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The Scottish and Manchester randomised trial of neo-adjuvant chemotherapy for advanced cervical cancer

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Abstract

204 eligible patients were entered into a multicentre randomised trial of neo-adjuvant chemotherapy prior to radical radiotherapy. The aim of this study was to assess whether there was any survival advantage in patients undergoing chemotherapy and radiotherapy compared with those given radiotherapy alone. Patients were aged up to 70 years, performance status 0–1/2, with bulky stage IIb, stage III or stage IVa squamous or adenosquamous carcinoma. Three cycles of methotrexate 100 mg/m^2 and cisplatin 50 mg/m^2 were given at 2-weekly intervals before radical radiotherapy. 104 eligible patients received the combination treatment and 100 radiotherapy only. The two arms of the study were well balanced for tumour and patient characteristics. The response rate to chemotherapy was 49%. 33% of patients in the radiotherapy (XRT) alone arm and 45% of the combination arm were clinically free of tumour at the end of treatment. The median follow-up for surviving patients is 5.4 years (range: 11 months–8 years) and 84% have been followed-up for more than 4 years. 134 patients have died (68 XRT only, 66 combined arm). The median survival RT alone was 111 weeks (95% confidence interval (CI) 72–151 weeks), combination arm 125 weeks (95% CI 79–170 weeks). The estimated death ratio is 0.79 ($P = 0.19$, 95% CI 0.56–1.12). The estimated 3-year survival is 40% (95% CI 30–50%) RT only compared with 47% (95% CI 37–57%) in the combination arm. Acute and late toxicity of radiotherapy was not increased by the addition of chemotherapy.

Keywords: Cervical cancer; Radical radiotherapy; Neo-adjuvant chemotherapy

1. Introduction

There are potential advantages in giving chemotherapy before radiotherapy in the treatment of locally advanced cervical cancer [1]. Both clinical studies and animal experiments have shown that radiation doses which will consistently eradicate small tumours will be effective in only a minority of larger lesions. However the maximum radiation dose that can be given to patients with carcinoma of the cervix is limited by the tolerance of surrounding organs such as the bladder or bowel. Even employing what we currently regarded as optimal external beam fractionation policies in combination with intracavity treatment, local control is seen in only approximately half of patients with advanced tumours. Attempts to increase pelvic radiation dosage have resulted in increased morbidity outweighing any increase in local control [2]. However, local control using conventional radiotherapy schedules could be increased if the tumour size were to be reduced by chemotherapy given before radiotherapy.

In a pilot study [1] the response rate following two pulses of cisplatin, vincristine and bleomycin combination chemotherapy was 53%. Patients then received full dose radical radiotherapy. The survival of chemotherapy responders was markedly superior to non-responders.

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The actuarial survival at 24 months of responders to chemotherapy was 71% against 37% for non-responders. The responding patients had an estimated reduction in mortality of 36% ($P=0.014$, 95% confidence interval (CI) 15–81%).

These results demonstrated the feasibility of this approach and a multicentre randomised trial was designed. A 2-weekly schedule of methotrexate and cisplatin was chosen. Both agents are active against cervical cancer and are relatively non-myelosuppressive allowing chemotherapy to be given every 2 weeks [3]. Three cycles of chemotherapy were given over 28 days and radiotherapy was only delayed by 6 weeks. This short period of chemotherapy may have two advantages. The first is pragmatic, as the delay in beginning potentially curative radiotherapy is short. The second is more theoretical and speculative as the scheduling and dose intensity of cisplatin may be important in obtaining tumour shrinkage.

2. Patients and methods

Patients in the trial had bulky stage IIb (tumour size >5 cm), stage III or stage IVa squamous or adenosquamous carcinoma of cervix. Performance status was normal or near normal (WHO performance status 0–2) and all were aged up to and including 70 years. Patients had to be fit for both chemotherapy and radiotherapy with adequate marrow reserves (white blood cell count (WBC) $>3\times10^9$/l and platelets $>100\times10^9$/l) and good renal function (glomerular filtration rates (GFR) >50 ml/min). The trial was approved by each participating Institution's ethics committee and all patients gave written informed consent before randomisation.

Before treatment minimum investigations were examination under anaesthesia, full blood count, serum biochemistry plus cystoscopy, abdominal ultrasound or computed tomography (CT) scan (depending on local availability) and chest X-ray. Additional investigations were carried out if indicated.

