapy as primary radical treatment. Ten patients (14.1%) received chemoradiotherapy as adjuvant treatment after radical surgery. The remaining five patients (7.0%) received chemoradiotherapy as salvage treatment for pelvic recurrences after previous surgery. Forty-seven (66.2%) patients had squamous cell carcinomas, whereas 24 (33.8%) patients had adenocarcinomas.**
Results: **The median follow-up for surviving patients was 64 months. The actuarial 5-year cause-specific survival for the 66 patients undergoing primary treatment (chemoradiotherapy ± surgery) was 54.6%. The cause-specific survival by International Federation of Gynecology and Obstetrics (FIGO) disease stage was 58.3% for stage I disease, 69.9% for stage II disease and 20.8% for stage III disease. The actuarial 5-year pelvic control rate for the same group of patients was 73.3% overall (stage I = 79.2%, stage II = 89.0%, stage III = 33.3%). Four of the five patients treated for recurrent disease are alive and well with a median follow-up of 70 months. Of the 66 patients undergoing primary treatment, seven (10.6%) had persistent disease after chemoradiotherapy. Of the 22 patients (33.3%) who relapsed >6 months after treatment, eight (36.4%) relapsed within the pelvis alone, 12 (54.5%) had metastatic disease alone, whereas two (9.1%) had both local and distant relapse. The overall rates of pelvic and distant relapse were 25.8 and 21.2%, respectively. Eight of 23 patients (34.8%) with adenocarcinomas developed metastatic disease compared with only six of 43 patients (14.0%) with squamous cell tumours. Thirteen patients (18.3%) had at least one complication that was classified as grade 3 or 4. Six patients (8.5%) had grade 3 or 4 urinary complications, five (7.0%) had grade 3 or 4 bowel complications and six (8.5%) had grade 3 or 4 complications affecting other organs. Five patients had grade 3 or 4 complications affecting more than one organ. The actuarial rate for grade 3 or 4 urinary complications was 14.5%, 9.4% for grade 3 or 4 bowel complications and 11.4% for grade 3 or 4 complications affecting other organs. The overall actuarial risk for grade 3 or 4 long-term morbidity in the study group was 28.2%. There were no significant correlations between the incidence of serious late toxicity and disease stage, field arrangement, treatment volumes or postoperative radiotherapy.**
Conclusions: **Our study has shown that the addition of chemotherapy to radiotherapy for cervical cancer probably improves the survival of patients treated outside research settings, but the benefit may not be as large as that obtained in clinical trials and the risk of serious late toxicity is increased. Further developments to improve survival and local control and to minimise toxicity are therefore necessary. Tan, L. T., Zahra M. (2008). *Clinical Oncology* 20, 358–364**

Key words: Cervical carcinoma, chemoradiotherapy, late toxicity, local control, survival

Introduction

Radiotherapy with concurrent platinum-based chemotherapy is now the standard of care for locally advanced or poor prognosis cancer of the cervix. Published evidence suggests that the addition of chemotherapy to radiotherapy results in an absolute improvement in overall survival of around 10% [1,2], and a significant reduction in local recurrence, but the late toxicity of treatment remains to be fully quantified [3].

We previously reported the acute toxicity of chemoradiotherapy for an unselected cohort of patients with cervical cancer treated at Addenbrooke's Oncology Centre, Cambridge [4]. This paper reports the long-term survival and late toxicity of treatment for the same patients.

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Materials and Methods

Patients

The original cohort consisted of 74 patients treated between May 1999 and April 2003. One patient, who had bulky stage IIIB disease and known artherosclerotic disease, died of bowel infarction due to mesenteric artery thrombosis during the second week of chemoradiotherapy. Another patient, also with bulky IIIB disease, developed severe non-neutropenic intra-abdominal sepsis during the third week of chemoradiotherapy and died a few weeks later. The exact cause of death was not established, as a post-mortem examination was not carried out. The third patient, also with bulky IIIB disease, suffered a massive fatal pulmonary embolism 1 week after completing treatment. These three patients were included in the previous analysis of acute toxicity, but have been excluded from this analysis of long-term cause-specific (cancer-related) survival and late toxicity of treatment.

