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Retrospective Analysis of 318 Cases of Uterine Sarcoma

K.S. Oláh, H. Gee, S. Blunt, J.A. Dunn, K. Kelly and K.K. Chan

A study of data from 318 cases of uterine sarcoma presenting during a 10-year period (1967–1976) is reported. All but 6 of the patients had at least a 5-year follow-up (98% 5-year follow-up). Overall 5-year survival was 31%, with the major prognostic indicator being tumour stage. Despite the tendency for mixed mesodermal tumours to present in older women with more advanced disease, survival was not statistically different to those patients with leiomyosarcomas. Thus, the propensity for tumour dissemination in leiomyosarcomas should not be underestimated. Leiomyosarcomas are less likely to present with abnormal symptoms than are other sarcomas, and their occurrence as an incidental finding on histological examination underlines the need for an adequate inspection of the intra-abdominal contents at hysterectomy. The tendency to treat all sarcomas as if they were endometrial tumours may be fallacious, and an alternative classification (such as the TNM system) may be required. Recurrence of tumour tended to be at distant sites (distant:pelvic recurrence rate 3:1). Adjuvant radiotherapy is unlikely to alter distant disease foci, and thus the development of combination chemotherapeutic regimens using agents which have shown to result in tumour response seem warranted. Such trials will need to be organised on a multicentre basis to attain statistically evaluable numbers of patients.
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INTRODUCTION

UTERINE SARCOMA is a rare tumour, accounting for only 1–3% of all female genital tract malignancy [1, 2], and between 3 and 7.4% malignant tumours of the corpus uteri [1, 3]. In order to provide more information for the clinician, a retrospective study of uterine sarcoma was undertaken using cases reported to the Birmingham Regional Cancer Registry during the 10-year period 1967–1976. It was hoped that such information would yield survival data for the various tumour types, and determine the influence, if any, of radiotherapy and chemotherapy on survival.

PATIENTS AND METHODS

The data were taken from the Birmingham Regional Cancer Registry, which serves a female catchment population of 2.582 million (1971 population census). It is considered that the West Midlands region contains proportions of industrial, commercial and agricultural subpopulations similar to those found nationally [4]. Efficiency of case registration exceeds 95% and less than 1% of registered cases are untraced [4].

Data were taken from the registry records of patients with uterine sarcoma registered in the 10-year period 1967–1976. In all but 6 of the 318 cases presented, a 5-year follow-up has been achieved (i.e. a 98% 5-year follow-up). Data were taken mainly from registry records, but where information was lacking, further details were sought from case notes. Written consent was obtained from the appropriate clinicians in the region.

Where survival data are presented graphically, actuarial survival curves are used. Logrank tests (Mantel–Cox) have been used for the statistical comparison of the curves.

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RESULTS

Incidence

In the 10-year period 1967–1976, 318 cases of uterine sarcoma were registered. This gives an annual incidence of 1.23/100 000 female population. There was no evidence of a changing incidence during this 10-year interval. For comparison, during the

Table 1. The classification of uterine sarcomas [5]

I. Pure mesenchymal
  a. Homologous
    1. Endometrial stromal sarcoma
      a. Endolymphatic stromal myosis (low grade stromal sarcoma)
      b. Stromal sarcoma (high grade)
    2. Smooth muscle
      Leiomyosarcoma
  b. Heterologous
    1. Rhabdomyosarcoma
    2. Chondrosarcoma
    3. Osteosarcoma
    4. Liposarcoma
  c. Of uncertain origin
    Tumours resembling malignant ovarian sex-cord tumours

II. Malignant Müllerian mixed tumours
  a. Homologous (carcinosarcoma)
  b. Heterologous

III. Müllerian adenosarcoma

IV. Lymphoma and leukaemia

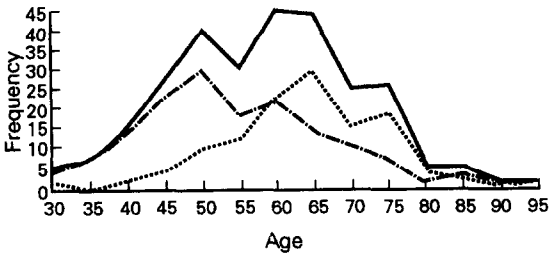

Fig. 1. Age distribution of cases of uterine sarcomas by tumour type (P=0.0001). - - - - = LMS, ···· = MMT, —— = both.

same period, 3489 endometrial adenocarcinomas were registered, giving a ratio of 1 sarcoma for every 11 adenocarcinomas.

