Prophylactic pelvic irradiation as part of primary therapy in uterine sarcomas

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Abstract. In a complete geographic series of 155 cases of primary uterine sarcomas, prophylactic pelvic irradiation was used as standard postoperative therapy in the majority of the cases. Vaginal brachytherapy was also added as a boost. The histology was leiomyosarcoma in 62 cases (40%), carcinosarcoma in 60 (39%), endometrial stromal sarcoma in 25 (16%), and other types in 8 cases (5%). The primary surgery was extended hysterectomy in 11 cases (7%), simple hysterectomy in 110 (71%), and supravaginal hysterectomy in 12 (8%). In 22 cases (14%) no major surgery was possible. In the complete series, 62 recurrences (40%) were recorded. Local (9%), regional (9%), and distant recurrences (28%) were the most frequent. The type of surgery was associated with the risk of tumor recurrence. Extended surgery reduced the risk of local and regional recurrences. The 5-year overall survival rate was 42% and the recurrence-free survival (RFS) was 37%. The number of mitoses was significantly (P=0.007) associated with survival. The locoregional RFS rate was 75% for patients treated with adjuvant irradiation and 83% for patients treated with primary surgery alone. Serious late tissue reactions from the bladder and intestine occurred in 7% of the irradiated cases. The locoregional tumor control rate was high in this series of patients, but no significant difference was found between patients treated with surgery alone and surgery plus postoperative pelvic irradiation. This was true for all histological subtypes of the uterine sarcomas. However, this was not a randomized study and selection bias cannot be ruled out.

Introduction

Uterine sarcomas are rare tumors and represent about 1% of all gynecological malignancies and 2-5% of all uterine malignancies (1,2). The incidence of sarcomas of the uterus reported in the literature is 1.7 per 100,000 women (2). The mean age of patients varies with the histology type. Patients with carcinosarcomas are significantly older than patients with other histological types of sarcomas. Mixed mullerian mesodermal tumors (MMMT; carcinosarcomas) are most frequent, followed by leiomyosarcomas (LMS) and endometrial stromal sarcomas (ESS). Other rare types (rhabdomyosarcomas, liposarcomas, chondrosarcomas, undifferentiated sarcomas) account for less than 5% of uterine sarcomas (3). The overall prognosis for all stages of primary uterine sarcomas is unfavorable and the 5-year survival rate is reported to be as low as 30-40% (4). Approximately 50% of patients with uterine sarcomas present with FIGO stage I disease at diagnosis. Advanced stages (FIGO III-IV) are recorded in 40% of the tumors (5). Uterine sarcomas spread hematogenously (6), and the prognosis in advanced stages is extremely poor. However, the rate of recurrence is also high (40-60%) in early stage disease (FIGO stage I-II) (7-10). In 35% of cases the recurrences are localized in the pelvis and in 65% as distant metastases (8).

Surgery is the cornerstone in the treatment of uterine sarcomas (11). Extended, radical surgery is not routine (12), and the value of pelvic and paraaortic lymphadenectomy has been questioned (7,9). Residual tumor seems to be an important prognostic factor (7,13,14). The benefits of postoperative radiotherapy and chemotherapy are still under debate (5,7,11,15-17). Tumor stage, patient age, parity, histology type and mitotic count are known prognostic factors (8,9,18). Depth of myometrial invasion, tumor grade, and lymphovascular space invasion and residual disease are probably also significant prognostic factors (7,19).

In the present retrospective study postoperative adjuvant pelvic radiotherapy was standard and an integrated part of the primary treatment of all uterine sarcomas for a long period of time. Chemotherapy was not used in the adjuvant setting. The clinical outcome is presented for a large series of sarcomas with this treatment concept. Recurrences, progression-free survival and overall survival are presented as well as side effects related to the combined treatment with surgery and pelvic irradiation.

Patients and methods

A complete geographic series of uterine sarcomas in FIGO stages I-IV, treated during the years 1975-2003 in the Örebro medical region, in central Sweden, was used in a retrospective study, evaluating the extent of surgery and postoperative

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Table I. Tumor characteristics of the complete series (n=155).