Patients were randomised to receive three cycles of chemotherapy followed by radiotherapy or radiotherapy alone. Each cycle of chemotherapy was given at 2-weekly intervals and radiotherapy was started 6 weeks after the first pulse of chemotherapy.

Chemotherapy consisted of an intravenous (i.v.) bolus of methotrexate 100 mg/m^2 given 4 h before any intravenous fluids. Then 1 l of 0.9% saline was given over 1 h. A dose of 50 mg/m^2 cisplatin was given over 6 h in 2 l of normal saline. A further 1.5 l of fluid was given in the next 12 h. Serum methotrexate levels were measured 24 h after administration. If the level was greater than 0.2 mg/l, 15 mg of folinic acid was given every 6 h for eight doses from 30 h to 72 h after methotrexate. If a methotrexate assay was not carried out, folinic acid was given routinely. Antiemetics (usually dexamethasone and ondansetron) were given prior to chemotherapy. Chemotherapy doses were not reduced. If the WBC and/or platelet count were less than 2×10^9/l or 100×10^9/l, respectively, chemotherapy was delayed 1 week. Chemotherapy was abandoned if the GFR fell below 50 ml/min, if there was tumour progression or excessive toxicity.

Pelvic radiotherapy consisted of external beam megavoltage radiotherapy followed by brachytherapy. There were some variations according to institutional policy, but if possible patients were treated using a four-field technique. The margins for the pelvic treatment volumes were usually 1 cm beyond the widest part of the bony pelvis laterally; the lower margin of the obturator foramen or a minimum of 1 cm below the tumour inferiorly; the bulk of pubic ramus anteriorly and the junction of second and third sacral segments posteriorly. The superior margin was taken as the junction between S1/L5 in Glasgow or L4/L5 in Manchester which included lead shielding of the corners of the field.

In Glasgow the external beam dose to the isocentre was 43 Gy in 20 fractions followed as soon as possible by medium dose rate brachytherapy delivering 24, 26 or 28 Gy to point A depending on dose rate (<145, 145–205 cGy/h). The total A point dose was 67–71 Gy.

The protocol dose in Manchester was 40 Gy in 20 fractions in 4 weeks followed by a selectron treatment of 33.75 Gy to point A at 1.7 cGy/h (total A point dose 73.75 Gy).

Patients in Aberdeen, Edinburgh and Middlesborough were treated according to the local protocols which were similar, 4-week schedules with a single intracavity insertion.

Response to chemotherapy was assessed immediately before radiotherapy and initial response after radiotherapy was assessed at 17 weeks from the start of treatment. This was 6 weeks after the end of radiotherapy in the combination arm and at 12 weeks for the radiotherapy only arm. Patients were then regularly followed-up and assessed for pelvic relapse, metastases and radiation toxicity. Late radiation toxicity was assessed using the ESTRO morbidity recording system [4].

The study was originally designed to have a 90% chance of detecting an improvement in survival from 30 to 45% and as a result it was planned to recruit 412 patients to observe 260 deaths. When the study was closed 204 eligible patients had been recruited in just over 5 years. At the time of this analysis 134 deaths had occurred. As a consequence the power to detect a 15% survival difference is only 65%.

A total of four confidential interim analyses were planned using P values derived using the O'Brien Fleming Method [5]. These were to take place after every 52 deaths. Two of these analyses took place before the study was closed, but did not approach statistical

significance. The results of these analyses were unknown to the investigators and did not influence the decision to close the trial prematurely. This decision was reached in view of the poor and declining recruitment into the study. (Only 17 were entered in the final year.)

Treatment allocations were obtained by calling the CRC West of Scotland Cancer Trials Unit. Stratified randomisation with random permuted blocks of length four was used. Centre and stage were stratification factors.

