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Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874)

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ABSTRACT

The management of uterine sarcomas continues to present many difficulties. Primary surgery is the optimal treatment but the role of post-operative radiation remains uncertain. In the mid-1980s, the European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study proposed a trial to evaluate adjuvant radiotherapy, as previous non-randomised studies had suggested a survival advantage and improved local control when post-operative radiation was administered. The study opened in 1987 taking 13 years to accrue 224 patients. All uterine sarcoma subtypes were permitted. Patients were required to have undergone as a minimum, TAH and BSO and wahsings (166 patients) but nodal sampling was optional. There were 103 leiomyosarcomas (LMS), 91 carcinosarcomas (CS) and 28 endometrial stromal sarcomas (ESS). Patients were randomised to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks. Hundred and twelve were recruited to each arm. The initial analysis has shown a reduction in local relapse (14 versus 24, $p = 0.004$) but no effect on either OS or PFS. No unexpected toxicity was seen in the radiation arm. No difference in either overall or disease-free survival was demonstrated but there is an increased local control for the CS patients receiving radiation but without any benefit for LMS. Prognostic factor analysis shows that stage, age and histological subtype were important predictors of behaviour which may explain differences

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between CS and LMS. CS appears to show more kinship to poorly differentiated endometrial carcinomas in behaviour. LMS did not show the same benefit from radiation. These results will help shape future management and clinical trials in uterine sarcomas.

1. Introduction

The management of early stage uterine sarcomas is primarily surgical but the issue of whether to use adjuvant therapy post-operatively has been a vexed question for many years. During the 1970s and 1980s, there had been a number of reports of non-randomised studies of post-operative adjuvant radiotherapy but until now there has been no reported randomised clinical trial comparing radiotherapy with no immediate treatment.[1–10,33,35,39] Adjuvant chemotherapy studies have shown no specific benefit in uterine sarcomas and this is supported by the meta-analysis of adjuvant chemotherapy for all soft tissue sarcomas reported.[11–13,41] The GOG has investigated an alternative approach comparing whole abdominal irradiation (WAI) versus chemotherapy in carcinosarcoma.[14] This was reported in abstract at ASCO 2006 and showed that neither treatment was particularly effective but that patients receiving chemotherapy had fewer relapses and it was concluded that better and newer approaches were required.

The historical literature has usually reported on studies of uterine sarcomas by lumping together carcinosarcomas (CS), leiomyosarcomas (LMS) and endometrial stromal sarcomas (ESS), but to make matters more muddled there has been confusion over the terminology of CS. In this paper, the authors have chosen to use the term carcinosarcoma to denote those tumours with mixed epithelial and sarcomatous mesenchymal tumours without elements of LMS or stromal components. Recent studies would seem to confirm that the aetiology of CS is distinct from LMS as the former may arise from a common stem cell that produces epithelial tumours with a bi-phasic development which allows the mixed histological appearances seen in CS.[15–20] These tumours were previously known as malignant mixed mesodermal tumour or malignant mixed mullerian tumour (MMMTs). The terms have often been used interchangeably and currently there is a proposal to rename them as metaplastic carcinomas,[15] which may reflect the uncertainty of their aetiology as sarcomas, and their probable derivation from a common epithelial source.[15–17] Future studies must address these issues by clarifying the terminology and by distinguishing LMS from CS.

It is commonly agreed that primary surgery is the best initial therapy. This should include total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), peritoneal washings and for CS pelvic lymph node dissection (PLND). Previous studies had suggested that there might be a survival advantage to patients receiving post-operative radiotherapy.[1–9] A number of early reports had shown improved local control when post-operative adjuvant radiation was administered, and in some of these early series this seemed to translate into an improved survival benefit compared to surgery alone. However, none of these studies was randomised and it is difficult to be certain about the case selectivity. In the mid-1980s, the European Organisation for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Co-operative Group (GCCG) now known as the Gynaecological Cancer Group (GCG) proposed a randomised clinical trial to address the question of whether adjuvant pelvic radiotherapy reduced the pelvic recurrence rate and would result in a survival benefit in surgical stages 1 and 2 patients. Historical data had suggested that about 50% of these patients would develop recurrence or relapse and that adjuvant treatment would therefore modify the outcome. The hypothesis proposed that there would be a 20% reduction in local recurrence, from 50% to 30% at three years which was predicted to lead to an improvement in survival.

2. Materials and methods

2.1. Eligibility and exclusion criteria and pathology inclusion

The study opened in July 1988 and closed in July 2001, and 224 patients with surgically staged uterine sarcomas, stages 1 and 2, were randomised in the study by 36 institutions. There were 99 leiomyosarcomas (LMS), 92 carcinosarcomas (CS) and 30 endometrial stromal sarcomas (ESS), one patient had myxoid LMS and for two patients the classification was missing. Patients were recruited into the study if they had a histologically confirmed high grade malignant uterine sarcoma which was permitted to include carcinosarcomas (CS)/MMMTs, endometrial stromal sarcomas (ESS) and leiomyosarcomas (LMS) of uterine origin. It was recommended that the malignant potential of the tumour would be defined as at least 10 mitoses per 10 high power fields. Myxoid leiomyosarcomas were allowed to be included. Patients were required to have undergone a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Lymph node sampling was recommended; however, no instruction was made regarding peritoneal washings or omentectomy as this predated current management recommendations. Patients had to be of good performance status, World Health Organisation (WHO) 0–2 and be able to give full informed consent. Neither prior radiation to the pelvis nor prior malignancies were permitted except for basal cell carcinoma of the skin and *in situ* carcinoma of the cervix. Patients entering into the trial were required to have pathological review of the tumour sample, which was carried out by a central pathology review board by Professors J. Baak and H. Fox. Signed informed consent was obtained from all patients and approval from the local ethics committees.

