

Retrospective analysis of clinical, pathological characteristics and prognosis of the patients with endometrial stromal sarcomas (ESS); the comparison of Low Grade-ESS and High Grade-ESS

Hacı Öztürk Şahin^{1*}, Mehmet Bayrak²

Abstract

Objective: Endometrial stromal sarcoma (ESS) is a rare mesenchymal tumor of the uterus. Literature has limited data about the ESS. The aim of the present study was to contribute to literature by reporting the histo-pathological findings, clinical characteristics of ESS patients and the data about the accuracy of preoperative diagnosis and prognosis.

Material and Methods: A total of 33 patients who were diagnosed and followed up with ESS at Department of Gynecology and Obstetrics of Bursa Uludağ University between 2007 and 2017 were retrospectively analyzed with regard to clinical and pathologic characteristics, surgical procedures they underwent and survival.

Results: Mean age of the patients was 49.5 years and 60.2 years for low grade ESS (LG-ESS) and high grade ESS (HG-ESS) ($p=0,01$). Post-menopausal hemorrhage was the most common complaint on admission. Correct histological diagnosis was made in only 72.7% of the patients from whom pre-operative endometrial biopsy was obtained. Twelve out of 16 cases (75%) were in Stage 1. While all patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO), 14 underwent pelvic and para-aortic lymphadenectomy for surgical staging. Lymph node involvement was detected in no patients who underwent lymphadenectomy. The patients with LG-ESS were found to have a good prognosis however the ones with HG-ESS had a high mortality rate even in the early stages (mean survival of 10 months).

Conclusion: High grade ESS cases show different clinical characteristics and prognosis than LG-HSS. Diagnostic accuracy of endometrial sampling is much lower when compared to epithelial uterine malignancies. Metastasis of pelvic-paraaortic lymph nodes of which removal is reported which not to contribute to survival is rare.

Key words: Endometrial stromal sarcoma, diagnosis, lymph node dissection, prognosis

Introduction

Endometrial stromal sarcomas (ESS) constitute <1% of uterine malignancies and <10% of uterine sarcomas (1) and the second most common uterine mesenchymal neoplasia following leiomyosarcoma (2-4). Endometrial stromal sarcomas were revised and classified again by World Health Organization (WHO) in the 2014. While vascular and myometrial invasion of LG-ESS is typically composed of uniform stromal cells and shows mild nuclear atypia and few mitotic features, HG-ESS shows higher nuclear atypia, pleomorphism, mitosis and widespread invasion (5).

While LG-HSSs usually have a good prognosis, HG-ESSs have bad progress and shows recurrence and results in death (1,5,6,7,8,9). Although 80% of ESSs is limited in the uterus during surgery, Stage 1 HG-ESSs show an aggressive course. High grade ESSs frequently recur before completing one year (10).

Adjuvant radiotherapy or chemotherapy was not shown to have a benefit on survival in HG-ESSs (11).

Although elevated serum lactate dehydrogenase (LDH) and CA-125 values can be used for pre-operative diagnosis, their value in preoperative diagnosis is controversial (12).

It is important to perform additional radiologic examinations for distant metastases and thereby avoiding from useless aggressive primary surgery for uterine sarcomas which tend to hematogenous spread besides making an accurate pre-operative diagnosis, intra-operative staging and more careful evaluation of extra-uterine tissues.

While ESSs show a heterogenous mass image on ultrasonography, low resistance index values on color Doppler examination, they yield an image with high signal density



on T1-weighted magnetic resonance images due to intra-tumoral hemorrhage and coagulation necrosis (13,14). While pathological examination of endometrial aspiration or dilation-curettage material has a high accuracy rate in uterine malignancies, it is not such efficient in sarcomatous histology (15,16,17).

Limited literature data about endometrial stromal sarcomas makes developing an optimal treatment method difficult. Unnecessary or insufficient treatments could be prevented with accumulating data about these tumors and the most appropriate approach algorithms could be created. In the present study, we retrospectively analyzed the cases with endometrial stromal sarcoma in our hospital and investigated clinical-pathological findings, surgical methods and survival and aimed to contribute to literature.

Method

Clinical-pathological findings, previous surgical procedures and survival of the patients who were diagnosed with ESS according to pathological examination at Department of Gynecology and Obstetrics between 2007 and 2017 were retrospectively analyzed. Data of 22 patients with LG-ESS and 11 patients with HG-ESS who underwent operation in our hospital could be reached.

Surgical staging was done based on FIGO/TNM 2017 guideline. All patients had undergone TAH+BSO. The addition of the procedures like intra-abdominal wash, infracolic omentectomy, pelvic and para-aortic lymphadenectomy was defined as surgical staging.

