

Prognostic factors and outcomes in surgically treated endometrial stromal sarcomas of the uterus. A literature review

Abstract

Endometrial stromal sarcomas (ESS) are rare mesenchymal tumors of the uterus characterized by an indolent behavior and favorable outcomes. However, late recurrence is a common event even in cases diagnosed in an early stage of the disease. The present review presents the largest studies which focused on determining the prognostic factors and outcomes after surgically treated ESS. In this respect, we also presents various answers for the most significant unsolved questions regarding the role of bilateral adnexectomy and the benefits of pelvic and para-aortic lymph node dissection.

Keywords: endometrial stromal sarcoma, bilateral adnexectomy, lymph node dissection, prognostic factors

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Introduction

Endometrial stromal sarcomas (ESS) are rare uterine malignancies arising from the mesenchymal tissues representing up to 0.2% of all uterine malignancies and 20-25% of all uterine sarcomas⁽¹⁾.

Although initially uterine ESS were classified as low and high grade uterine tumors, the differentiation between the two categories being established by a threshold of 10 mitoses/10 HPF, nowadays the notion of ESS refers only to the low grade tumors, the others being categorized as undifferentiated sarcomas⁽²⁾.

This modification was related to the biological behavior and the patterns of spread: low grade ESS originate from endometrial stromal cells in the proliferative phase which invade the tumor borders and behave like a low grade sarcoma associated with potential for local and distant recurrences. High grade sarcomas are usually associated with a more likely invasive pattern of growth with destructive myometrial invasion rather than lymphatic invasion and marked cellular pleomorphism^(3,4).

Prognostic Factors and Outcomes in Surgically Treated ESS

ESS are tumors with indolent behavior and favorable prognosis with 5 year overall survival rates of 80-100%⁽⁵⁾.

However, recurrent tumors are encountered even in patients diagnosed in an early stage of the disease, being encountered in up to one third of the cases^(5,6).

The diagnosis of uterine ESS can be a challenging problem, especially in younger women. In these cases the diagnosis of malignancy might be overlooked preope-

ratively and the patient is usually submitted to surgery on the principles of benignity and the final diagnosis of malignant lesion is given only postoperatively⁽⁷⁾.

When it comes to the most appropriate surgical treatment for cases with uterine confined disease, two different opinions have been proposed: total interadnexial hysterectomy and total hysterectomy with bilateral adnexectomy.

While sustainers of the first category consider that ovarian sparing surgery is safe and does not predispose to an increased recurrence rate^(5,8-12), scientists who sustain total adnexectomy with bilateral adnexectomy showed an unacceptable recurrence rate after ovarian preserving surgery⁽¹¹⁻¹³⁾.

This data are also sustained by other laboratory studies which come to demonstrate the idea that uterine ESS are hormonally sensitive tumors, with a reported estrogen and progesterone receptors of up to 70-95%⁽¹⁴⁻¹⁶⁾.

Bilateral Adnexectomy and Pelvic and Para-aortic Lymph Node Status

Another unsolved question is the necessity and the relevance of lymph-node status^(13,17-19). Although a nodal involvement rate of 33-45% for cases submitted to lymph-node dissection at the moment of primary or secondary surgery, most studies failed to demonstrate a benefit in terms of survival for cases submitted to lymph node dissection⁽¹³⁾.

In Yoon's study the outcomes of 114 patients diagnosed with ESS were retrospectively analyzed⁽²⁰⁾. Preoperatively the initial diagnosis was uterine sarcoma in 11 cases, ESS in 15 cases, while the other 88 cases were

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submitted to surgery for presumptive benign disease including leiomyoma or adenomyosis.

Ninety-two patients were diagnosed in International Federation of Gynecologists and Obstetricians (FIGO) stage I, nine in FIGO stage II, four in FIGO stage III and nine in FIGO stage IV.

At the moment of initial surgery 111 patients underwent total hysterectomy, while in 53 patients bilateral adnexectomy was associated.

Concurrent pelvic and/or para-aortic lymph node dissection was performed in 45 cases, with 3 cases of positive lymph nodes with no other evidence of extra-uterine disease.

Complete R0 resection was performed in 105 patients; adjuvant therapies were administered however in 35 patients of the 105 cases submitted to R0 resection and consisted in chemotherapy in 14 cases, radiotherapy in 11 cases and hormonal therapy in 10 cases.

All the 9 cases in which complete resection were not achieved were submitted to adjuvant chemotherapy. After a median follow up of 46 months, 10 patients were dead of disease: five patients had been initially diagnosed in FIGO stage I, one in stage II, two cases in FIGO stage III and two cases in FIGO stage IV.