2.2. Objectives of the studies

The primary objective of the study was to evaluate whether adjuvant pelvic radiotherapy could decrease pelvic recurrence

rate in patients with surgically completely resected uterine sarcomas and thereby decrease the recurrence of distant metastases. Secondary objectives included the evaluation of overall and progression-free survival benefit and toxicity profile.

2.3. Baseline investigations and surgical staging

Initial investigations to permit entry into the trial included a chest X-ray, an intravenous pyelography or renal ultrasound, abdominal CT scanning to look for disseminated disease such as para-aortic lymph node metastases or liver metastases and a full blood count and full biochemical profile. It was recommended that a minimum surgery would consist of TAH and BSO. It was recognised that not all patients would be referred to specialist gynaecological oncologists but where the skill and facilities were available patients would be recommended to undergo additional pelvic lymph node sampling or pelvic lymph node dissection (PLND). At the time of development of the protocol, the routine use of peritoneal washings was not standard although increasingly during the course of the enrolment period this became accepted as a standard option, similarly PLND increasingly became established particularly in the specialist Centres.

2.4. Treatment

Patients who have fulfilled the eligibility criteria were randomised to receive either radiation therapy or observation. Radiation therapy was recommended to start within eight weeks of surgery. External radiotherapy was to be given by megavoltage photon beam using a linear accelerator of at least 5 MeV energy. Radiotherapy was to be given according to the dose specification of target absorbed dose of the ICRU report 29 published in 1978.[23] The recommended technique was either a three- or a four-field pelvic brick or box technique although parallel opposed pair radiation fields were permitted. The intended radiation dose was to deliver 50.40 Gy in 28 fractions over five to six weeks, delivering 1.80 Gy per fraction. All fields were to be treated daily. The upper limit of the anterior posterior field was advised as the upper border of fifth lumbar vertebra and the lower border was set at the lower margin of the foramina ossis pubis. The lateral margins of the pelvic field would be taken at a point 2 cm lateral to the widest transverse diameter of the pelvic brim and the upper limit on the lateral portals would be taken at the upper border of fifth lumbar vertebra with the anterior limit being the upper margin of the symphysis pubis, and the lower limit being the lower margin of the obturator foramina and the posterior border of the junction between second and third sacral vertebrae. Patients randomised to the observation arm would be followed up and assessed clinically and by imaging at prescribed intervals as outlined below. None of the patients is known to have received any adjuvant chemotherapy (Table 3).

2.5. Follow-up arrangements

Patients who completed the radiotherapy were to be followed up for 10 years in the outpatient clinic with a physical examination, a chest X-ray to be carried out at least twice yearly and measurement of a full blood count and a full biochemical profile. Patients were seen three monthly for the first two years and then six monthly through to year five and then recommended for annual visits up to the tenth year. The management of relapsed disease was left to the discretion of the individual clinician.

2.6. Criteria for assessing response

The loco-regional recurrence rate would be determined by the site of failure which would be classified as local recurrence in vagina or para-vaginal tissues, or regional recurrence if confined to the pelvis or distant if metastases were beyond the pelvis.

3. Statistics

The value of radiotherapy in surgical stages I and II uterine sarcomas was to be assessed by the reduction in local recurrence rate which was considered to be the main end-point of the study. As background to the study it was expected that patients not treated with adjuvant radiotherapy would experience about 50% local recurrence rate at three years. These figures were derived from published literature from non-randomised trials in the 1960s and 1970s. In order to detect improvement in the local recurrence-free interval from 50% to 70%, 100 patients in each arm should be entered and followed for three years (alpha = 0.05, 1; beta = 0.80, two-sided log rank test). At least 77 local recurrences would need to be observed before the final analysis would be possible. The expected accrual rate for the study was predicted to be 75 patients per year and it was anticipated that the trial would be complete within three years! Stratification was carried out according to the histological sub-type, i.e. whether LMS, ESS or CS, and secondly according to surgical procedure, i.e. whether the patients underwent TAH and BSO or TAH, BSO and PLND. Overall survival (OS) and progression-free survival (PFS) were calculated as the time interval from the date of randomisation to death and disease progression whichever occurred first. Patients who were alive (and without progression) at the end of the study were censored at the last follow-up date. Progression-free survival and overall survival were estimated using the Kaplan–Meier method[24] and the two treatment groups were compared using a two-sided log rank test.[25] Response rates were compared by the χ^2 test.[26] Due to the confounding problem of competing risks, cumulative incidence methods were used to estimate the loco-regional recurrence and distant metastases risks and differences between the treatments were assessed via Gray test.[27] All tests were done according to the intention-to-treat principle.