Tumor characteristics	Number	Percent
Stage		
I	95	61.3
II	1	6.4
III	26	16.8
IV	24	15.5
Histology		
Leiomyosarcomas	62	40.0
Endometrial stromal sarcomas	25	16.1
Carcinosarcomas	60	38.7
Other types[a]	8	5.2
Mitoses per 10 HPF		
1-5	9	5.8
6-10	21	13.5
11-20	14	9.0
21-30	19	12.2
>30	7	4.5
Unknown	85	54.8

[a]Rhabdomyosarcomas, adenosarcoma, unspecified sarcoma. HPF, high-power fields.

Table II. Surgical techniques used in the complete series.

Surgical technique	Number	Percent
Type of surgery		
Radical hysterectomy	11	7.1
Total hysterectomy	110	71.0
Supravaginal hysterectomy	12	7.7
Multiple excisions	3	1.9
No surgery	19	12.3
Surgical outcome		
Radical surgery	102	65.8
Uncertain radicality	2	1.3
Non-radical surgery	32	20.6
No surgery	19	12.3
Lymph node dissection		
Yes	11	7.1
No	144	92.9

adjuvant radiotherapy. In all, 155 patients were included in the study (Table I). The mean age of the patients was 64.5 years (range 31-94 years). All histological slides were reviewed at the Department of Pathology, Örebro University Hospital. Ninety-five tumors were in FIGO stage I (61%), 10 in stage II (6%), 26 in stage III (17%), and 24 in stage IV (15%). The primary surgery was total abdominal hysterectomy in 110 cases (71%), supravaginal hysterectomy in 12 cases (8%) and Wertheim-Meigs surgery in 11 cases (7%). In 22 cases (14%) only multiple biopsies were taken due to advanced disease (Table II). The surgery was performed at three departments of gynecology and obstetrics, but all patients were then referred to the Department of Gynecological Oncology, Örebro University Hospital, for postoperative evaluation and treatment. The time interval between surgery and external beam radiotherapy was 4-6 weeks. The main type of radiotherapy was adjuvant pelvic irradiation. Two- or four-field techniques were used. Photon beams were used for treatment daily, 5 days a week. The doses and fractionation of radiotherapy are presented in Table III. All patients treated with external beam therapy also received intracavitary vaginal brachytherapy as a boost to the upper two-thirds of the vaginal walls. The dose per fraction varied from 2.5 to 7.0 Gy (specified at 5 mm below the surface of the vaginal wall). The number of fractions varied from 2 to 6. Most treatments were given on an outpatient basis.

Table III. Radiotherapy types, targets and schedules used in the complete series.

Radiotherapy	Number	Percent
Type		
Postoperative	97	62.6
Preoperative	11	7.1
None	47	30.3
Target		
Whole abdomen	3	1.9
Lower abdomen	9	5.8
Pelvis (A-P fields)	58	37.4
Pelvis (4 fields)	38	25.2
Schedule		
1x1.4 Gy x14[a]	3	2.8
1x1.8 Gy x22[b]	9	8.3
1x2.0 Gy x20[c]	48	44.4
1x2.0 Gy x23[c]	30	27.8
1x2.0 Gy x25[c]	12	11.1
Other schedules	6	5.6

[a]Whole abdominal A-P fields, [b]lower abdominal A-P fields, [c]pelvic fields.

All patients were followed-up for at least 10 years and no cases were lost in follow-up. The mean follow-up time was 160 months (range 21-367 months). During all visits symptoms and signs related to the therapy were recorded.

The first follow-up visit was after 1 month, then every 3 months during the first year, every 4 months during the second and third years, every 6 months up to five years and then annually up to 10 years. All data were collected in a computerized database at the Department of Gynecological Oncology, Örebro.

In the statistical analyses, survival curves were generated using the Kaplan-Meier technique and differences were tested with the Chi-square or log-rank tests. The Chi-square

Table IV. Sites of recurrences.

Site	Number	Percent[a]
Vagina	4	2.6
Pelvis	6	3.9
Abdomen	12	7.7
Liver	5	3.2
Lung	37	23.9
Bone	7	4.5
CNS	1	0.7
Site	**Number**	**Percent[b]**
Local	8	12.9
Regional	10	16.1
Distant metastases	35	56.5
Local + regional	1	1.6
Local + distant	5	8.1
Regional + distant	3	4.8

[a]Percent of all patients (n=155). [b]Percent of all recurrences (n=62).

Table V. Type of surgery and tumor recurrences.