The clinicopathological features of the 71 patients included in this analysis are shown in Table 1. The median age of the patients was 43 years (range 22–79 years). Of the patients, 66.2% (47/71) had squamous cell carcinomas, whereas 33.8% (24/71) had adenocarcinomas. Fifty-six of 71 patients (78.9%) patients received chemoradiotherapy as primary radical treatment. In five of the patients (all with stage Ib1 disease), staging pelvic lymph node dissection was carried out 3 days before planned radical hysterectomy and definitive surgery was abandoned when they were found to have node involvement. The rationale was to avoid combining radical surgery with postoperative radiotherapy as this has been shown to increase toxicity without improving survival [5]. Ten of 71 patients (14.1%) received chemoradiotherapy as adjuvant treatment after radical surgery. The remaining five patients (7.0%) received chemoradiotherapy as salvage treatment for pelvic recurrences after previous surgery.

Of the 66 patients receiving primary curative treatment, 40.9% (27/66) had pelvic lymph node involvement on biopsy or enlarged nodes ($\geq$ 1.5 cm) on imaging. Five of these 66 patients (7.6%) also had enlarged para-aortic lymph nodes on imaging.

Treatment

A detailed description of the treatment given was previously reported [4]. A brief summary is given here.

All patients were treated with initial external beam radiotherapy to the pelvis, 45–50 Gy in 25–28 fractions. Twenty-six of 71 patients (36.6%) were treated with opposed anterior–posterior fields, whereas 45 patients (63.4%) were treated with a three- or four-field brick technique. In the five patients with enlarged para-aortic nodes on imaging, extended-field radiotherapy was given to include the para-aortic nodes to the level of the upper border of the L1 vertebra. The treated volumes ranged from 2472 to 18 121 cm^3 (median = 4399 cm^3). Treatment volumes were calculated by multiplying the length and width of the anterior–posterior treatment field by the patient separation in the two-field technique, or by the width of the lateral fields in the brick technique, while excluding any shielded areas.

On completion of external beam radiotherapy, 47 of 56 patients (83.9%) undergoing primary chemoradiotherapy proceeded to a single brachytherapy insertion, 20–30 Gy to point 'A' at a median dose rate of 1.34 Gy/h (range 1.08–1.48 Gy/h). Of the remainder, one patient proceeded to brachytherapy after further chemotherapy, seven patients received external beam boosts of 15–20 Gy in five to 10 fractions, whereas the remaining patient with stage IVa disease was not offered any further treatment. The five patients with pelvic recurrences after previous surgery were also given external beam boosts, 16 Gy in eight fractions, whereas the 10 patients receiving adjuvant treatment proceeded to vault brachytherapy. All patients also received between one and seven cycles (median five cycles) of cisplatin chemotherapy during external beam radiotherapy. Patients were given blood transfusions as required to maintain their haemoglobin above 12 g/dl during radiotherapy.

Table 1 – Clinicopathological features and outcome of patients in the study group

Stage	Patients	Histology		Positive nodes*		Relapse		
		Adeno	Squamous	Pelvic	Pelvic + PA	Pelvis	Metastases	Both
Ib1	5	2	3	5	0	0	1	0
Ib2	12	4	8	4	0	4	2	0
IIa	5	3	2	0	0	0	2	0
IIb	20	10	10	3	1	1	3	2
IIIb	12	2	10	3	3	8	1	0
IVa	2	0	2	1	0	1	0	0
p1b1	6	0	6	6	0	1	2	0
p1b2	1	0	1	0	0	0	0	0
p2b	3	2	1	0	1	0	1	0
Recurrence	5	1	4	3	0	1	0	0

PA, para-aortic. *Histologically proven or $\geq$ 1.5 cm on imaging.

Analysis of Treatment Outcome

Treatment failures were classified as central, pelvic sidewall (including pelvic node relapse) or distant (including para-aortic node relapse). Late radiotherapy toxicity was prospectively graded according to site and severity using the RTOG/EORTC late radiation morbidity scoring scheme. Late toxicity was defined as complications present at or after 6 months from the completion of radiotherapy. Fistulae, hydronephrosis, lymphoedema and other problems directly attributable to known tumour recurrence were not scored as complications.