Interim evaluations: because of slow accrual in the study, an unplanned interim analysis was carried out in April 1995 after 135 patients had been randomised and 23 loco-regional recurrences had occurred which concluded to continue the trial as planned without modifications until the sample size was completed. A second unplanned interim analysis took place on 10th December 2001 to determine if sufficient events had occurred to allow the study to be closed. At that time, 68 local recurrences had been observed out of the 77 required. It was estimated that it would take at least further 3 years to

obtain the last 9 events needed. Guided by an O'Brien–Fleming group sequential strategy[28] for rejection of the null hypothesis, i.e. loco-regional recurrences do not differ between the radiotherapy and no-treatment arms] with 80% power and three looks at the data at 23, 68 and 77 events, the Independent Data Monitoring Committee decided that the results were robust enough based on the current data and therefore should be published.

4. Results

4.1. *Efficacy*

Between July 1988 and July 2001, 224 patients were randomised in the study by 36 institutions and achieved a median follow-up of 6.8 years. For five patients (two in observational arm), insufficient follow-up data were available, so only 219 contributed to the efficacy and safety analysis. There were 99 LMS, 92 CS and 30 ESS. The entry criteria for both arms were well balanced in terms of usual risk factors (see Tables 1 and 2). At the time of the analysis, 57% were still alive and this proportion of deaths was very similar between the two arms (Figs. 1 and 2). The main cause of death was malignant disease in 39 out of 48 patients (81%) for radiation arm and 43 out of 46 patients (93%) for the observation arm. Likewise, the proportion of patients who progressed was similar amongst the two treatment arms with 52 of 110 (47%) in the radiation arm and 54 of 109 (50%) in the treatment observation arm (Tables 4–6). There were differences in local control between the two arms (Table 5). For those receiving pelvic radiation, there were four initial isolated local relapses and 16 had local relapse concurrent with distant metastases, and a further four developed local relapse after distant first relapse giving a total local relapse rate of 22% (24 out of 110). In the observation arm, these figures were 27 isolated local relapses, 14 simultaneous local and distant and three delayed distant recurrences yielding a total local relapse rate of 40% (44 out of 109). Distant metastases occurred in 49 (46%) patients treated with radiation as opposed to 35 (32%) in the observation arm. The difference in local or regional progression between the two arms was statistically significant at 24 of 110 (22%) versus 44 of 109 (40%) with a p-value of 0.004 (see Fig. 3).

Median progression-free survival was 6.22 years in the radiotherapy arm and 4.93 years in the observation arm with a hazard ratio of 1.19 (95% CI = 0.82–1.72; $p = 0.3524$). The progression-free survival rate at 3 years was improved from 51.9% in the observation arm to 57.7% in the radiotherapy arm. For overall survival, a median survival time of 8.53 years in the radiotherapy arm as opposed to 6.78 years in the observation arm with a hazard ratio of 1.02 (95%CI = 0.68–1.53; $p = 0.923$) was observed. However, none of these was statistically significant. The cause-specific 5-year loco-regional recurrence cumulative incidence rates were 18.8% versus 35.9% and the corresponding overall Gray test was significant ($p = 0.0013$). The 5-year cumulative incidence rates for distant metastases were 45.3% and 33.6%, and did not reach statistical significance (Gray test p-value = 0.2569).

4.2. *Radiotherapy*

Radiation was delivered to the majority of the patients using the prescribed radiation doses and techniques. Forty percent

Table 1 – Baseline characteristics 1

	Radiotherapy	Observation	Total
	112	112	224
Variable	N (%)	N (%)	N (%)
Histological type			
Leiomyosarcoma (LMS)	50 (44.6)	49 (43.8)	99 (44.2)
Carcinosarcoma (CS)	47 (42.0)	45 (40.2)	92 (41.1)
Endometrial stromal sarcoma (ESS)	15 (13.4)	15 (13.4)	30 (13.4)
Myxoid leiomyosarcoma	0 (0.0)	1 (0.9)	1 (0.4)
Missing	0 (0.0)	2 (1.8)	2 (0.9)
Type of surgery			
TAH and BSO	83 (74.1)	83 (74.1)	166 (74.1)
TAH and BSO and node sampling	28 (25.0)	27 (24.1)	55 (24.6)
Missing	1 (0.9)	2 (1.8)	3 (1.3)
FIGO stage			
I	95 (84.8)	102 (91.1)	197 (87.9)
II	15 (13.4)	8 (7.1)	23 (10.3)
III	2*(1.8)	0 (0.0)	2 (0.9)
Missing	0 (0.0)	2 (1.8)	2 (0.9)
Menopausal status			
Median age/range	59 (36–80)	58 (36–80)	59 (36–80)
Pre-menopausal	28 (25.0)	26 (23.2)	54 (24.1)
Peri-menopausal	11 (9.8)	10 (8.9)	21 (9.4)
Post-menopausal	73 (65.2)	72 (64.3)	145 (64.7)
Missing/unknown	0	4 (3.5)	4 (1.7)

