original article

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Impact of adjuvant treatment modalities on the management of patients with stages I–II endometrial stromal sarcoma

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Purpose: To explore whether adjuvant treatment options may impact on the prognosis in localized endometrial stromal sarcomas (ESSs; stages I and II). The historical options usually discussed in addition to hysterectomy and bilateral salpingoophorectomy (BSO) are active surveillance, pelvic radiotherapy, chemotherapy and hormonal therapy, alone or in combination.

Patients and methods: Among 84 consecutive patients treated for ESS at a single referral center, 54 with localized stage disease were identified. Recurrence-free survival and overall survival were estimated and patterns of recurrences described. Univariate and multivariate analyses were carried out.

Results: With a median follow-up of 58 months, only one patient had died. None of the 23 patients who had received adjuvant therapy relapsed compared with 13 of 31 patients who had not received any adjuvant therapy. Adjuvant treatments were hormonal therapy (n = 10) and brachytherapy with/without pelvic radiotherapy (n = 13). Almost the majority of relapses were local (92%) and extra-pelvic metastasis was observed in nearly half of the patients (46%). In the multivariate analysis, the major determinants of relapse-free survival were adjuvant treatment, myometrial invasion (P = 0.005) and no BSO (P = 0.005).

Conclusions: In this series, adjuvant treatment of localized ESSs was associated with the absence of recurrence.

Key words: adjuvant treatment, endometrial stromal sarcoma, hormonal therapy, prognosis, radiotherapy, recurrence

introduction

Endometrial stromal sarcomas (ESSs) are rare uterine malignancies that account for <0.5% of all malignant uterine tumors and for ∼7% to 17% of uterine sarcomas [1, 2]. ESS develops in the mesenchymal stroma of the endometrium and belong to the endometrial stromal tumors group, classified by the World Health Organization (WHO) (2003) as follows: endometrial stromal nodules (the benign lesion), ESSs (previously referred as low-grade ESSs) and undifferentiated uterine sarcomas (UUSs) (previously referred as high-grade ESSs) [2–4]. The histologic classification is on the basis oftumor differentiation and similarity with endometrial stroma. The other major histologic criteria are the intensity of the nuclear atypia, mitotic count and tumor cell necrosis [2, 3, 5]. Whereas UUSs tumors exhibit highly aggressive features, ESSs are characterized by their indolent evolution and their hormonosensitivity.

Surgery combining total abdominal hysterectomy and bilateral salpingooophorectomy (BSO) is the cornerstone of treatment of localized ESS (stages I–II). However, some authors observed similar recurrence rates in women with and without BSO, creating controversies about leaving ovaries *in situ*, especially in young premenopausal women [6–8]. ESSs often express a high level of estrogen and/or progesterone receptors and are reported to respond to hormonal therapy [8, 9]. Given the rarity of the disease, the impact of firstly surgical castration and secondly adjuvant treatment modalities, including hormonal therapy, chemotherapy and radiotherapy, need to be assessed further, especially for patients with stages I–II disease, where recurrence rates range between 18% and 45% [10–12].

Currently, there is no standard approach for the management of patients with localized stage. Some authors recommend adjuvant treatments and others prefer ovarian-sparing surgery without adjuvant therapy [11, 13]. The historical options usually discussed in addition to hysterectomy and BSO are active surveillance, pelvic radiotherapy, brachytherapy, chemotherapy and hormonal therapy, alone or in combination.

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Reasons for heterogeneous treatments were related to the lack of a consensus about the optimal adjuvant treatment and the evolution of treatments during the last 30 years. In routine practice, there are no clear indications for adjuvant chemotherapy or hormonal therapy in ESS. Since 1984, adjuvant radiation has been reported to reduce the incidence of local recurrences [14]. Objective responses to hormonal therapy in the metastatic setting, particularly with megestrol acetate, have been reported since 1982 [15]. The efficacy of antiaromatase inhibitors was first described in 2001 [9]. In the present study, we retrospectively analyzed the records of 54 ESS patients with stages I–II disease and explored the impact of surgical/medical treatment modalities in a single institution.

patients and methods

patient population

We conducted a retrospective chart review through the Institut Gustave Roussy tumor registry for ESS cases treated in our institution from 1 January 1977 to 31 December 2007. Eighty-four patients with a pathological diagnosis of ESS were identified at our institution. As a referral center for sarcomas, patients were referred after initial primary surgery or at relapse.