Kaplan—Meier curves for cause-specific survival, local pelvic control and late radiotherapy toxicity were computed using SPSS statistical software. Cause-specific survival was calculated by censoring one patient who died of septicaemia 16 months after diagnosis. Time intervals for survival and pelvic control rates were calculated from the date of diagnosis to the date of event or last follow-up appointment. Time intervals for toxicity were calculated from the date of the completion of radiotherapy and were censored for patient death. Correlations between factors that potentially affected the incidence of late toxicity were assessed using Spearman's non-parametric test.

Results

Survival and Local Control

The median follow-up for surviving patients was 64 months (range 19—104 months). The actuarial 5-year cause-specific survival for the 66 patients undergoing primary treatment (chemoradiotherapy ± surgery) was 54.6%. The cause-specific survival by International Federation of Gynecology and Obstetrics (FIGO) disease stage was 58.3% for stage I disease, 69.9% for stage II disease and 20.8% for stage III disease (Fig. 1). The actuarial 5-year pelvic control rate for the same group of patients was 73.3% overall (stage I = 79.2%, stage II = 89.0%, stage III = 33.3%; Fig. 2). Four of the five patients treated for recurrent disease are alive and well with a median follow-up of 70 months (range 53—80 months).

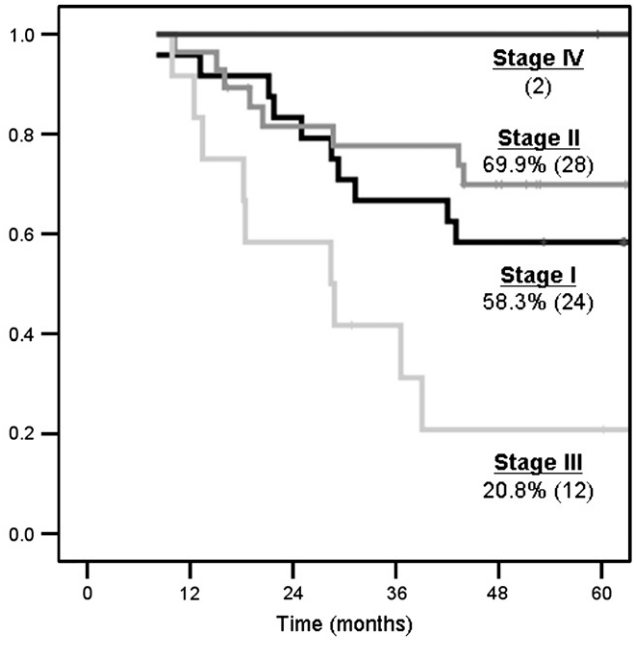

Fig. 1 — Five-year actuarial cause-specific survival by International Federation of Gynecology and Obstetrics (FIGO) disease stage.

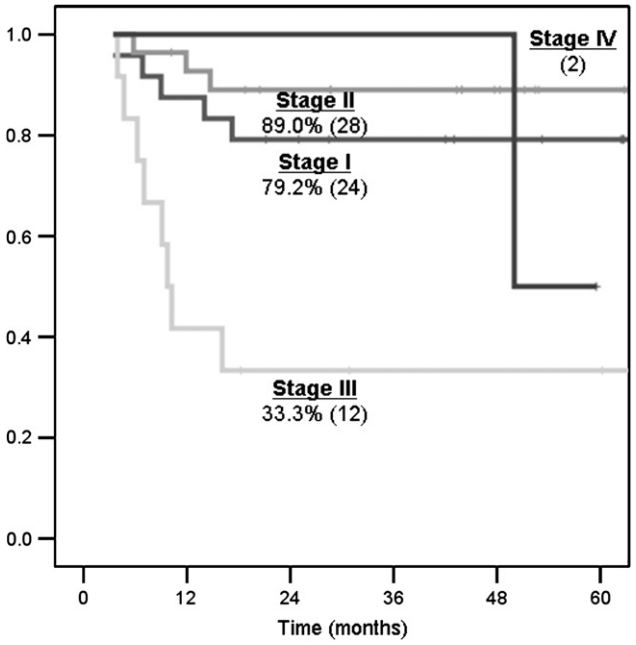

Fig. 2 — Five-year actuarial local control by International Federation of Gynecology and Obstetrics (FIGO) disease stage.