Overall survival and time to progression were calculated from the randomisation date. All eligible patients were included and all causes of death have been analysed. For time to progression, causes of death other than progression have been treated as censoring events. Kaplan–Meier [6] estimates were used to construct survival curves. Progression times were adjusted in the analysis to occur at the exact times specified in the protocol for follow-up assessment. This was used to overcome the problem of overestimating the risk of progression by applying Kaplan–Meier techniques to unadjusted data. Comparison of treatments in terms of survival and time to progression were made using Cox's proportional hazards model [7] after stratification for centre with stage included as a covariate. These models were tested for the inclusion of interactions and time-varying hazards and it was found that there was no strong evidence for the inclusion of such terms. The proportions of patients clinically free of disease at 17 weeks from the start of treatment were compared using logistic regression [8] including centre and stage as covariates in the model. Again the model was tested for the inclusion of interaction terms and no evidence was found for their inclusion. Ordinal categorical variables (e.g. acute radiation toxicities and the late treatment toxicities) were compared using the Mann–Whitney *U* test [9].

3. Results

215 patients were randomised into the study. 11 patients were judged to be ineligible when patient details were checked prior to analysis. The reasons for exclusion are listed in Table 1. Only entered eligible patients were considered for subsequent analysis. Although all but one of the excluded patients were in the radiotherapy only arm there was no suggestion of problems with the randomisation or that their exclusion led to a bias in the comparisons. The clinical and pathological characteristics of the 204 eligible patients are listed in Table 2. The two groups were well balanced in terms of patient and tumour prognostic features.

Eighty-eight per cent of patients (91 patients) received three courses of chemotherapy. Of 292 courses of chemotherapy, only 11 were delayed by more than 3 days. Chemotherapy was generally well tolerated. Only 2% of patients developed Grade 3 leucopenia and 16% Grade 3 and 4 nausea and vomiting. The worst WHO

Table 1
Exclusion criteria

	XRT only	XRT + chemotherapy
Entered (5/4/90–24/8/95)	110	105
Ineligible		
Metastases at presentation	3	0
Incorrect stage	1	0
Non-squamous histology	6	1
Entered eligible patients	100	104

XRT, radiotherapy.

Table 2
Patient and tumour characteristics in each arm of the trial

	XRT alone *n* (%)	XRT + chemotherapy *n* (%)
Treatment centre		
Glasgow	60 (60)	64 (62)
Manchester	20 (20)	20 (19)
Aberdeen	13 (13)	11 (11)
Edinburgh	5 (5)	8 (8)
Middlesborough	2 (2)	1 (1)
Stage		
IIb	21 (21)	22 (21)
III	67 (67)	69 (66)
IVa	12 (12)	13 (13)
Age (yrs)		
Median	48	49
IQ range	40–58	39–58
Range	24–70	25–69
Performance status		
0	54 (54)	56 (54)
1	45 (45)	48 (46)
2	1 (1)	0
Histological type		
Squamous	95 (95)	98 (94)
Adenosquamous	5 (5)	6 (6)

XRT, radiotherapy.

Table 3
Worst WHO grade of toxicity recorded during chemotherapy

	Grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Anaemia[a]	74	22	3	1	–
Thrombocytopenia[a]	98	–	1	1	–
Leucopenia[a]	84	5	10	2	–
Alopecia	88	11	2	–	–
Nausea/vomiting	39	22	23	13	3
Diarrhoea	90	4	6	–	–
Peripheral neuropathy	96	3	1	–	–
Oral	73	17	10	–	–
Constipation	83	14	2	1	–

All percentages in the table are based on 104 patients except for those marked [a] which are based on 103.

Table 4
External beam radiotherapy dosage

	XRT alone ($n=96$) n (%)	XRT plus chemotherapy ($n=103$) n (%)
Time to starting XRT (days from regular or last chemotherapy cycle)		
Median	6	16
IQ range	3–12	13–20
Range	0–49	6–49
Anatomical volume given as per protocol		
Yes	92 (96)	97 (94)
No-greater volume	2 (2)	1 (1)
No-lesser volume	2 (2)	5 (5)
Isocentre dose given		
Median	4300	4300
IQ range	4250–4300	4250–4300
Range	3800–4500	3690–4500
Number of fractions dose		
19	2 (2)	7 (7)
20	92 (96)	96 (93)
>20	2 (2)	0 (0)
Duration of external beam (days)		
24–28 days	64 (67)	64 (62)
29–35 days	29 (30)	38 (37)
>35 days	3 (3)	1 (1)

XRT, radiotherapy.