Type of surgery	Number	Percent
Complete series (n=155)[a]		
Radical hysterectomy	2/11	18.2
Simple hysterectomy	53/110	48.2
Supravaginal hysterectomy	2/12	16.7
No surgery	4/22	18.2
Stage I-II (n=91)[b]		
Radical hysterectomy	2/8	25.0
Simple hysterectomy	40/78	51.3
Supravaginal hysterectomy	2/5	40.0

[a]Pearson Chi-square =12.378, P=0.006. [b]Pearson Chi-square =2.155, P=0.340.

test was also used for comparison of the proportions and the independent t-test and ANOVA statistics were used to compare the means. Logistic regression analysis was used in multivariate analyses of the risk of tumor recurrences and late tissue reactions. P-values <0.05 were regarded as statistically significant. The Statistica (StatSoft Inc., Tulsa, AZ, USA) software package (version 7.1, 2005) was used for the statistical analyses.

Results

In the complete series of 155 uterine sarcomas 62 recurrences (40.0%) were recorded. Local and regional (pelvic lymph nodes) recurrences were each recorded in 9% of cases, and distant metastases in 28% (Table IV). The median time from treatment to recurrence was 12 months. Type of surgery was associated with the risk of tumor recurrence. More extensive surgery (Wertheim-Meigs) was associated with fewer recurrences than conventional hysterectomy with bilateral salpingo-oophorectomy. Supravaginal hysterectomy did not seem to further deteriorate local tumor control in stage I sarcomas (Table V). The surgery was radical (tumor-free margins) in 102 cases (75%), non-radical in 32 cases (24%) and with uncertain surgical margins in 2 cases (1.5%). Pelvic lymph node dissection was performed in only 11 patients (8%) as part of Wertheim-Meigs surgery, but this extensive procedure was not standard treatment in this series of uterine sarcomas. In 19 cases no surgery was performed.

Table VI. Tumor recurrences (all sites) versus radiotherapy in stages I-II.

Radiotherapy	Number	Percent
Complete series (n=105)[a]		
Radiotherapy	41/83	49.4
No radiotherapy	8/22	36.4
Leiomyosarcomas (n=40)[b]		
Radiotherapy	16/30	53.3
No radiotherapy	4/10	40.0
Carcinosarcomas (n=40)[c]		
Radiotherapy	20/36	55.6
No radiotherapy	2/4	50.0
Endometrial stromal sarcomas (n=21)[d]		
Radiotherapy	3/14	21.4
No radiotherapy	2/7	28.6

[a]Pearson Chi-square =1.187, P=0.276. [b]Pearson Chi-square =0.533, P=0.465. [c]Pearson Chi-square =0.045, P=0.832. [d]Pearson Chi-square =0.131, P=0.717.

Radiotherapy was administered in 109 cases (70%) in total. In 97 cases (63%) it was administered as postoperative adjuvant therapy, and in 12 cases (8%) as preoperative radiotherapy with curative intent. In 46 cases (30%) no radiotherapy was given. Whole abdominal irradiation was used in 3 cases, lower abdominal irradiation in 9 cases and pelvic irradiation (A-P fields or 4-field technique) in 96 cases (88%). In 101 cases (65%) brachytherapy was added to the external beam therapy. In 87 cases (56%) vaginal irradiation was added as part of the postoperative radiotherapy, and in 14 cases (9%) intrauterine irradiation was given as preoperative therapy or as a definitive local therapy in cases with a remaining uterus.

All types and sites of tumor recurrences (Table VI) as well as local and regional tumor control and the risk of recurrences were similar for cases treated with adjuvant radiotherapy and for cases treated with surgery alone in stages I-II (Table VII). The odds ratio for locoregional recurrences in stage I (all histological types) was 0.91 (95% CI: 0.26-3.19) for adjuvant radiotherapy versus surgery alone. Distant metastases were slightly more frequent, but

Table VII. Locoregional recurrences versus radiotherapy in stages I-II.

Radiotherapy	Number	Percent
Complete series (n=105)[a]		
Radiotherapy	14/83	16.9
No radiotherapy	4/22	18.2
Leiomyosarcomas (n=40)[b]		
Radiotherapy	5/30	16.7
No radiotherapy	2/10	20.0
Carcinosarcomas (n=40)[c]		
Radiotherapy	8/36	22.2
No radiotherapy	1/4	25.0
Endometrial stromal sarcomas (n=21)[d]		
Radiotherapy	0/14	0.0
No radiotherapy	1/7	14.3

[a]Pearson Chi-square =0.021, P=0.884. [b]Pearson Chi-square =0.058, P=0.810. [c]Pearson Chi-square =0.159, P=0.900. [d]Pearson Chi-square =2.100, P=0.147.