The patterns of failure by disease stage for the 66 patients undergoing primary treatment are shown in Table 1. Seven patients (10.6%) had persistent disease after chemoradiotherapy. Of the 22/66 patients (33.3%) who relapsed >6 months after treatment, 36.4% (8/22) relapsed within the pelvis alone, 54.5% (12/22) had metastatic disease alone, and 9.1% (2/22) had both local and distant relapse. The overall rates of pelvic and distant relapse were 25.8% (17/66) and 21.2% (14/66), respectively. The patterns of failure by histological type are shown in Fig. 3. Eight of 23 patients (34.8%) with adenocarcinomas developed metastatic disease compared with only six of 43 patients (14.0%) with squamous cell tumours.

Late Toxicity

The incidence of late complications by site and severity in the whole study group is shown in Table 2. Thirteen of 71 patients (18.3%) had at least one complication that was classified as grade 3 or 4: 8.5% of patients (6/71) had grade 3 or 4 urinary complications, 7.0% (5/71) had grade 3 or 4 bowel complications and 8.5% (6/71) had grade 3 or 4 complications affecting other organs. Details of these complications are given in Table 3. Five patients had grade 3 or 4 complications affecting more than one organ.

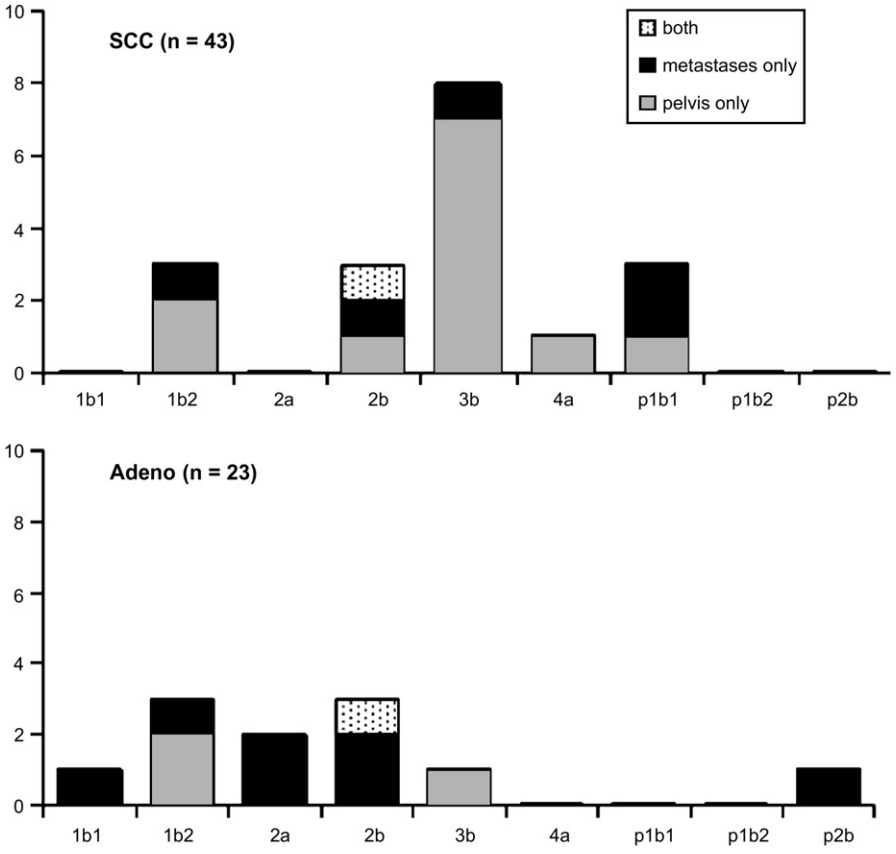

Fig. 3 — Patterns of failure by histological type.