Table 5
Brachytherapy

	XRT alone ($n=93$) n (%)	XRT + chemotherapy ($n=101$) n (%)
Time to starting interactivity from end of external beam		
⩾3 days	2 (2)	3 (3)
−3 to 0 days	5 (5)	7 (7)
1 to 14 days	72 (77)	73 (72)
15 to 28 days	9 (10)	16 (16)
>28 days	5 (5)	2 (2)
Type of source used		
40 mCi selectron	74 (80)	78 (77)
30 mCi selectron	5 (5)	7 (7)
20 mCi selectron	1 (1)	1 (1)
15 mCi selectron	5 (5)	6 (6)
Conventional caesium	6 (6)	7 (7)
Other	2 (2)	2 (2)
Dose at 'A' point		
>3500	2 (2)	2 (2)
>3000	24 (26)	26 (26)
>2500	44 (47)	43 (43)
>2000	15 (16)	23 (23)
>1500	4 (4)	6 (6)
⩽1500	4 (4)	1 (1)
Dose at rectum (maximum)[a]		
>2500	3 (4)	5 (6)
>2000	9 (12)	12 (14)
>1500	44 (59)	50 (59)
>1000	18 (24)	15 (18)

[a] Not recorded for 19 patients on XRT alone and 16 patients on the combination.

Table 6
Response at end of treatment

	XRT alone ($n=100$) n (%)	XRT plus chemotherapy ($n=104$) n (%)
Clinically free of tumour	33 (33)	47 (45)
Suspicious of tumour persistence	21 (21)	17 (16)
Definite tumour persistence	34 (34)	30 (29)
Suspicious of tumour progression/recurrence	1 (1)	1 (1)
Definite tumour progression/recurrence	9 (9)	8 (8)
Inevaluable	2 (2)	2 (2)

grade of toxicity recorded during chemotherapy is listed in Table 3.

Response to chemotherapy was assessed in 96 patients who had at least two cycles of chemotherapy. 13 of these patients were non-evaluable because the appropriate assessments were not repeated or were not made at the start of chemotherapy. Amongst the remaining 83 patients, 40 (48%) had a partial response, 1 (1%) had a complete response and 40 (48%) had stable disease. 2 patients (2%) progressed locally during chemotherapy. One of these patients was subsequently disease-free after radiotherapy. The overall response rate was 49% (43% if non-evaluable patients were included).

199 patients (98%) completed external beam radiotherapy. 5 patients, 4 from the R/T arm and 1 from the combined arm did not complete treatment. Brachytherapy was not given to 7 patients in the R/T arm and 3 in the combined arm. Details of external beam radiotherapy are given in Table 4. Brachytherapy details are listed in Table 5.

Although poorly recorded (rates for missing toxicities ranged from 18 to 31%) there was no suggestion that acute radiation toxicity was different in the two arms. Table 6 lists tumour response at the end of radiotherapy. There was a higher rate of clinical complete response in the combined arm (45%) compared with R/T alone (33%). The estimated odds ratio (CT/RT versus R/T alone) for the proportion clinically free of tumour is 1.73 ($P=0.07$ 95% CI 0.96–3.12).

Ninety-six per cent of living patients have been followed-up for at least 3 years, 84% for at least 4 years and 50% for at least 5.4 years. The minimum follow-up is 11 months (patient lost to follow-up) and the maximum follow-up is just over 8 years.

A total of 134 patients have died to date, 68 in the radiotherapy alone arm and 66 in the combination arm. The median survival in the radiotherapy alone arm is 111 weeks (95% CI 72–151 weeks). In the combination arm the survival is 125 weeks (95% CI 79–170 weeks) (Fig. 1). The estimated death rate ratio (combination/XRT alone) is 0.79 ($P=0.19$, 95% CI 0.56–1.12). The estimated percentage surviving at 3 years is 40% (95% CI 30–50%) in the radiotherapy alone arm compared with 47% (95% CI 37–57%) in the combination arm. If attention is restricted to only those who died of malignant disease the estimated death rate ratio is 0.81 ($P=0.28$, 95% CI 0.55–1.19).

The estimated percentage progression-free at 3 years is 40% (95% CI 30–50%) in the radiotherapy alone arm compared with 45% (95% CI 35–55%) in the combination arm (Fig. 2). The progression rate ratio is 0.89 ($P=0.55$, 95% CI 0.62–1.28). The sites of tumour progression are listed in Table 7.