The overall recurrence rate was 26.1% and was encountered as it follows: 24 cases in FIGO stage I, 4 cases in FIGO stage II, 2 cases in FIGO stage III and 3 cases in FIGO stage IV. In 51.5% of cases diagnosed with recurrences a pelvic isolated relapse was seen, while in the other 48.5% of cases an association of pelvic and extra-pelvic disease was seen.

In univariate analysis the most significant prognostic factors correlated with an improved survival were an initial early stage of the disease (FIGO stage I versus FIGO stages II-IV, $p=0.006$), hormone receptor status ($p=0.027$) and the absence of lymph node metastases ($p=0.003$).

However, in multivariate analysis none of these factors were statistically significant.

Li et al. included in their study 53 patients diagnosed with stage I ESS. In 37 patients a low grade ESS was found, in 11 cases an undifferentiated ESS was seen while in the other 5 cases the lesions were considered as unclassified⁽¹⁰⁾.

In 23 cases inter-adnexial hysterectomy or total hysterectomy with unilateral adnexectomy were performed 27 cases bilateral adnexectomy was also performed, while the other three cases were submitted to radical hysterectomy with bilateral adnexectomy and pelvic lymph node dissection.

In all cases histopathological studies revealed negative lymph nodes.

Postoperatively 10 cases were submitted to adjuvant chemo-irradiation, 22 cases were submitted solely to adjuvant radiation therapy, 8 cases were submitted to adjuvant chemotherapy while in the other 13 cases no adjuvant therapy was instituted; however the postoperative treatment was administered with no well-defined protocol.

A total of 19 patients developed local or distant recurrence; among patients with ovarian preservation all cases reported recurrences, while among cases submitted to total adnexectomy with bilateral adnexectomy only 22.7% of patients developed recurrent disease ($p<0.001$)⁽¹⁰⁾.

Leath and contributors included in their study 105 patients diagnosed with ESS in five centers and retrospectively reviewed their data⁽²¹⁾.

The main histopathological subtypes included low grade ESS in 72 cases, high grade ESS in 31 cases and unclassified tumors in 2 cases. Early stage of the disease (FIGO stages I and II) were more frequently seen in low grade ESS when compared to high grade ESS (68% vs. 39%, $p=0.002$).

At the moment of surgery a total hysterectomy was performed in all cases. In 64 cases diagnosed with low grade ESS and in all cases diagnosed with high grade ESS bilateral adnexectomy was associated.

Concurrent pelvic lymph node dissection was performed in 23 cases with low grade ESS and 11 cases with high grade ESS while para-aortic lymph node dissection was performed in 23 cases with low grade ESS and 13 cases with high grade ESS.

In both cases with unclassified tumors a total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection were associated. Other concurrent surgical procedures were omentectomy, peritoneal stripping and bowel resection.

The incidence of positive pelvic lymph nodes was higher for cases with high grade ESS when compared to those with low grade ESS (18% vs. 9%, $p=0.44$).

The same correlation was established for positive para-aortic lymph nodes (15% vs. 0%, $p=0.15$).

The median time to recurrence time was 55 months for low grade ESS and 5 months for high grade ESS ($p<0.0001$), while the recurrence rate on the entire cohort was 37%⁽²¹⁾.

Standard Therapeutic Protocol

Due to the paucity of data and inconstant findings among different studies, no standard therapeutic protocol regarding the extent of lymph node dissection has been established.

Owning the fact that most positive lymph nodes were found in cases with gross extra-uterine disease, lymph node dissection has not been recommended for cases diagnosed in early stages.

When it comes to cases diagnosed in advanced stages, it is not clear whether a complete lymph node dissection should be performed or the gesture should be limited to resecting only enlarged lymph nodes^(22,23).

On the other hand, the association of adjuvant therapies, cases presenting significant percents of positive hormone-receptors may be submitted to hormone receptor-targeted treatment^(7,24).

However when hormonal therapy is exhausted or in cases in which complete resection could not be achieved, adjuvant chemotherapy with ifosfamide and doxorubicin based protocols seem to be efficient^(25,26).

Conclusions

ESS represents rare tumors with indolent growth which are classified in low grade and high grade malignancies. Low grade ESS report positive outcomes with high rates of 5 year overall survival and improved results even if late recurrence occur. The standard treatment remains total hysterectomy with bilateral adnexectomy,

although some investigators consider that ovarian preserving surgery does not increase the recurrence rate. Postoperatively adjuvant therapies including hormone receptor targeted therapies, doxorubicin and ifosfamide based chemotherapeutic protocols and even adjuvant radiation therapy might be performed especially in cases diagnosed with high grade ESS. ■

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