The 5-year actuarial rates of serious late complications are shown in Fig. 4. The actuarial rate for grade 3 or 4 urinary complications was 14.5%, 9.4% for grade 3 or 4 bowel complications and 11.4% for grade 3 or 4 complications affecting other organs. The overall actuarial risk for grade 3 or 4 long-term morbidity in the study group was 28.2%. There were no significant correlations between the incidence of serious late toxicity and disease stage ($P = 0.8$), field arrangement ($P = 0.9$), treatment volumes ($P = 0.9$) or postoperative radiotherapy ($P = 0.6$).

Discussion

We previously reported that cisplatin-based chemoradiotherapy for carcinoma of the cervix is well tolerated when given to a largely unselected population of patients outside research settings [4]. The addition of chemotherapy to radiotherapy did not lead to an increase in the number of unscheduled treatment gaps. It was therefore hoped that the effectiveness of the treatment should mirror the efficacy obtained in clinical trials.

A direct comparison of our results with those reported in randomised studies is limited due to the relatively small number of patients in our study and the heterogeneity of the various chemoradiotherapy trials in terms of patient population and methods of reporting their analyses. In particular, many of the trials required formal evaluation of para-aortic nodes and most did not report survival rates by

Table 2 — Incidence of late complications in the study group ($n = 71$)

Complication	Urinary	Bowel	Other
Grade 0	51	48	54
Grade 1	7	11	10
Grade 2	7	7	1
Grade 3	3	4	5
Grade 4	3	1	1

Table 3 — Details of severe late complications in the study group

Complication	Urinary	Bowel	Other
Grade 3	Frequency (2) Haematuria (1)	Diarrhoea (2) Rectal bleeding (1) Ileus (1)	Cervix ulcer (3) Sensory neuropathy (1) Motor neuropathy (1)
Grade 4	Cystectomy (3)	Colectomy (1)	Avascular necrosis of hips (1)

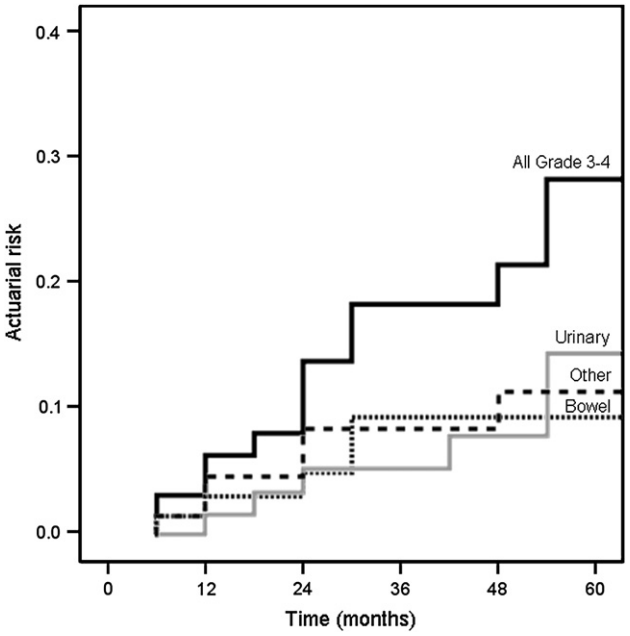

Fig. 4 — Actuarial late toxicity rates.

FIGO stage. In general, however, our 5-year survival and local control rates were broadly similar to those reported in the randomised studies. For example, the 5-year survival of the patients in the GOG 120 study [6] was 60% and compared with 54.6% in our study. Where survival data by FIGO stage are available, our results for the less advanced stage patients again seem to be comparable with those in the recent updates from the RTOG 90-01 [7] and GOG 120 studies [6], but those for the more advanced stages are inferior.

A more meaningful comparison perhaps is obtained from a comparison with non-randomised data from the 26th FIGO annual report on the results of treatment in gynaecological cancer [8]. This confirmed the benefit of chemoradiotherapy over radiotherapy alone outside research settings with a hazards ratio of 3.5 compared with 4.7 (Table 4). Again, our survival rates seem to be comparable with those in the FIGO report, with the exception of stage IIIb disease, which was inferior.