5 patients treated by radiotherapy only required surgery for bowel damage leading to obstruction, one developed both a recto-vaginal and a vesico-vaginal fistula and required both a urostomy and colostomy. In the combination arm, a total of 6 patients required surgery for treatment-induced complications. One patient developed a double fistula. Another developed both small and large bowel damage and required a urinary diversion. 2 patients required resection of small bowel and one of colon because of strictures and 1 required a colostomy.

Late radiation toxicity was recorded using the ESTRO late toxicity scale [3]. These were compared between the two arms in terms of the maximum toxicity recorded for patients at risk throughout each successive year following external beam radiotherapy. Data completion was relatively good during the first 2 years post-radiotherapy (<20% missing data for all items on the toxicity scale), got poorer in year 3 and by year 4 all toxicity items had more than 20% of data missing on at least one of the study arms. There were no statistically significant differences ($P<0.01$ used as the level of significance because of the large number of comparisons)

Table 7
Sites of tumour progression

	XRT ($n=60$) n (%)	Chemotherapy +XRT ($n=61$) n (%)
Local	24 (40)	22 (36)
Metastatic	18 (30)	22 (36)
Local and metastatic	13 (22)	10 (16)
Unknown	5 (8)	7 (11)

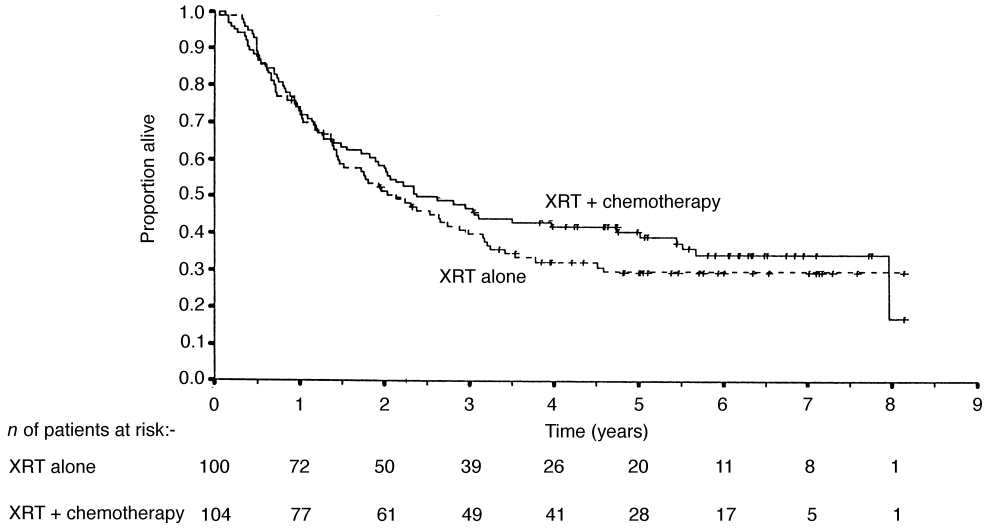

Fig. 1. Survival in the two arms of the study.

in late toxicity between the two arms in any of the toxicity items compared, though these comparisons may be unreliable for items with large amounts of missing data in years 3 and 4.

Detailed toxicity data is available upon request from the authors.

4. Discussion

Trials of neo-adjuvant chemotherapy have so far produced conflicting results. Survival was better in the radiotherapy control arm in two studies but the majority showed no significant differences between each arm. In contrast, three cycles of vincristine, bleomycin and cisplatin given at 10-day intervals has improved survival in patients with bulky stage Ib and stage IIIb tumours (see Table 8).

The most striking negative finding was seen in patients treated in the countries of the Pacific rim [10]. 260 patients with stage IIb, III and IVa tumours were randomised to receive standard pelvic radiotherapy or three cycles of cisplatin 60 mg/m^2 and epirubicin 100 mg/m^2 every 3 weeks before radiotherapy. Both local control and survival was significantly inferior in those patients receiving combined treatment. The inferior results of the combination arm of a Brazilian study [11] (39% 5-year survival rate in the radiotherapy arm — 23% in the combination arm) may be due to chemotherapy toxicity. A particularly high dose of bleomycin was given (120 mg/1.M. over 4 days) for three cycles resulting in fatal pulmonary toxicity in 4 patients.