The classification used for uterine sarcoma follows that proposed by Clement and Scully (1981) [5] (Table 1). Leiomyosarcomas (LMS) accounted for 48.2% (153 cases), mixed mesodermal tumours (MMT) 38.0% (121 cases) and endometrial stromal sarcoma (ESS) 6.3% (20 cases). Other rarer histological types have been grouped together (9 cases) with those cases with indeterminate histology (15 cases). The histological distribution is similar to that described for other series of uterine sarcoma [6].

Table 2. Mean age at presentation and distribution of tumour type by menopausal status

	Age†	Premeno-pausal	Perimeno-pausal	Postmeno-pausal	Not known
LMS	56.2 (12.1)*	49 (32%)	13 (8%)	87 (57%)	4 (3%)
MMT	65.7 (9.9)*	6 (5%)	6 (5%)	109 (90%)	0 (0%)
ESS	57.9 (17.0)	5 (25%)	1 (5%)	14 (70%)	0 (0%)
Others	61.6 (12.3)	5 (22%)	1 (4%)	18 (74%)	0 (0%)
Total		65 (20%)	21 (7%)	228 (72%)	4 (1.3%)

*$P < 0.001$.
†Mean (S.D.).
For analysis: premenopausal + perimenopausal vs. postmenopausal, $0.01 > P > 0.001$.
Mean age at menopause was 50.2 years.

Table 3. Presenting symptoms

Postmenopausal bleeding	155 (49%)
Menorrhagia	39 (12%)
Menstrual irregularity (unspecified)	48 (15%)
Abdominal pain	87 (27%)
Abdominal distension	63 (20%)
Urinary symptoms	34 (11%)
Other symptoms	64 (21%)
Weight loss	18
Bowel symptoms	17
Infertility	3
Unspecified	26

Aetiology

A link between uterine sarcoma and previous pelvic irradiation has been described [7, 8]. In this series 21 (6.6%) cases had received pelvic irradiation, 13 of which were MMT. This incidence is higher than could be expected by chance ($0.5 > P > 0.01$). Of those cases of MMT that were associated with previous radiation, 3 cases (23%) had been irradiated for malignancy whereas the remainder had been irradiated for benign conditions. Previous studies have suggested that uterine sarcomas are more likely to occur after radiotherapy for malignant conditions, uterine adenocarcinomas being more likely to occur when previous therapy has been for benign conditions [8].

In the population of women developing uterine sarcoma there was a tendency to lower parity than in the general population ($P < 0.001$). Over 20% (67) patients in the study were nulliparous compared with 14% of the general population [9]. This is consistent with previous findings [10].

Presentation

The age range of presentation was from 24–95 years with a mean of 60.5 years. Approximately 90% were aged 45 or over. A bimodal distribution is demonstrable (Fig. 1), the earlier peak being due to the occurrence of LMS tumours, and the latter peak to MMT. This has been noted previously [11]. Over 70% of the women were postmenopausal, and MMT were the most common tumour of the postmenopausal woman. There were proportionately more LMS in the premenopausal group (Table 2). This may have been expected from the age distribution of these tumours already described and noted by other studies [12–14].

In this series 77.2% patients presented within 6 months of

Table 4. Signs present at the time of diagnosis

Enlarged uterus	247 (78%)
Mass visible on speculum examination	57 (18%)
Parametrial involvement	38 (12%)
Pelvic mass (other than uterus)	27 (8.5%)
Other	
Lymphadenopathy	9 (3%)
Ascites	8 (2.5%)
Hepatomegaly	5 (1.5%)

Table 5. Staging at time of presentation

Stage	LMS	MMT	ESS	Other	Total
I	95 (65%)	60 (50%)	15 (75%)	10 (42%)	184 (60%)
II	4 (3%)	9 (7%)	1 (5%)	0 (0%)	14 (4%)
III	13 (8%)	25 (21%)	3 (15%)	3 (12%)	44 (14%)
IV	28 (19%)	21 (17%)	1 (5%)	7 (30%)	57 (17%)
Not known	9 (6%)	6 (5%)	0 (0%)	4 (17%)	19 (5%)
Total	153	121	20	24	318

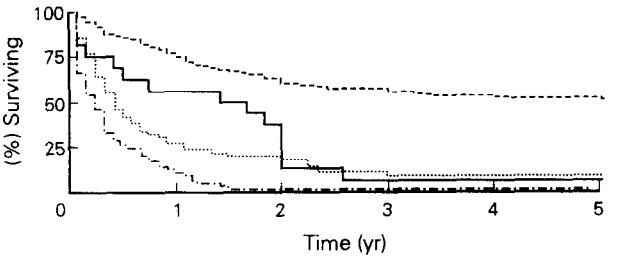

Fig. 2. 5-year survival: FIGO staging. - - - = stage I, —— II, ···· = stage III, - · - · - = stage IV.