Demographic information, pathology, risk factors, the surgical procedure, postoperative treatment, time to recurrence and the site of local recurrences and/or metastases were extracted from the medical records. When necessary, follow-up was ensured by personally contacting the patients, the patients' families or family physicians. Pathology slides were centrally reviewed by two pathologists who were unaware of the clinical outcome, for the WHO Classification and for the expression of estrogen and progesterone receptors. Clinical staging of disease was carried out using the International Federation of Gynecology and Obstetrics (FIGO) staging classification: stage I, sarcoma confined to the uterine corpus; stage II, sarcoma confined to the corpus and cervix; stage III, sarcoma confined to the pelvis and stage IV, extra-pelvic disease.

adjuvant treatments

Different adjuvant treatments had been administered over the 30-year period. For hormonotherapy, there has been a shift in adjuvant hormonal treatment since 2001. Before 2001, adjuvant treatment consisted of megestrol acetate. After 2001, adjuvant therapy consisted of anti-aromatase inhibitors, which gives rise to fewer side-effects.

statistical methods

Statistical analysis was carried out with SAS 9.1 software. Association between factors was assessed by chi-square tests or Fisher's exact test. Median follow-up was estimated using the Schemper's method. Overall survival (OS) was defined as the interval between the diagnosis of ESS and death resulting from any cause. Recurrence-free survival (RFS) was defined as the interval between the diagnosis of ESS and recurrence or death from any cause. The OS and RFS were estimated using the Kaplan–Meier method. The duration of local control was measured as the interval between the diagnosis and local or locoregional recurrence, a competing event, or the most recent follow-up. Competing events included distant recurrence and death before local failure. The duration of distant control was defined as the interval between the diagnosis and distance recurrence. To determine the independent prognostic significance of factors survivals, multivariate analysis was conducted using the Cox proportional hazards regression method.

results

patient characteristics

Among 84 women identified with ESS, 54 with stages I–II disease were eligible for the study. Forty-eight patients had stage I and six patients had stage II disease. The median age of patients was 47 years (range 25–73 years). Forty-one (76%) of the 54 patients were premenopausal. Tumors were typically discovered incidentally after a resection for uterine fibromas (50%), during exploration of non-specific menometrorrhagia (39%) and/or abdominal pain (11%). Positive estrogen and/or progesterone receptors were detected in all tested specimens.

primary treatment

Forty-eight patients (89%) had undergone total abdominal hysterectomy with a BSO, and six patients (11%) had undergone a total abdominal hysterectomy without BSO. Two patients had positive microscopic surgical margins. None of the four patients who had undergone a pelvic lymphadenectomy had positive pelvic lymph nodes. Patient characteristics are detailed in Table 1.

Adjuvant treatment options used were hormonal therapy or pelvic radiotherapy with/without brachytherapy. The characteristics of these patients according to the adjuvant treatment realized are reported in Table 2. Age was the only

Table 1. Clinical and hormonal receptor features of patients

	ESS ($n = 54$)	Percentage
Menopausal status		
Premenopausal	41	76
Postmenopausal	13	24
Modified FIGO stage		
I	48	89
II	6	11
Hysterectomy		
With BSO	49	91
Without BSO	5	9
Pelvic lymphadenectomy		
Yes	4	7
No	50	93
Myometrial invasion		
None	30	56
≤50%	13	24
>50%	11	20
Positive surgical margins		
Yes	2	4
No	52	96
Hormonal receptors		
Estrogen (O) +	34	87
Progesterone (P) +	34	87
O and/or P +	39	100
Missing	17	–
Hormonal replacement treatment after surgery		
Yes	4	7
No	49	93

n, number of patients; BSO, bilateral salpingooophorectomy; ESS, endometrial stromal sarcoma; FIGO, International Federation of Gynecology and Obstetrics.

significant factor associated with the administration of adjuvant therapy (Table 2). Among the 54 patients, 30 had undergone surgery alone without adjuvant treatments, 14 patients had received brachytherapy and/or pelvic radiotherapy and 10 patients had received hormonal therapy (Table 3). Among the five patients who had not undergone BSO, three were premenopausal and two were menopausal women and had started hormonal replacement treatment (HRT) after surgery.