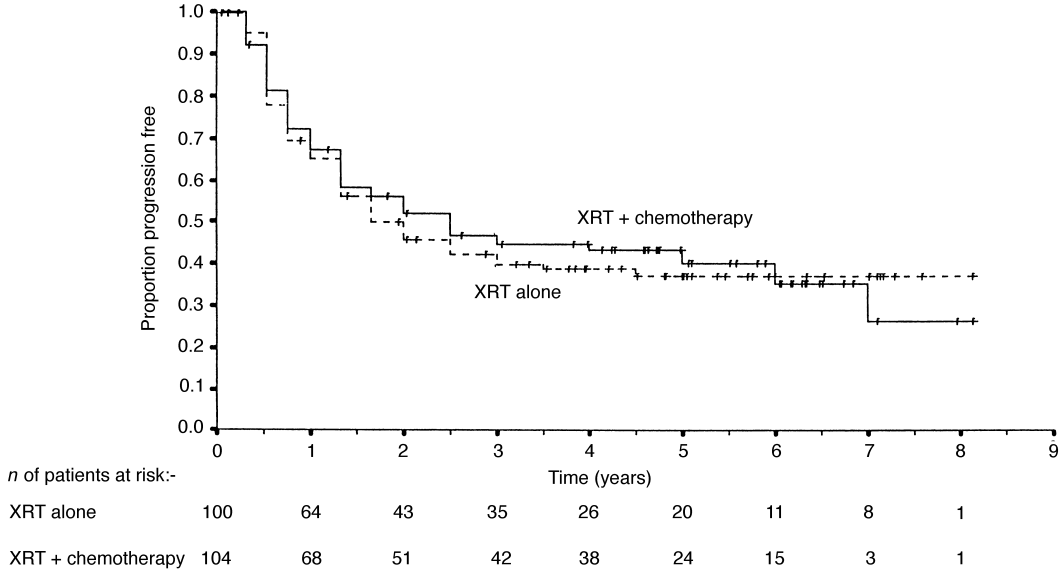

Fig. 2. Time to progression in the two arms of the study.

Table 8
Review of literature

Study [Ref.]	Stage	No. of patients	Chemotherapy	No. of cycles	Interval between cycles (days)	Median survival (months)	
						XRT	XRT + chemotherapy
Tattersall [10][a]	IIb–IVa	260	Cisplatin, epirubicin	3	21	37	22
Souhami [11][b]	IIIb	107	Bleomycin, mitomycin, vincristine, cisplatin	3	21	26	11
Sundfor [12]	IIIb–IVa	94	Cisplatin, 5-fluorouracil (5-FU)	3	21	25	23
Chiara [18]	IIb–III	64	Cisplatin	2 before XRT, 4 after XRT	15	83% alive at 3 years	72% alive at 3 years
Kumar [14]	IIb–IVa	184	Bleomycin, ifosfamide, cisplatin	2	21	22	30
Sardi [15,16][c]	Ib	105	Vincristine, bleomycin, cisplatin	3	10	15	>48
Sardi [17][c]	IIIb	161	Vincristine, bleomycin, cisplatin	3	21	19	34
Chauvergne [13]	IIb–N1,III	151	Methotrexate, chlorambucil, vincristine, cisplatin	2 or 4 to responders	21	42	45
Symonds [1]	IIb–IVa	204	Cisplatin, methotrexate	3	14	26	29

XRT, radiotherapy.
[a] Statistically significant difference in favour of XRT alone ($P=0.02$).
[b] Statistically significant difference in favour of XRT alone ($P=0.02$).
[c] Statistically significant difference in favour of combination ($P=0.005$).

Most studies published to date are relatively small (100–200 patients) and as such unlikely to demonstrate conclusively a moderate survival difference. In a Scandinavian study, 94 patients were randomised to receive three cycles of cisplatin 100 mg/m^2 plus 5-fluorouracil (5-FU) 1000 mg/m^2 daily for 4 days followed by radiotherapy or initial radiotherapy [12]. In spite of an initial 72% response rate to chemotherapy there was no significant difference in survival between the two arms, but the chemotherapy group had a non-statistically significant trend ($P=0.07$) for better metastases-free survival.