Table 2 – Baseline characteristics 2

	Radiotherapy	Observation	Total
	112	112	224
Variable	N (%)	N (%)	N (%)
Tumour grade			
Well differentiated	8 (7.1)	14 (12.5)	22 (9.8)
Moderately differentiated	24 (21.4)	18 (16.1)	42 (18.8)
Poorly differentiated	48 (42.9)	40 (35.7)	88 (39.3)
Not recorded	32 (28.6)	37 (33.0)	69 (30.8)
Missing/unknown	0 (0.0)	3 (2.7)	3 (1.5)
Number of mitosis per 10 HPF			
<10	16 (14.3)	14 (12.5)	30 (13.4)
10–20	40 (35.7)	38 (33.9)	78 (34.8)
>20	41 (36.6)	42 (37.5)	83 (37.1)
Missing/unknown	15 (14)	18 (17)	33 (14.5)
Myometrial invasion			
Inner third	36 (32.1)	37 (33.0)	73 (32.6)
Middle third	25 (22.3)	20 (17.9)	45 (20.1)
Outer third	40 (35.7)	39 (34.8)	79 (35.3)
Missing/unknown	11(10)	16 (14.3)	27 (12)
Peritoneal washings			
Positive	6 (5.4)	3 (2.7)	9 (4.0)
Negative	71 (63.4)	73 (65.2)	144 (64.3)
Not done	17 (15.2)	19 (17.0)	36 (16.1)
Missing/unknown	18 (16.1)	17 (15.2)	35 (15.6)

of the patients treated with radiation received parallel-opposed pair of fields whereas 55% received a four-field brick (or box) technique, data for 5% were missing and 93% of patients received the intended dose of radiation. Only 2 patients in the observation arm were given pelvic radiotherapy. The toxicity due to the radiation was generally mild and predictable and within the expected incidence ranges for this dose of pelvic radiation. There was no finding of significant adverse effects in the radiation arm (Table 3).

4.3. *Tumour type*

Some differences were seen in the local and distant progression rates for the different tumour types. The number of patients with ESS was too small to permit any analysis and therefore comments can only be made with reference to CS and LMS. There was no significant difference in local or distant progression rates for LMS depending on radiation treatment (see Tables 5 and 6). However, there is a trend that patients with CS who were treated with radiation had better local control but conversely had higher distant metastatic rates. In terms of overall survival, there were no significant treatment differences in either the CS or LMS group, but it is worth noting that radiotherapy had an adverse effect in the LMS patients (HR = 0.64, 95%CI = (0.36, 1.14)) but was beneficial in the CS patients (HR = 1.58, 95%CI = (0.83, 3.01)). A similar effect was noticed for disease-free survival. Not surprisingly factors like tumour differentiation or grade, number of mitoses and depth of myometrium invasion showed differences in overall survival. Those with well-differentiated tumours fewer than 10 mitosis per 10 HPF and earlier stage disease confined to the inner two thirds had a better prognosis.

4.4. *Side-effects and toxicity*

No serious or significant toxicity was identified for either arm. No deaths were attributed to the treatment. Twenty four percent were recorded as having transient symptoms during external beam radiotherapy (EBRT), three patients were reported to have serious delayed gastro-intestinal problems, two of whom required surgery with good results.

5. Discussion

This is the first randomised clinical trial to report on the comparison between external beam pelvic radiation therapy and observation in the management of stages I and II surgically treated uterine sarcomas. The primary objective of the trial was to look at a reduction in the risk of local recurrence and to see whether this translated into a survival benefit. The trial has confirmed a benefit in local control for carcinosarcomas which failed to translate into any difference in overall survival between immediate post-operative pelvic radiotherapy and those randomised to observation.

An improvement in local control was seen in the patients with CS, although this was not shown for LMS. The number of patients with ESS was too small to see any effect. However, these differences in pelvic relapse rates did not translate into any survival advantage within any tumour type. Care should be taken not to over-emphasise these findings in view of the limiting factors that this study bears. Apart from the potential bias inherent to subgroup analyses (small numbers, multiple testing) the two outcomes of interest, loco-regional and distant relapses, are directly entwined. The occurrence of one type of relapse (and its resulting treatment) will inevitably