Four of 30 patients who had undergone a surgery alone had received HRT. Among these patients, two menopausal women had undergone a hysterectomy without BSO and two premenopausal patients had undergone a hysterectomy with BSO. There were no grades III and IV toxic effects related to radiotherapy.

Table 2. Characteristics of patients according to adjuvant treatment

	No adjuvant treatment	Adjuvant treatment	*P* value
Menopausal status			
No	24	17	NS
Yes	7	6	
Myometrial invasion			
No	16	14	NS
<1/2	7	6	
≥1/2	8	3	
BSO			
Yes	27	22	NS
No	4	1	
Age			
≤45 years	17	6	0.02
>45 years	13	18	
Positive surgical margins			
No	31	21	NS (0.09)
Yes	0	2	

BSO, bilateral salpingooophorectomy; NS, non significant.

Table 3. Adjuvant treatments in localized stages

Adjuvant treatment status	FIGO stages I–II patients ($n = 54$)		
	Number of patients	Number of recurrences	Hormonal replacement therapy
No adjuvant treatment	31	13	4
Hysterectomy without BSO	5	4	2
Hysterectomy with BSO	26	9	2
Adjuvant treatment			
Brachytherapy and pelvic radiotherapy	10	0	–
Association with cisplatin-based chemotherapy	3	0	–
Brachytherapy alone	1	0	–
Pelvic radiotherapy alone	2	0	–
Hormonal treatments	10	0	–
Antiaromatase inhibitors	6	0	–
Megestrol acetate	4	0	–

FIGO, International Federation of Gynecology and Obstetrics.

recurrence and survival

With a median follow-up of 58 months (range 3–348 months), 13 patients (24%) had relapsed and only 1 patient had died within 24 months from metastatic disease. The 5- and 10-year RFS rates were 73% and 62%, respectively (Figure 1). Currently, 47 of the 54 (87%) patients show no evidence of disease and 6 patients (13%) are alive with evidence of disease. As a result, at 5 and 10 years, OS was 98%.

None of the patients (0/23) who had received adjuvant treatment had relapsed in contrast to 13 of 31 patients who had not received adjuvant treatments (Figure 2). A univariate analysis of prognostic factors for RFS was carried out for the following variables: age, FIGO stage, menopausal status, myometrial invasion, adjuvant treatment, BSO and a surgical microscopic residue (Table 4). Factors associated with poor prognosis in univariate analysis were age ≤45 ($P = 0.02$), myometrial invasion ≥1/2 ($P = 0.04$), no BSO ($P = 0.01$) and no adjuvant treatment ($P = 0.001$). In the multivariate analysis, the factors associated with a poor prognosis were no adjuvant treatment ($P = 0.001$), myometrial invasion ($P = 0.005$) and surgery without BSO ($P = 0.005$).

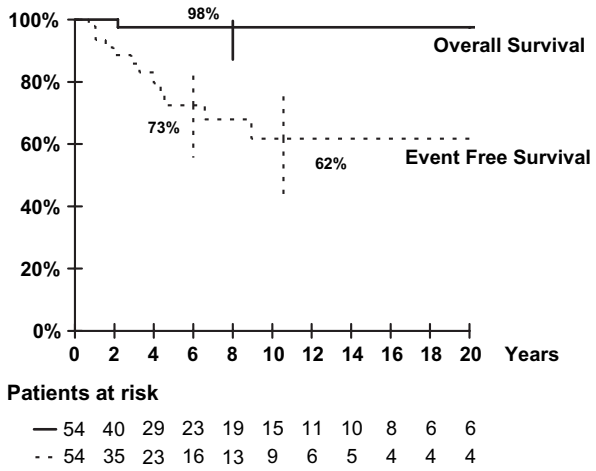

Figure 1. Overall survival and progression-free survival.