Chlorambucil is of very questionable value in the treatment of cervical cancer and the inclusion of this agent along with methotrexate, vincristine and cisplatin as well as the relatively small numbers (151) in a French study [13] may account for the non-statistically significant difference in median survival (45 and 42 months) and 5-year survival (40 versus 35%) in favour of the group treated by chemotherapy.

Stage imbalance between the two arms of an Indian study may be one of the reasons for a lack of difference between treatments. 184 patients had either two cycles of bleomycin, ifosfamide and cisplatin before radiotherapy or radiation only. There was a marked stage imbalance in favour of the radiotherapy group. 14 patients in the combination arm had stage IVa disease compared with only 2 in the radiotherapy group. There were also more stage IIb patients in the radiotherapy only group. However, when survival of stage IIIb patients was compared (38 combination, 39 radiotherapy) survival at 30 months was 50% in the combination arm against only 27% in the radiotherapy group [14].

The only unequivocal positive results seen after neoadjuvant chemotherapy are associated with the 'quick VBP' regimen. In this schedule three cycles of vincristine (1 mg/m^2) bleomycin (25 mg/m^2 daily for 3 days) and cisplatin 50 mg/m^2 were given every 10 days [15]. The latest published analysis lists 205 patients with stage Ib who were randomised to VBP before radical hysterectomy and postoperative adjuvant radiotherapy or hysterectomy and radiation alone [16]. No survival benefit was seen in patients with tumours smaller than 4 cm. However, patients with bulky tumours larger than 4 cm who had chemotherapy had significantly better survival at 5 years (81 versus 63%). A similar survival advantage in favour of VBP was seen in patients with stage IIIb cancers. 53 patients were treated by radiotherapy only with a 4-year survival of 37%. In contrast, survival was 53% in 52 patients treated by chemotherapy and radiotherapy and 63% in the group of 50 patients treated by chemotherapy, surgery and postoperative radiotherapy [17].

The pattern of growth of this cancer may also explain the different results seen in these trials. The median potential doubling time of this tumour is short (4 days) and cell kinetic measurements are predictive of local control after radiotherapy [19]. As the tumour has a short potential doubling time the scheduling of chemotherapy may be very important. The improved survival seen by Sardi and colleagues [15–17] may be because VBP was given at 10-day intervals and definitive therapy instituted within 1 month of starting chemotherapy. One explanation for the negative result in the trial of Tattersall and colleagues [10] is that chemotherapy was given at 3-weekly intervals and radiotherapy did not begin until 9 weeks later. Although tumours may shrink after chemotherapy, regrowth may be accelerated and chemoresistant clones may emerge. These cells may also be relatively radioresistant. Such tumours have been described as 'leaner and meaner'.

The US National Cancer Institute has recently issued a clinical alert to American Oncologists after reviewing the preliminary results of five separate studies [20]. All show a reduction in mortality. A Gynaecology Oncology Group Study (GOG 120) included 526 women with stage IIb, III or IVa tumours treated with radiation plus hydroxyurea or weekly cisplatin or 3-weekly 5-FU and cisplatin. Both the groups that had cisplatin had a 65% 3-year survival compared with 47% for the radiation and hydroxyurea group [21]. A Radiation Therapy Oncology Study (RTOG 9001) showed a survival difference of similar magnitude in 386 patients (stage IIb–IVa) who were randomised to receive either radiation alone or radiotherapy plus 3-weekly 5-FU and cisplatin. The 5-year survival was 67% for the combination group compared with 40% for those treated only by radiation [22].

Combined platinum/radiation seems to be of value in bulky stage Ib tumours (GOG 123). 369 patients were randomised to receive either radiotherapy or radiation plus cisplatin. All received an adjuvant hysterectomy. So far approximately half have been followed up for 36 months and 83% of the combined arm are alive compared with 70% of those treated with radiotherapy alone [23].

Our data do show that chemotherapy given at 14 day intervals produced a non-statistically significant improvement in survival. Our data and the results of Sardi and colleagues [15–17] suggest if neo-adjuvant chemotherapy is to be given, the agents should be given in an intensive manner at 7–14-day intervals with radiotherapy or surgery to begin 4–6 weeks after chemotherapy. However, the recently published results of concomitant chemotherapy indicate this may be a more effective method of combining chemotherapy and radiotherapy.

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