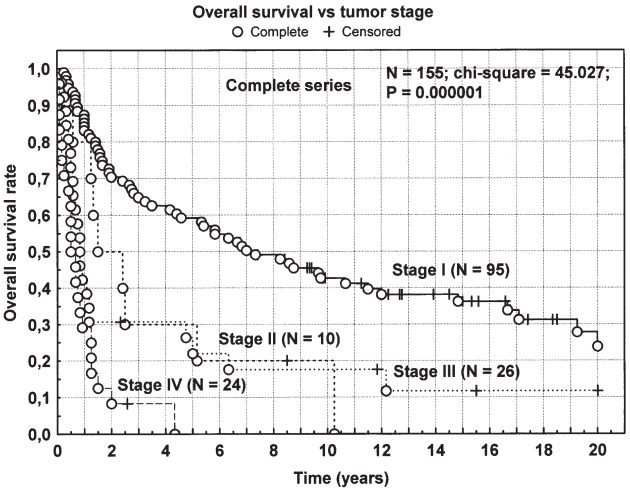

Figure 1. The overall survival rate versus tumor stage in the complete series (n=155).

not statistically significant, in the radiotherapy group and this was true for all histological types. The odds ratio for distant metastases in stage I (all histological types) was 2.06 (95% CI: 0.67-6.33) for adjuvant radiotherapy versus surgery alone. This may reflect a selection bias with regard to radiotherapy. Age was not associated with the risk of any type of tumor recurrence (OR=1.00; P=0.951).

The 5-year overall survival rate for the complete series was 42%. In stage I the survival rate was 59% and in stage II 30% (Fig. 1). In the complete series 95 patients (61%) died due to their sarcomas and 19 patients (12%) due to other, non-sarcoma related, diseases. The 5-year recurrence-free survival (RFS) rate was 37%. In stages I-II the RFS was

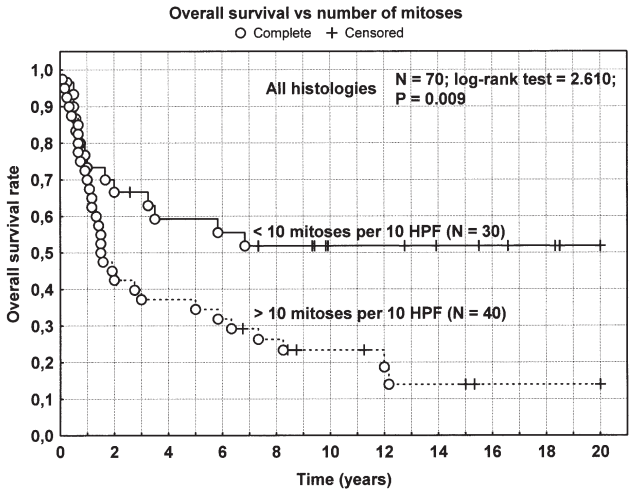

Figure 2. The recurrence-free survival rate versus number of mitoses in evaluable cases (n=70).

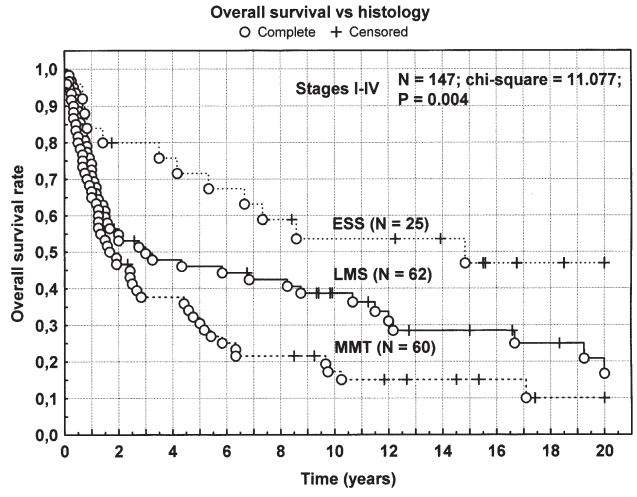

Figure 3. The overall survival rate versus type of histology in the complete series (n=147).