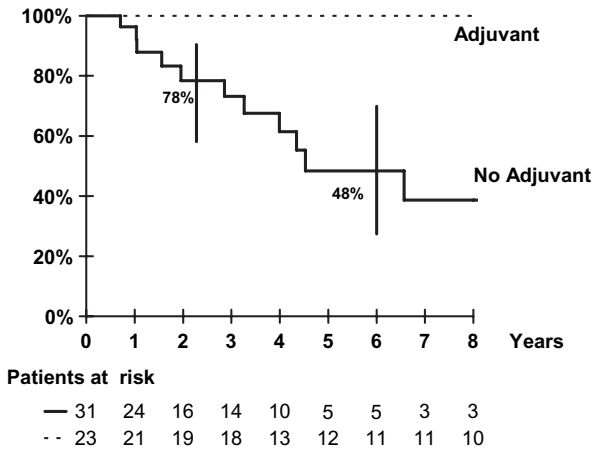

Figure 2. Recurrence-free survival according to adjuvant treatments or not.

Table 4. Prognostic factors for RFS in localized stages

Factors	Number of patients	5-Year RFS (SE)	10-Year RFS (SE)	Univariate analysis (*P*)	Multivariate analysis (*P*)	Hazard ratio	95% Confidence interval
Menopausal status							
No	41	68% (9)	68% (9)	NS	NS	–	–
Yes	13	89% (10)	44% (23)				
Myometrial invasion							
No or <1/2	43	81% (7)	74% (10)	0.02	0.005	1.4–29.5	1
≥1/2	11	43% (19)	–				8.0 (1.9–34.2)
BSO							
No	5	40% (22)	–	0.01	0.005	1.1–31.4	1
Yes	49	77% (8)	72% (9)				8.8 (2.0–39.7)
Age							
≤45 years	23	52% (13)	42% (14)	0.02	NS	0.5–8.7	
>45 years	31	91% (6)	82% (10)				

RFS, recurrence-free survival; SE, standard error.

pattern of recurrences

The sites of the first recurrence among the 13 patients who had relapsed were pelvis alone ($n = 6$), lung alone ($n = 1$) and pelvic ± extra-pelvic sites ($n = 6$). Extra-pelvic sites were peritoneum ($n = 3$), retroperitoneum ($n = 1$), muscle ($n = 1$) and lung ($n = 1$). Of note, the six patients who had relapsed >4 years after surgery had pelvic and extra-pelvic relapses. In contrast, recurrences that had occurred during the 4 years following initial surgery were pelvic alone.

discussion

To our knowledge, this is one of the largest cohorts of localized ESS described to date with a comprehensive review of the clinical course of the disease according to treatment modalities.

Our series corroborates the relatively good outcome of patients with localized-stage disease [16, 17]. Among the 54 patients, only 1 patient had died within 24 months. Our analysis confirms the previous finding that the recurrence rate is relatively high. Relapses may occur late during the clinical course of the disease [10, 17]. Five- and 10-year RFS were 73% and 62%, respectively. A local recurrence was observed in the majority of patients (92%), and extra-pelvic metastases were observed in nearly half of patients (46%) who had relapsed, indicating the existence of initial micrometastases outside the uterus and the treated field. Interestingly, all extra-pelvic metastases had occurred in patients who had developed a late recurrence, defined as a relapse after 4 years from the diagnosis.