Table 4 — International Federation of Gynecology and Obstetrics (FIGO) analysis of treatment modalities

Treatment	Patients	Hazards ratios	95% confidence interval
Surgery	2780	Reference	
Radiotherapy	3813	4.7	3.8—5.9
Radio-surgery	387	3.1	2.3—4.2
Neoadjuvant chemotherapy + surgery	385	3.4	2.5—4.7
Surgery + adjuvant radiotherapy	1629	2.8	2.3—3.5
Surgery + adjuvant chemotherapy	215	3.2	2.3—4.6
Chemoradiotherapy	1657	3.5	2.8—4.4

There are few published reports of chemoradiotherapy for cervix cancer outside research settings with more than 50 patients. King et al. [9] reported a 3-year survival of 87% for their series of 79 patients. However, their median follow-up was only 35 months and eight patients were alive with disease at the time of their analysis. Moreover, 87% of their patients had squamous cell carcinomas compared with only 66% in our series. Adenocarcinomas were shown to have a poorer prognosis on multivariate analysis in the FIGO report [8], with a hazards ratio of around 1.5 compared with squamous cell tumours. Chen et al. [10] reported a 4-year actuarial survival rate of 74% for their series of 70 patients. They concluded that the addition of chemotherapy did not improve survival compared with an earlier cohort of patients treated with the same radiotherapy protocol. Novetsky et al. [11] reported a 5-year disease-free survival of 74% for their series of 77 patients. Again 89% of their patients had squamous cell carcinomas and although their median follow-up was 42 months, the minimum follow-up was only 4 months.

A detailed analysis of our stage IIIb patients was carried out to identify possible reasons for their poor outcome (Table 5). Eleven of 12 patients had bulky central disease $\geq$ 5 cm in diameter. Six patients had pelvic node disease, three of whom also had para-aortic node disease. Eight patients relapsed within the pelvis and another relapsed with metastases within the para-aortic nodes. Of the eight patients with pelvic relapse, four had persistent disease at the end of radiotherapy, suggesting that the tumours were inherently radioresistant. As such, most of the patients had multiple poor prognostic features, some of which cannot be overcome with dose escalation alone.

The 5-year survival of patients with stage I disease in our audit was inferior to that of patients with stage II disease (58% vs 70%). Similar results were reported in the FIGO analysis (hazards ratio 0.8—0.9) [8]. There are a number of possible explanations for this finding. First, only those stage I patients with poor prognosis features, i.e. nodal involvement or bulky disease, were selected for chemoradiotherapy (good prognosis patients were treated with surgery alone), whereas all stage II patients received chemoradiotherapy regardless of tumour bulk or nodal status. The FIGO report [8] showed that the survival of patients with pelvic node involvement is about 50% of that of similar stage patients with node-negative disease. In addition, our patients with stage Ib2 disease treated with chemoradiotherapy alone had a 5-year survival of only 50% and a local control rate of only 66.7%. It is well recognised that there is a dose—response effect in cervix cancer [12] and it may be for these subgroup of patients, some form of dose escalation or tumour debulking would be beneficial.

Of our patients, 18.3% had serious late complications with an actuarial risk of 28.2%. Although this is broadly similar to published reports from randomised and non-randomised studies (Table 6), it is significantly higher than the Clatterbridge series [13] where patients were treated

Table 5 — Details of stage IIIb patients ($n = 12$)

Age (years)	T (cm)	*N* (mm)	Histology	Treatment	Time to relapse (months)	Site of relapse
25	5	Pelvis (20)	SCC	Pelvis + PA strip	Persistent	Central, pelvic nodes
40	5		SCC	Pelvis		
48	10	Pelvis + PA (25)	SCC	Pelvis + PA strip	Persistent	Central, pelvic nodes
50	6	Pelvis + PA (40)	SCC	Pelvis + PA strip	7	Central, pelvic nodes
53	7	Pelvis + PA (30)	Adeno	Pelvis + PA strip	14	Pelvic nodes
56	5		SCC	Pelvis	Persistent	Central, pelvic nodes
60	3		SCC	Pelvis		
68	6		SCC	Pelvis	8	Central
70	8	Pelvis (30)	SCC	Pelvis	9	Central, pelvic nodes
72	5		Adeno	Pelvis		
73	6		SCC	Pelvis	11	PA nodes
79	7	Pelvis (20)	SCC	Pelvis	Persistent	Central, pelvic nodes