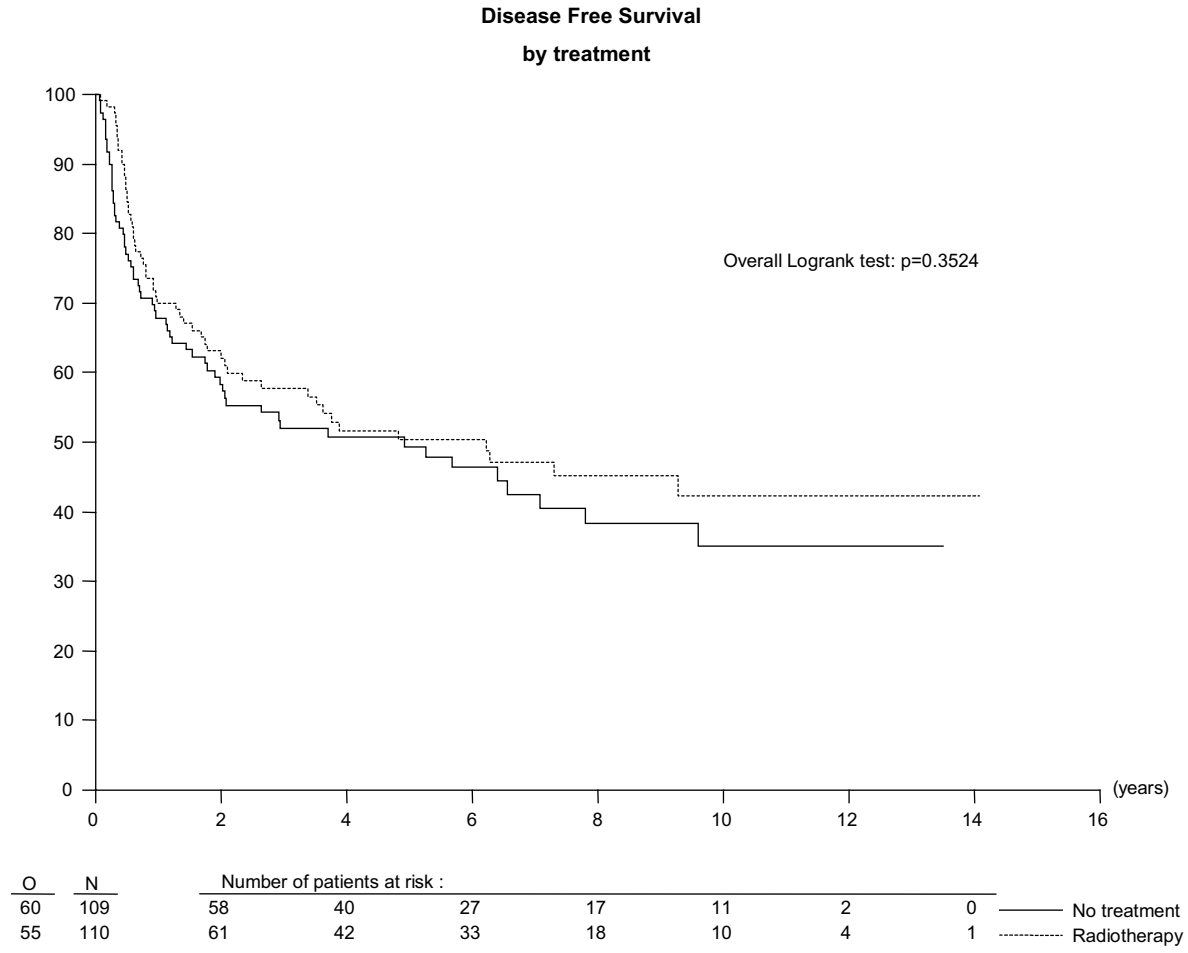


Fig. 1 – Disease-free survival.

impact on the incidence of the other type. Hence, even with specialised methodology such as the cause-specific Gray test, it is impossible to completely separate the two events. Nevertheless, these results today are not surprising in light of our current knowledge and understanding of the disease processes of early stage uterine sarcomas. It is now strongly believed that LMS are different tumours from both CS and ESS. There is increasing evidence emerging that CS are most probably epithelial tumours with a bi-phasic component which represent the more aggressive end of the spectrum.[15–20] The common aetiology is supported by molecular biological studies and furthermore the patterns of spread of disease for CS are very similar to epithelial carcinomas whereas LMS are much more likely to have early haematogenous spread with a high incidence of early lung metastases and a relatively low incidence of lymph node metastases. This was clearly demonstrated by the GOG study (Major et al.[29]) showing the much higher incidence of pelvic lymph node metastases in CS but the higher prevalence of distant first metastases in LMS.[29] For higher grades CS and ESS, the risk of local nodal disease falls between 12% and 18% and there is a greater risk of local or loco-regional recurrence which runs between 5% and 15% hence, local treatment might have been predicted to show a benefit. Whereas the incidence of lymph node metastases in LMS lies at about 4% and with a much higher incidence of lung metastases at presentation, hence one would anticipate that these tumours would be more likely to develop early distant recurrence rather than local recurrence and local pelvic treatment would be predicted to have lower benefit.[31,36,37]

This is supported by CS demonstrating that an improved local control is seen but unfortunately does not translate itself into a substantial survival benefit, whilst for LMS in this study there is no gain at all for either local control or survival. So why is this case? It appears that there is a greater likelihood of developing first relapse at a distant site in the irradiated CS group despite their improved local control. This pattern has been seen in the previous studies of radiation in endometrial cancer. Can we explain this by the tumour biology or perhaps immunology? It seems to mirror the situation in uterine epithelial carcinomas as seen in PORTEC 1 and GOG 99 studies[21,22] where improved local control was seen without any survival benefit in the irradiated patients, and would help to support the hypothesis that uterine CS and epithelial tumours have a common aetiology and behaviour. What seems clear is that LMS and CS are likely to be distinct tumours and require a different strategy for post-operative adjuvant therapy. Local control is necessary but how is this best achieved?