the onset of symptoms; 9.1% within 6–12 months and 13.7% of patients had symptoms for longer than 1 year. The presenting symptoms and the clinical signs present at diagnosis are summarised in Tables 3 and 4. Due to the origins of the various tumour types, MMT and ESS are more likely to present with abnormal bleeding or a visible polyp/mass on examination than LMS tumours. In this series 31% MMT tumours presented with a mass visible on speculum examination compared to 8.5% LMS ($P < 0.001$). Leiomyosarcoma should be suspected when there is rapid growth of a fibroid uterus, and the occasional finding of malignant changes within fibroids on histological examination underlines the need for an adequate inspection of the intra-abdominal contents at the time of hysterectomy.

There is no agreed staging for uterine sarcoma, and the FIGO staging for adenocarcinoma of the uterine corpus has customarily been adopted. The use of a staging for a tumour arising within the endometrial cavity may have validity for MMT and ESS, but is questionable (both for staging and with respect to response to therapy) for LMS which arise within the myometrium. Furthermore, the tendency to treat these sarcomas as if they were endometrial tumours may be fallacious, and it may be more appropriate to assess tumour size, spread and nodal involvement in a manner similar to that used in the TNM classification.

Tumour stage in this study was largely assigned in retrospect from the operative findings. However, there was little disparity between the staging preoperatively (when performed) and the operative staging. As found in other studies [1, 12, 15] it can be seen that MMT patients tend to present with more advanced disease than those with either LMS or ESS. The differences are statistically significant (Table 5). Similarly, older patients, in whom MMT tumours are more common, tend to present with more advanced disease. The tumour differentiation for each histological tumour type is given in Table 6. It can be seen that MMT tend to be more poorly differentiated than either LMS or ESS. This difference is significant ($P < 0.01$).

Table 6. Tumour differentiation

	LMS	MMT	ESS	Other
Well differentiated	47 (31%)	18 (15%)	6 (30%)	6 (25%)
Moderately differentiated	32 (21%)	29 (24%)	6 (30%)	5 (21%)
Poorly differentiated	50 (33%)	58 (48%)	3 (15%)	4 (17%)
Not recorded	24 (15%)	16 (13%)	5 (25%)	9 (37%)
Total	153	121	20	24

For analysis: LMS + ESS vs. MMT, $P<0.01$.

Survival data

The overall 5-year survival rate in this series was 31%, the majority of deaths occurring in the first 3 years (Fig. 2). There was no difference in survival between each histological tumour type (Fig. 3). Similar findings have been previously described [12].

As expected, prognosis was closely related to the spread of tumour [12, 15]. Analysis of the effect of tumour grade/differentiation was made by examining survival in stage I disease since survival was universally poor in other stages irrespective of tumour grade. The differences in survival for stage Ia did not reach statistical significance ($P > 0.05$). However, those seen in stage Ib did ($0.01 > P > 0.001$).

Survival declined with advancing age. A statistically significant difference can be shown in survival between patients under the age of 50 years and those above this age ($P < 0.001$). Similarly, there was a statistically significant reduction in survival in postmenopausal women compared with those who were either premenopausal or perimenopausal ($P < 0.001$). Younger patients tended to present with less advanced disease (81.3% premenopausal women had stage I disease compared with 54.8% postmenopausal women), thus accounting for some of the differences seen.

Univariate analysis of the data shows that stage, age and menopausal status had a significant effect on survival. Histology had no apparent effect. However, there were significant associations between all of these factors. Postmenopausal women were older, presented with more advanced disease and were more likely to have poorly differentiated MMT tumours. Therefore, the significance of any factor might not be due to its own effect on survival but might reflect its association with one of the others. When control was made for stage and age an effect of histology on prognosis could be seen, with LMS giving a worse prognosis than MMT ($\chi^2 = 9.27$, 1 d.f.; $P = 0.0023$). This is in contrast to previous reports [12, 16, 17] and our own findings in the univariate analysis.

The primary therapy for all but the advanced cases of uterine

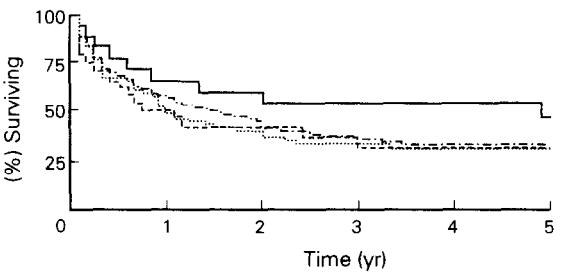

Fig. 3. 5-year survival: histology. —— ESS, - · - · - LMS, ···· other, - - - MMT.