We must emphasize the impact of adjuvant treatment on the reduction of relapses. No relapses occurred among the 23 patients who had received adjuvant treatment of stages I–II disease. In contrast, relapses occurred in 13 of 30 patients who had not received adjuvant treatment. The multivariate analysis showed that prognostic factors for recurrence in localized disease were no adjuvant treatment, myometrial invasion and surgery without BSO. These results are in accordance with previous reports that indicate that adjuvant radiotherapy could improve local control but not survival [6, 17]. For example, Li el al. [17] showed that the recurrence rates in stage I ESS patients who did or did not receive adjuvant radiotherapy in addition to surgery were 12.5% and 55.6%, respectively. Of note, only 50.9% of patients in that study had undergone BSO in addition to hysterectomy and only 1 of 37 patients (3%) had died. Moreover, it was reported in other studies that the addition of pelvic radiotherapy to surgery not only decreased pelvic recurrences but also increased survival in patients with stages I and II disease [18, 19]. Mansi et al. [20] proposed adjuvant radiotherapy alone after recurrent ESS.

In the current study, the recurrence rates of ESS with limited myometrial invasion and age > 45 years were 19% and 9%, respectively (Table 4). In the multivariate analysis, only myometrial invasion and surgery without BSO were found as independent factors for recurrence in addition to adjuvant treatments. The outcome of these cases indicates that adjuvant treatment may not be indicated in patients with limited myometrial invasion because of the excellent survival of patients, even after a recurrence. Deep myometrial invasion was previously reported to be a poor prognostic factor for recurrence [21]. According to our results, five of eight patients with deep myometrial invasion who had not received adjuvant treatments developed local and distant recurrences, while none of the three patients who had received adjuvant treatments had relapsed. It could be hypothesized that this subgroup (with deep myometrial invasion) might benefit from adjuvant treatment.

Hormonal therapy is another modality of adjuvant option for ESS because tumors often express estrogen and/or progesterone receptors [22]. Historically, progestins were the agents most used, but the third generation of aromatase inhibitors were reported to be effective in the metastatic setting and were therefore largely used [9, 23]. Tamoxifen is contraindicated because it exerts a proliferative effect on endometrial stroma [24]. Our study showed that no relapses occurred among the 10 patients who had received adjuvant hormonal therapy. Therefore, it could be inferred that hormonal therapies constitute an alternative to pelvic radiotherapy.

Despite its retrospective and non-randomized nature, our series highlights the impact of adjuvant treatment on the recurrence rate, at least in patients with myometrial invasion,

but not on OS. Pelvic radiotherapy with/without brachytherapy or hormonal therapy represents the possible adjuvant therapy options. The high rate of extra-pelvic metastases in localized-stage disease indicates the interest of systemic adjuvant treatment compared with brachytherapy and/or pelvic radiotherapy. Moreover, the high rate of recurrences highlights the importance of closer patient monitoring. However, none of the patients in our series who had received adjuvant radiotherapy relapsed. Therefore, the impact of multimodality treatment should be considered for patients with treatment-naive and recurrent disease.

Finally, no other subject has fueled debate during the last decade as much as the impact of BSO on RFS. Although BSO was not shown to exert an impact on OS in the recent USA population-based analysis, the impact on RFS of ovarian-sparing procedures in stages I–II disease remains contradictory [16]. Like others, our series revealed a higher frequency of recurrence among women who had not undergone BSO in addition to hysterectomy [17]. Moreover, the two menopausal women who received HRT after surgery recurred. These results are not surprising, as we know the influence of hormones in the physiopathology of the disease and the expression of estrogen and/or progesterone receptors. Considering these results, we believe that surgical castration and adjuvant therapies should be discussed with the patient on an individual basis taking into account age and the extent of myometrial invasion.

This retrospective analysis had several important limitations. It spanned nearly a 30-year period, during which progress has been made in the diagnosis and treatment of ESS. Our study population was shaped by the referral of patients with recurrence. Our findings indicate that ESS have unique clinical, pathological and immunohistochemical features and that may have clinical implications. The good outcome observed indicates that adjuvant treatment should be considered to prevent recurrences since half of them occur at extra-pelvic sites and most require further surgery with adjuvant treatment. We advocate the conduct of international trials to refine treatment modalities for these patients. As adjuvant treatment has no effect on OS, progression-free survival should be used as a primary end point.