SCC, squamous cell carcinoma; PA, para-aortic.

with a virtually identical radiotherapy protocol but without concurrent chemotherapy. Of note, there seemed to be an increase in serious musculoskeletal and neurological complications in our patients. One patient developed grade 3 sensory and motor neuropathy at 12 months. Another developed avascular necrosis of the right femoral head 48 months after treatment and necrosis of the other hip 12 months later. She was subsequently diagnosed with chronic myeloid leukaemia at the age of 38 years. Other groups [18] have also reported cases of avascular necrosis in patients treated with chemoradiotherapy.

Our analysis suggests that the addition of chemotherapy to radiotherapy probably improves the survival of patients treated outside research settings, but the benefit may not be as large as that obtained in clinical trials and the risk of serious late toxicity is increased. Ongoing efforts to improve survival and local control and to minimise toxicity are therefore necessary.

Table 6 — Comparison of rates of serious morbidity in published reports

Reference	Patients	Treatment	Morbidity
Clatterbridge [13]	223	Radiotherapy alone	5.0%
Cookridge, Leeds [14]	371	Radiotherapy alone	19.0%
Bristol [15]	270	Radiotherapy alone	32.5%
French Co-operative Study [16]	1383	Radiotherapy alone	27.6%
Washington University [17]	970	Radiotherapy alone	18.4%
Addenbrooke's	71	Chemoradiotherapy	18.3%
Birmingham [9]	79	Chemoradiotherapy	12.7%
China Medical University, Taiwan [10]	70	Chemoradiotherapy	14.3%
Albert Einstein College of Medicine, New York [11]	77	Chemoradiotherapy	6.0%
RTOG 90-01 [7]	191	Chemoradiotherapy	12.6%
GOG 120* [6]	215	Chemoradiotherapy	2.8%

*Urological + gastrointestonal complications only.

In February 2005, we replaced our conventional triple source brachytherapy technique with the Vienna conformal brachytherapy technique [19], which uses a ring applicator instead of ovoids. The technique involves individualised dose volume adaptation for patients, which has in turn allowed dose escalation without increasing the risk of serious toxicity. Recent published results [20] for this technique are extremely promising, particularly for tumours >5 cm, where a 3-year local control rate of 82% was achieved but the incidence of serious late gastrointestinal and urinary toxicity was only 2%. Early indications from our patients treated with this technique suggest that the incidence of serious late toxicity has decreased; this will be reported at a later date when more mature data are available.

Our 12 patients with stage Ib2 tumours had a local control rate of only 66.7% and yet three patients (25%) had grade 3 or 4 late toxicity. As our analysis did not find a correlation between previous hysterectomy and the risk of toxicity, we are exploring the value of surgical debulking followed by postoperative chemoradiotherapy to the pelvis for these patients. There is evidence from non-randomised studies that suggests that this policy is associated with improved local control [21] without an increase in serious late toxicity [22].

We also identified that some of our patients seemed to have tumours that are intrinsically radioresistant, as evidenced by the presence of persistent disease after treatment. Alternative strategies, such as novel sequencing of treatments, alternative fractionation regimens or addition of hypoxic cell sensitisers, hyperthermia or biological modifiers, may be necessary to improve the outcome for these patients. There is currently considerable interest in developing predictive tools for identifying such tumours [23] that may allow targeted evaluation of alternative therapies in this group of patients.

Finally, our analysis suggests that adenocarcinomas have a greater propensity for metastatic spread than squamous cell carcinomas. Similar findings have been reported by other groups [24]. Randomised clinical trials to evaluate the

role of adjuvant chemotherapy for this group of patients should be considered.

Conclusions

The addition of chemotherapy to radiotherapy for cervical cancer probably improves the survival of patients treated outside research settings, but the benefit may not be as large as that obtained in clinical trials and the risk of serious late toxicity is increased. Further developments to improve survival and local control and to minimise toxicity are therefore necessary.

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