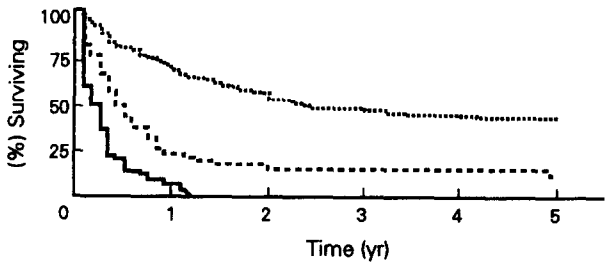

Fig. 4. 5-year survival: surgical treatment. —— = biopsy alone, ···· = complete resection, - - - = incomplete resection.

sarcoma was hysterectomy, with or without radiotherapy (Table 7). Complete excision was possible with stage I and II disease, but there were no specific criteria for the use of adjunctive radiation therapy, which tended to be given on an *ad hoc* basis. Radiotherapy was used as an adjunct to surgery, or to palliate residual disease in stage III/IV tumours. Preoperative radiotherapy was given in 21 patients (6.6%), and postoperative irradiation in 45 (14.1%). Of those treated preoperatively, the majority (12 patients, 57%) received intracavity radiation (range 24–75 Gy, mean 49.2), whilst 5 (23.9%) had external irradiation (range 20–58 Gy, mean 34.8) and 4 (19.0%) received both (range 25–74 Gy, mean 43.5). Of those patients treated postoperatively, 27 (60%) were given external radiation (range 20–78 Gy, mean 40.12), 15 (33.4%) received intracavity (vaginal) therapy (range 12–85 Gy, mean 50.8), and 3 patients (6.7%) were treated with a combination of both (range 49–56 Gy, mean 51.7). Chemotherapy was combined with surgery in only a small number of cases (see Table 7). Chemotherapy regimens varied widely both from patient to patient and from time to time in any 1 individual. As a result, no conclusions could be drawn with regard to agent or regimen effectiveness. In general, if surgical resection of the tumour was possible, the prognosis was greatly improved (Fig. 4). If surgical resection was not possible, the prognosis was generally poor. In this series, the prognosis appeared worse for those patients who had complete tumour resection with adjunctive radiotherapy than for those who had surgery alone (Fig. 5). This may have been due to to the selection of patients by the clinicians involved i.e. those patients who were considered to be at higher risk of recurrence were given adjuvant radiotherapy. Radiotherapy may be of some benefit, and MMT patients may show a variable, but on occasion marked response to treatment. In this series 3 patients with stage III disease responded well to radiotherapy and are long-term survivors.

Recurrence

The overall recurrence rate was 34% (77 cases). Of these, 24.7% (19 cases) were pelvic and 75.3% (58 cases) were distant

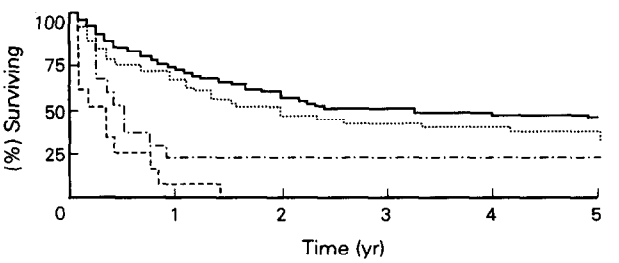

Fig. 5. Surgical therapy: effect of radiotherapy. —— = complete resection, ···· = complete resection plus radiotherapy, - · - · - = incomplete resection plus radiotherapy, - - - = incomplete resection.

Table 7. Treatment

	Surgery alone	Surgery + radio-therapy	Surgery + chemo-therapy	Surgery + radiotherapy + chemo-therapy
Complete resection	181 (76%)	51 (21%)	4 (1.7%)	2 (0.8%)
Incomplete resection	12 (33%)	14 (39%)	6 (17%)	4 (11%)
Total	193	65	10	6

from the pelvis, a ratio of distant to pelvic metastases of 3:1. This was similar to that reported in previous studies [1, 12, 15]. These findings suggest that the tumour had already metastasised from the pelvic organs at the time of surgery. With resection alone, 16 cases (9.1%) developed pelvic recurrences and 49 (28%) developed distant metastases ($P > 0.05$). The recurrence rate in the pelvis was the same whether radiotherapy was used or not, reflecting the poor radiosensitivity of uterine sarcoma in general.