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disclosure

None of the authors declare conflicts of interest.

references

1. Echt G, Jepson J, Steel J et al. Treatment of uterine sarcomas. Cancer 1990; 66: 35–39.
2. Pautier P, Genestie C, Rey A et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. Cancer 2000; 88: 1425–1431.
3. Norris HJ, Roth E, Taylor HB. Mesenchymal tumors of the uterus. II. A clinical and pathologic study of 31 mixed mesodermal tumors. Obstet Gynecol 1966; 28: 57–63.
4. Oliva E, Clement PB, Young RH. Endometrial stromal tumors: an update on a group of tumors with a protean phenotype. Adv Anat Pathol 2000; 7: 257–281.
5. Leath CA, 3rd, Huh WK, Hyde J Jr. et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. Gynecol Oncol 2007; 105: 630–634.
6. Gadducci A, Sartori E, Landoni F et al. Endometrial stromal sarcoma: analysis of treatment failures and survival. Gynecol Oncol 1996; 63: 247–253.
7. Li AJ, Giuntoli RL, 2nd, Drake R et al. Ovarian preservation in stage I low-grade endometrial stromal sarcomas. Obstet Gynecol 2005; 106: 1304–1308.
8. Chu MC, Mor G, Lim C et al. Low-grade endometrial stromal sarcoma: hormonal aspects. Gynecol Oncol 2003; 90: 170–176.
9. Maluf FC, Sabbatini P, Schwartz L et al. Endometrial stromal sarcoma: objective response to letrozole. Gynecol Oncol 2001; 82: 384–388.
10. Chang KL, Crabtree GS, Lim-Tan SK et al. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol 1990; 14: 415–438.
11. Amant F, De Knijf A, Van Calster B et al. Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. Br J Cancer 2007; 97: 1194–1199.
12. Kim WY, Lee JW, Choi CH et al. Low-grade endometrial stromal sarcoma: a single center's experience with 22 cases. Int J Gynecol Cancer 2008; 18: 1084–1089.
13. Reich O, Regauer S. Hormonal therapy of endometrial stromal sarcoma. Curr Opin Oncol 2007; 19: 347–352.
14. Piver MS, Rutledge FN, Copeland L et al. Uterine endolymphatic stromal myosis: a collaborative study. Obstet Gynecol 1984; 64: 173–178.
15. Gloor E, Schnyder P, Cikes M et al. Endolymphatic stromal myosis. Surgical and hormonal treatment of extensive abdominal recurrence 20 years after hysterectomy. Cancer 1982; 50: 1888–1893.
16. Chan JK, Kawar NM, Shin JY et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer 2008; 99: 1210–1215.
17. Li N, Wu LY, Zhang HT et al. Treatment options in stage I endometrial stromal sarcoma: a retrospective analysis of 53 cases. Gynecol Oncol 2008; 108: 306–311.
18. Weitmann HD, Knocke TH, Kucera H et al. Radiation therapy in the treatment of endometrial stromal sarcoma. Int J Radiat Oncol Biol Phys 2001; 49: 739–748.
19. Vongtama V, Karlen JR, Piver SM et al. Treatment, results and prognostic factors in stage I and II sarcomas of the corpus uteri. AJR Am J Roentgenol 1976; 126: 139–147.
20. Mansi JL, Ramachandra S, Wiltshaw E et al. Endometrial stromal sarcomas. Gynecol Oncol 1990; 36: 113–118.
21. Bodner K, Bodner-Adler B, Obermair A et al. Prognostic parameters in endometrial stromal sarcoma: a clinicopathologic study in 31 patients. Gynecol Oncol 2001; 81: 160–165.
22. Reich O, Regauer S, Urdl W et al. Expression of oestrogen and progesterone receptors in low-grade endometrial stromal sarcomas. Br J Cancer 2000; 82: 1030–1034.
23. Leunen M, Breugelmans M, De Sutter P et al. Low-grade endometrial stromal sarcoma treated with the aromatase inhibitor letrozole. Gynecol Oncol 2004; 95: 769–771.
24. Reich O, Regauer S. Estrogen replacement therapy and tamoxifen are contraindicated in patients with endometrial stromal sarcoma. Gynecol Oncol 2006; 102: 413–414; author reply 414.