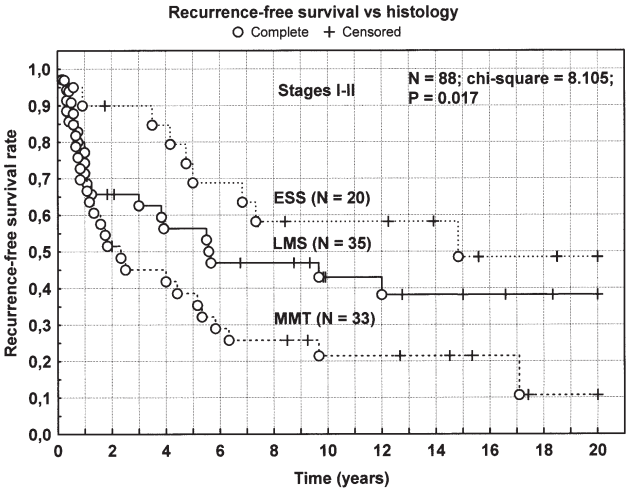

Figure 4. The recurrence-free survival rate versus histology type in the series of stage I-II tumors (n=88).

Table VIII. Radiation reactions (n=109).

Radiation reactions	Number	Percent
Early		
Intestinal grade 1 (diarrhea)	84	77.1
Intestinal grade 2 (diarrhea with blood)	1	0.9
Late		
Intestinal grade 1 (diarrhea)	14	12.8
Intestinal grade 2 (diarrhea with blood)	10	9.2
Intestinal grade 3 (strictures)	5	4.6
Intestinal grade 4 (fistulas)	2	1.8
Bladder grade 2 (hematuria)	2	21.8
Bladder grade 3 (fistula)	1	0.9

51%, and in stages III-IV the progression-free survival was only 8%. The 5-year pelvic disease control was 81% in stage I, 80% in stage II, and 58% for more advanced stages. The number of mitoses was associated with the recurrence-free and overall survival rate (Fig. 2). The most efficacious cut-off level for the number of mitoses was 10 per 10 high-power fields (HPF). Carcinosarcomas showed a higher mitosis density (80% >10 mitoses/HPF) than leiomyosarcomas (53% >10 mitoses/HPF) and stromal cell sarcomas (45% >10 mitoses/HPF). The mean number of mitoses per 10 HPF was significantly different for the various types of sarcomas (ANOVA analysis; P=0.043). The mean number of mitoses per 10 HPF was 16.5 for leiomyosarcomas, 20.3 for endometrial stromal sarcomas and 30.1 for carcinosarcomas. In stages I-II, type of surgery (radical hysterectomy, conventional total abdominal hysterectomy or supravaginal hysterectomy) was associated with recurrence rate. The overall recurrence rate was 25% after Wertheim-Meigs surgery but 50% after ordinary total hysterectomy and bilateral salpingo-oophorectomy or supravaginal hysterectomy. This difference was not statistically significant (Pearson Chi-square; P=0.175), however probably due to the small number of patients (n=8 in FIGO stages I-II) in the extended surgery group.

In the complete series the locoregional recurrence-free survival rate was 75% for patients treated with adjuvant irradiation and 83% for patients treated with surgery alone. For patients with stage I tumors the corresponding figures were 81 and 82%, respectively.

There was a statistically significant difference (P=0.004) in overall survival with regard to the histological type of the sarcoma (Fig. 3). Endometrial stromal cell sarcoma cases had the best survival (71% 5-year survival) and carcinosarcoma cases (mixed mullerian tumors) the worst (30% 5-year survival) with leiomyosarcoma cases in between with a 47% overall survival rate. Recurrence-free survival was also highly significantly (P=0.017) different for the three main types of uterine sarcomas in the complete series and also for stage I-II tumors (Fig. 4). The stage distribution was different (P=0.007) for endometrial stromal sarcomas (84% stage I) and for leiomyosarcomas (65% stage I) and carcinosarcomas (53% stage I).

Postoperative complications were not recorded in this series. Acute tissue reactions during irradiation were common, e.g. diarrhea, and were recorded in 55% of the cases. Late tissue reactions after irradiation (any type and grade) were recorded in 30 cases (19%). In 8 cases (7%) serious late reactions from the intestine or bladder, e.g. strictures or fistulas, were recorded (Table VIII).