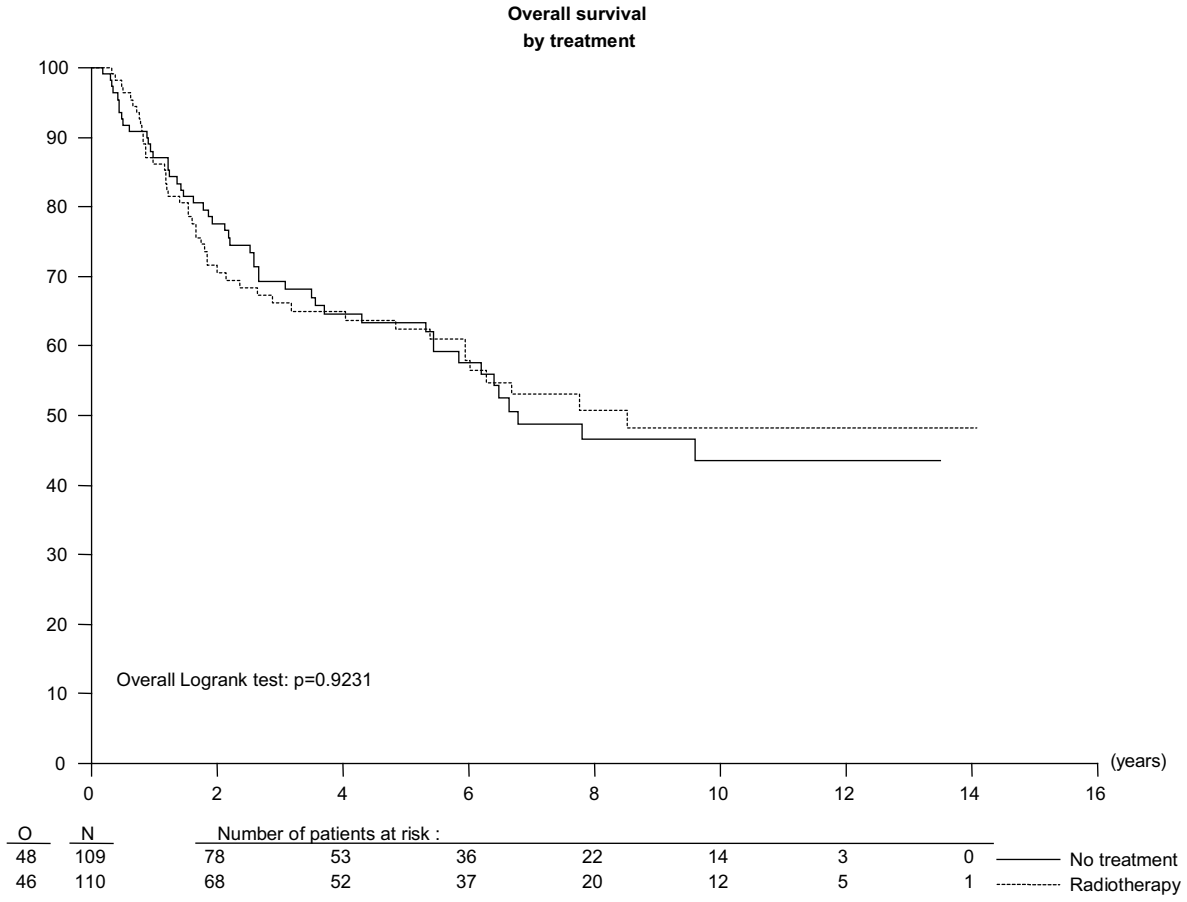


Fig. 2 – Overall survival.

Table 3 – Radiation therapy details

Variable	Radiotherapy, n = 101 Number and range
Total dose (Gy)	50.4 (5.4–65)
Duration of radiotherapy (days)	42 (3–87)
No. of treatment days	28 (3 –65)
Dose (Gy) per fraction	1.8 (1.6–2.6)
Observed dose intensity (Gy/week)	8.4 (4–12)
Observed relative dose intensity (%)	93 (44–140)
Radiation fields	Number (%)
Parallel opposed	40 (35)
Four fields	61 (54)
Data missing	10 (9)

What lessons can be learned from these results and can we use them to develop new clinical trials? Adjuvant post-operative radiation therapy leads to improved local control in CS and ESS but without any survival benefit mainly because there seems to be a higher risk of developing earlier distant metastases which lead to premature death. The side-effects and toxicity in this study were acceptable and were comparable with those expected from historical studies. The incidence of radiation damage was low and did not lead to any serious complications. This may be helpful if we are to consider integrating radiation into future studies. Thus do we need a radical new approach? There are also some small selected series where an aggressive approach of surgery and post-operative chemo/radiotherapy was administered reporting remarkably high levels of local control and survival, Manolitsas et al.[32] but this has never been validated in a randomised trial. However for the present we cannot advocate the routine use of pelvic external radiotherapy for optimally

Table 4 – Summaries for DFS, survival status and cause of death are presented for the 219 patients with follow-up information

	Radiotherapy	Observation	Total
	110	109	219
Disease free survival status			
No event (%)	55 (50.0)	49 (45.0)	104 (47.5)
Relapse or death	55 (50.0)	60 (55.0)	115 (52.5)
Survival status			
Alive	64 (58.2)	61 (56.0)	125 (57.1)
Dead	46 (41.8)	48 (44.0)	94 (42.9)
Cause of death			
Malignant disease	43 (39.1)	39 (35.8)	82 (37.4)
Infection/CVS disease	2 (1.5)	4 (3.3)	7 (3)
Not known	1 (0.5)	5 (4.6)	5 (2.3)

Table 5 – The following table displays the different possible sequences of events up to last follow-up and the corresponding frequencies per treatment arm

	Radiotherapy	Observation	Total
	110	109	219
Sequence of events			
No recurrence – alive	55 (50.0)	49 (45.0)	104 (47.5)
No recurrence – dead	3 (2.7)	5 (4.6)	8 (3.7)
Loco-regional recurrence only	3 (2.7)	20 (18.3)	23 (10.5)
Distant metastases only	28 (25.5)	11 (10.1)	39 (17.8)
Loco-regional recurrence followed by distant metastases	1 (0.9)	7 (6.4)	8 (3.7)
Distant metastases followed by loco-regional recurrence	4 (3.6)	3 (2.8)	7 (3.2)
Loco-regional recurrence and distant met. at same time	16 (14.5)	14 (12.8)	30 (13.7)
Local relapse at any time	24 (21)	44 (40)	68 (31)