The role of chemotherapy and the response of sarcomas to these agents has not been evaluable in this survey since standardisation of regimens has not been achieved, and small numbers were treated.

DISCUSSION

The incidence, patient background and presentation described here are compatible with those of other reported series [6, 16, 17], though in some MMT is more common than LMS [12].

The overall 5-year survival was 31%. As in other gynaecological malignancies, tumour stage was the main prognostic indicator. Not only did the spread of the tumour affect prognosis, but the size of the primary tumour did also [18].

Increasing age was closely associated with decreased survival. Postmenopausal women had a poorer prognosis, even when data was age-corrected [13]. No difference in survival was found between the main histological variants of uterine sarcoma when a univariate analysis was performed. Thus, overall survival for MMT cases was similar to that of other sarcomas despite a tendency towards less differentiation, wider dissemination at the time of diagnosis and a greater age of the patient, the vast majority of whom were postmenopausal. However, multivariate analysis showed that if like cases for age and stage were compared then MMT carried a better prognosis than LMS.

It has been suggested that MMT are more likely to develop following irradiation than other forms of sarcoma [7]. In this series, a high proportion of the cases that occurred following pelvic irradiation (13 of 21) were MMT. Thus, pelvic irradiation would appear to be a possible factor in the development of such tumours, although in this study, the majority of such cases followed irradiation for benign conditions. This is in contrast to a previous report [8].

It has been shown that 35–37% stage I–II sarcomas have positive pelvic lymph-nodes, with 14.3% having aortic lymph-node involvement [6]. In some series as many as 45% of stage I sarcomas had lymph-node metastases to both pelvic and para-aortic nodes [19]. This high rate of nodal involvement was associated with deep myometrial invasion, uteri sounding larger than 8 cm, patients older than 65 years and LMS tumours [19].

However, metastatic disease at distant sites including the lungs, brain, heart, kidney and bone has been shown to be independent of para-aortic nodal metastases or intraperitoneal disease [20]. Hematogenous spread best explains this metastatic pattern. This combination of early lymphatic and hematogenous spread renders adjuvant pelvic irradiation of little value in terms of long-term survival. Pelvic recurrences have been shown to be reduced by pelvic irradiation [14, 15], but these studies failed to demonstrate an improved survival. The response of some MMT patients to radiotherapy means that this therapy may be worthwhile, and evidence of an improved survival in these cases has been documented [21]. However, even if the tumour was radiosensitive, spread beyond the pelvis in the majority of tumours would render such therapy ineffective. Chemotherapy would be the only hope of affecting these metastasised tumour cells.

Although doxorubicin is considered to be the most active single agent in the treatment of adult soft tissue sarcomas, the drug has only limited activity in uterine sarcomas. On the other hand, cisplatin is inactive in soft tissue sarcomas, but activity has been reported in uterine sarcomas [22–25]. Single agent activity has been noted with doxorubicin, methotrexate and cisplatin (5–11% response rate) [26]. Increasing the dosages of single agent drugs causes more severe side-effects and toxicity without increasing the response rate. Effective combination regimes include cyclophosphamide, vincristine, doxorubicin and dacarbazine (CYVADIC, 23% response), cisplatin and dacarbazine (21% response) vincristine, actinomycin and cyclophosphamide (VAC, 18% response) and cyclophosphamide, hexamethylmelanine, doxorubicin and cisplatin (CHAP-5, 80% response in 6 MMTs) [22, 26]. There is no apparent difference in response rate among the various histological types [26]. However, the results from various studies are inconclusive with regard to the benefit to be derived from such treatment. Some series suggested that, like pelvic radiotherapy, chemotherapy reduces recurrence rates without influencing survival [27–29]. One series suggested that recurrence rates are not reduced using chemotherapy [30]. However, single agent cisplatin has been reported to have a beneficial effect in advanced and recurrent MMTs [23–25] and preliminary studies have suggested that adjuvant VAC in stage I uterine sarcoma may be of benefit [31].

In view of the recurrence patterns in uterine sarcoma, it would seem that if progress is to be made with regard to patient survival, chemotherapy will have a large part to play. However, prospective controlled trials with adequate patient numbers are rare, in part due to the rarity of the tumour. Such trials will need to be organised on a multicentre basis to attain statistically evaluable numbers of patients in a reasonable length of time (e.g. the EORTC Soft Tissue Sarcoma Trial). In addition, active drug combinations need to be sought for this aggressive tumour.

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