Discussion

Uterine sarcomas belong to a heterogeneous group of female malignancies with unfavorable prognosis despite the fact that 50% of cases are diagnosed in stage I, and a consensus on standardized treatment is still lacking. Surgery is a cornerstone in primary therapy but the extent of surgery and the value of lymph node dissection have been under debate (7,20,21). The value of adjuvant postoperative therapy is even more controversial and this is true for both radiotherapy and chemotherapy (17,22). A number of non-randomized, retrospective studies have suggested the benefit of radiotherapy, especially with regard to local and regional tumor control (5,23-29). In a number of other studies no convincing improvement in tumor control or survival rate was shown (30,31). Over the years, interest has been focused on the role of chemotherapy both as an adjuvant treatment and in combination regimens (16,32-35). The problem is the same as for radiotherapy with diverging results and conclusions from existing studies, including both randomized and non-randomized trials (7,36). Postoperative sequential treatment with chemotherapy and radiotherapy has also been proposed (37). Palliative chemotherapy for patients with advanced, unresectable disease who are symptomatic is a reasonable treatment (38). Uterine sarcomas spread hematogenously, but the rate of locoregional recurrences is also high (40-60%), even in early stages. The concept of pelvic and vaginal irradiation is therefore of interest and should be further evaluated. Since more than 60% of recurrences are distant metastases adjuvant chemotherapy is also worthwhile as a single treatment or in combination with radiotherapy.

In the present retrospective study a large series of uterine sarcomas were treated with primary surgery and postoperative adjuvant pelvic radiotherapy as the main line. A smaller number of the patients did not receive any radiotherapy. Since this study was not randomized this smaller group of patients may not be comparable with respect to a number of background factors when compared with the main group receiving radiotherapy. Due to primary advanced disease a smaller number of patients did not undergo primary surgery, but only palliative measures.

Tumor stage, histology type and number of mitoses were confirmed to be important prognostic factors in this series. Age was not a significant prognostic factor, however. Extended surgery according to Wertheim-Meigs seems to be of benefit compared with conventional total abdominal hysterectomy or supravaginal hysterectomy performed in certain cases with an unknown primary diagnosis. Adjuvant postoperative pelvic irradiation with or without vaginal irradiation was part of standard therapy in this series of patients. In a retrospective series like this it is difficult to

evaluate the additive value of this type of radiotherapy. The results for the complete series can be presented as the outcome for patients treated according to this concept of primary surgery and postoperative adjuvant radiotherapy. The outcome data, e.g. recurrence rate, recurrence-free and overall survival rate compare well with data presented from other studies in the literature. The 5-year pelvic disease control was 80% in stage I-II compared to 67% in a series from France reported on by Benoit *et al* (11). However, the prognosis is still poor for this group of patients and this is especially true for women with carcinosarcomas showing a 5-year overall survival rate of only 30%. Since a small group of patients did not receive radiotherapy in this series, a comparison was made of the outcome for this subgroup and for patients treated according to the standard protocol for this time period. No significant differences were found between these groups with regard to tumor control, recurrences or survival. Even after correction for differences with regard to tumor stage, histology, and number of mitoses (Cox multivariate analyses) no differences appeared. Local and regional tumor control and recurrences were also similar for these groups. For high-risk endometrial carcinomas it has been shown that the addition of chemotherapy to postoperative pelvic radiotherapy significantly increased the survival rate in a randomized multicenter study. Since carcinosarcomas are thought to belong to endometrial carcinomas and constitute a new high-risk group within this diagnosis, a combination of radiotherapy and chemotherapy is probably the treatment choice for this group until further studies are available (39). Leiomyosarcomas and endometrial stromal cell sarcomas are separate entities and they should probably be treated according to other, and diagnosis specific, protocols. Radiotherapy increased early and late tissue reactions and side effects but was overall rather well tolerated. In this series as in others, 5-10% serious late radiation reactions from bladder and intestine were expected to occur.

Further studies are needed to define the role of radiotherapy, but also chemotherapy, and a combination of both. More attention must also be paid to vaginal brachytherapy and in some cases external beam therapy may be omitted or perhaps replaced by chemotherapy. Hormonal therapy (40,41) and targeted drug therapy (42,42) should be further evaluated in forthcoming trials. The different types of uterine sarcomas should be studied separately and carcinosarcomas studied together with high-risk endometrial carcinomas.

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