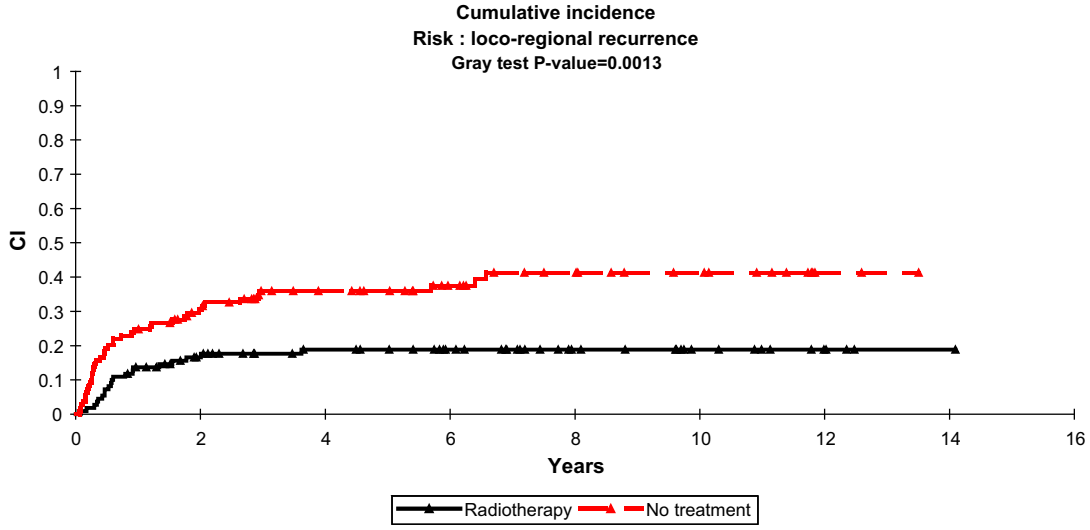


Fig. 3 – Cumulative incidence of local recurrence.

resected uterine sarcomas but reserve it for localised relapse. Similarly, whole abdominal irradiation has also been shown to be of little benefit. It may even be argued that EBRT is contraindicated in LMS which have been completely excised.

6. Conclusion

This is the first randomised clinical trial to report on the use of adjuvant pelvic external beam radiotherapy versus no

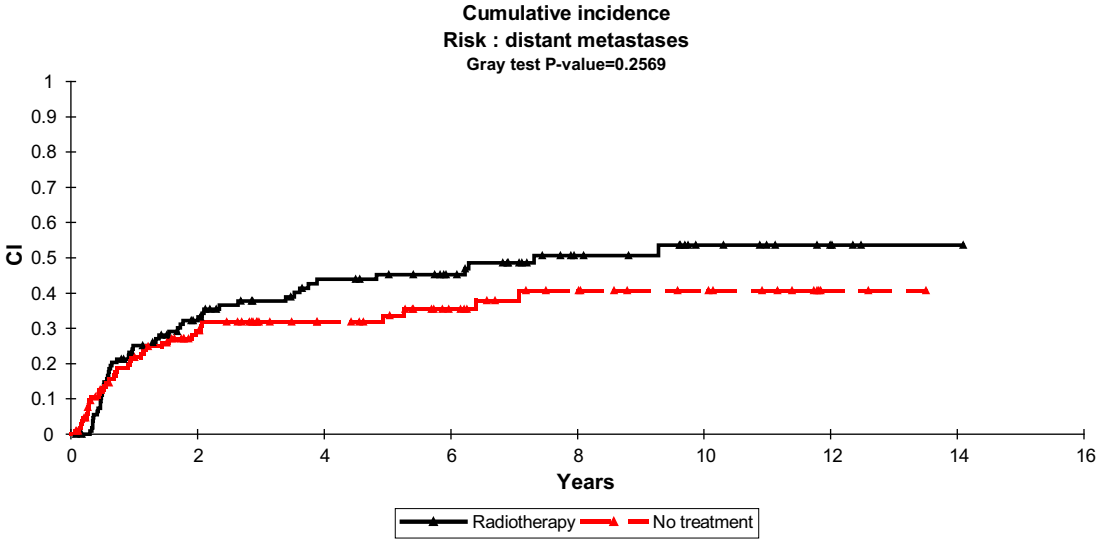


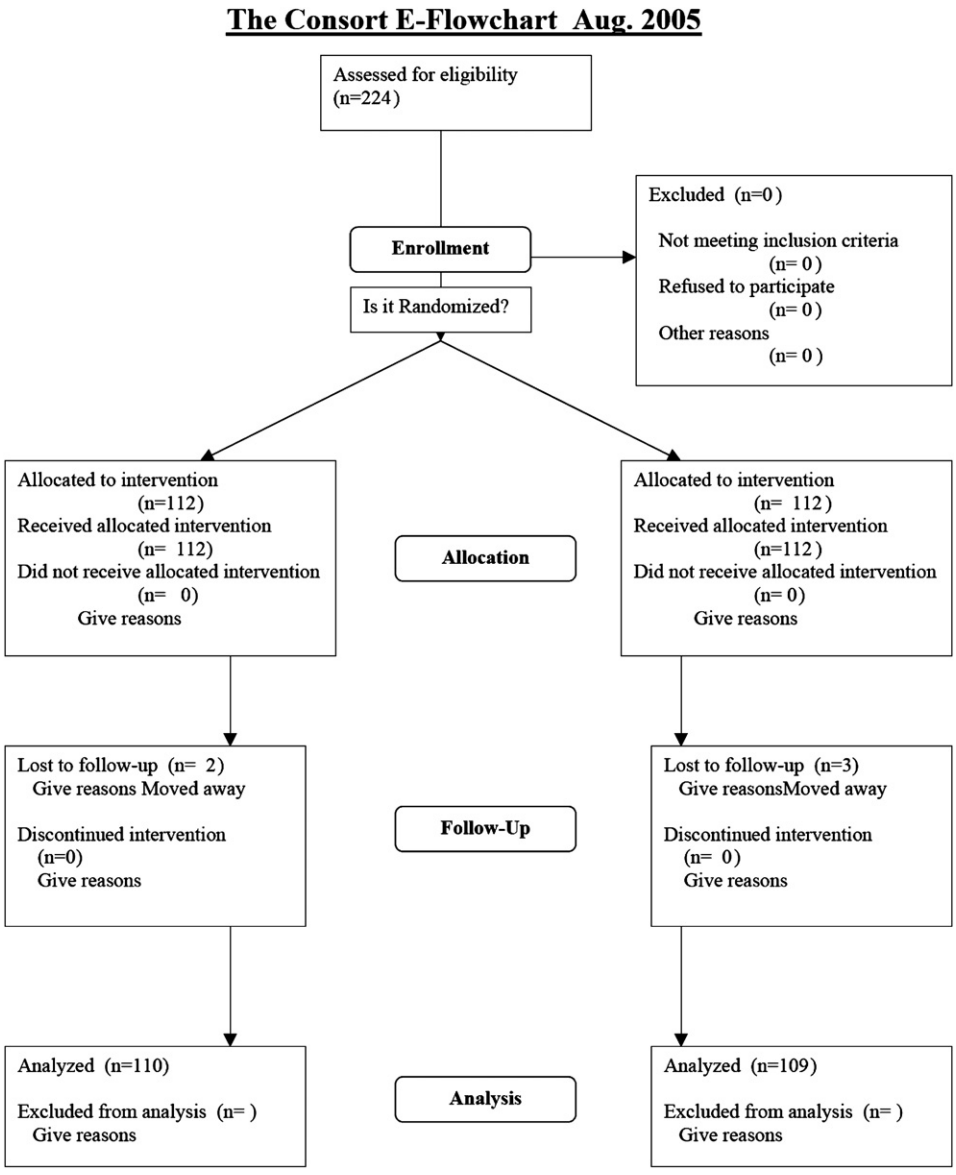
Fig. 4 – Cumulative incidence of distant metastases.

Table 6 – Sites of recurrence

	Sites of recurrence			
	CS, $n = 91$		LMS, $n = 99$	
	Radiotherapy ($n = 46$)	Observation ($n = 45$)	Radiotherapy ($n = 50$)	Observation ($n = 49$)
No local recurrence	28 (61%)	21 (47%)	22 (44%)	26 (53%)
Local recurrence only	2 (4%)	11 (24%)	1 (2%)	7 (14%)
Distant metastases	7 (15%)	3 (7%)	18 (36%)	7 (14%)
Local followed by distant	1 (2%)	3 (7%)	0 (0%)	2 (4%)
Distant followed by local	2 (4%)	0 (0%)	2 (4%)	3 (6%)
Simultaneous local and distant	6 (13%)	7 (16%)	7 (14%)	4 (8%)
Any local recurrence	11 (24%)	21 (47%)	10 (20%)	12 (24%)
Any distant metastases	16 (35%)	13 (29%)	27 (54%)	16 (33%)

immediate treatment in the management of uterine sarcomas. The study has shown an improved local control for patients with CS, but has shown no survival benefit. Future trials must distinguish between LMS and CS, and at present one cannot recommend any adjuvant treatment with radiation or chemotherapy for LMS. CS are increasingly being recognised as aggressive variants of endometrial epithelial tumours and management reflects the treatment of endometrial carcinomas. Future studies should probably be directed towards achieving optimal local control and address issues of reducing metastatic spread perhaps by using chemotherapy.[40]

Since adjuvant radiation confers no survival benefit, is there any place to consider its use? Optimal local control will be achieved by high quality surgery which will include pelvic lymph node dissection if the patient is fit enough. Local pelvic radiation may only be indicated when there is cervical stromal involvement by using brachytherapy; the argument to consider EBRT when pelvic lymphadenectomy is not performed remains unproven. More extensive radiation is also unproven; the Gynecologic Oncology Group (GOG) in their trial 150, which randomised to whole abdominal irradiation (WAI) or chemotherapy, still had an unacceptably high failure rate.[14,34] The recently presented NSGO 9501 study from the Nordic Society of Gynaecological Oncology of chemotherapy and radiation in high risk stages 1 and 2 endometrial carcinomas demonstrated superiority in PFS of sequential chemotherapy and radiation.[42] At present, it is difficult to be clear about whether there is any place for radiation therapy as an adjuvant; whilst local control is improved, the additional morbidity and failure to impact on survival makes its inclusion not routinely acceptable. However, if we extrapolate from epithelial endometrial carcinomas, radiotherapy may be used as salvage treatment. The higher rate of first metastases at a distant site supports the view that adjuvant chemotherapy should be explored as part of the initial treatment for CS again emphasising the difference in clinical behaviour between LMS and CS and perhaps tailored radiation may be offered to selected high risk groups.



Conflict of interest statement

None declared.

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