Statistical Analysis

Data distribution was evaluated with Kolmogorov-Smirnov test. Inter-group comparisons were done by using Mann-Whitney U test and independent samples t test. Analyses were done with SPSS 22.0 program and a p level of <0.05 was accepted as statistically significant.

Results

Age range of the patients was 33 and 85 years. While mean age of the patients with LG-ESS was 49.5 years, it was 60.2 for HG-ESS (p=0.01). Post-menopausal hemorrhage was the most common complaint (36.8%) followed by the presence of an incidental mass lesion detected with radiologic or pelvic examination (26.3%) and pelvic pain (21%). Pathological examination was reported as benign endometrial pathology in 4 out of 22 patients who underwent pre-operative endometrial sampling, high grade malignant tumor in 2 however the main histological type was not reported. Ratio of pre-operative diagnostic accuracy was found to be 72.7% in our study.

Serum LDH values were known pre-operatively in 12 patients and mean values were 175.4 U/L and 200.3 U/L for LG-ESS and HG-ESS, respectively (p=0.078). CA-125 values were found to be elevated in only 2 out of 15 patients whose values could be reached. While estrogen receptor (ER) was found to be positive in 11 and progesterone receptor (PR) was found to be positive in 9 out of 12 LG-ESS cases whose ER, PR status could be known, estrogen and progesterone receptors were positive in only 2 patients out of 5 with HG-ESS whose receptor status was known. While only TAH+BSO was applied in only 17 out of 33 cases, complete surgical staging was done in 16 (48.4%). Of them, 14 had undergone lymphadenectomy and pelvic or para-aortic lymph node involvement was detected in none of them. Omental involvement was detected in 3 patients who were accepted to be in Stage 3 (Table 1). Post-operative follow-up records could be reached in 11 patients (4 with HG-ESS and 7 with LG-ESS). Three out of 4 patients with HG-ESS had died and mean survival was 10 months. Omental involvement (Stage 3A) was present in 1 of 7 LG-ESS cases and this patient was lost due to bone marrow metastasis at 30th month of follow up. Remaining patients were surviving healthily (36-140 months) (Table 2).

Table 1. Distribution of endometrial sarcomas according to the stages

	Stage 1	Stage 2	Stage 3*	Stage 4
L-ESS	6	-	2	-
H-ESS	6	1	1	-

*:Omental involvement. L-ESS: Low grade endometrial stromal sarcoma, H-ESS: High grade endometrial stromal sarcoma.

Table 2. Clinical data and survival data of the patients whose records could be reached

	Age	Ess	Surgical staging	Stage	Recurrence (months)	Location of recurrence	Survival
1	80	H-ess	+	1b	-	-	44 months healthy
2	62	H-ess	+	1b	+(3. month)	Pelvis	Ex(4.month)
3	66	H-ess	-	-	+(2. month)	Abdomen	Ex(5. Month)
4	61	H-ess	+	1b	+(9. month)	Liver	Ex(22. Month)
5	51	L-ess	-	-	-	-	36. Month healthy
6	56	L-ess	-	-	-	-	40. Month healthy
7	70	L-ess	-	-	-	-	76. Month healthy
8	48	L-ess	-	-	-	-	127. Month healthy
9	45	L-ess	-	-	-	-	123. Month healthy
10	33	L-ess	+	3a	+(28. month)	Bone Marrow	Ex(30. Month)
11	45	L-ess	-	-	-	-	140. Month surviving

L-ESS: Low grade endometrial stromal sarcoma, H-ESS: High grade endometrial stromal sarcoma

Discussion

Endometrial stromal sarcomas are rare uterine malignancies and therefore sufficient literature data and a universal treatment plan are not available.

While Abeler and Nagai reported that the mean age for ESSs was 50.7 and 60.3 years, respectively, it was found to be 53.1 years in our study (3,18). Mean age of LG-ESSs and HG-ESSs was found to be statistically significant, as in our study.

Endometrial stromal sarcomas may be misdiagnosed as leiomyoma or benign uterine pathology pre-operatively (19). Atypical vaginal hemorrhage, metrorrhagia, palpable masses or uterine enlargement are the most common complaints. Guintoli reported abnormal vaginal hemorrhage as the most common complaint on admission (56%) (20). Post-menopausal hemorrhage was the most common (36.8%) complaint also in our study. However these symptoms are non-specific and not lead to differential diagnosis.

Serum CA-125 and LDH values were reported to be the markers which could be used for pre-operative diagnosis of sarcomas (12, 21). While Ning Li detected elevated CA-125 values in 53.8% of the patients (22), CA-125 elevation (>35 U/L) was detected in only 2 patients (13.3%) in our study. Not serum CA-125 values but LDH values were reported to be able to be used for discriminating sarcoma and benign lesions (18).

Lymph node positivity was reported as 10.3% and 18% in LG-ESS and HG-ESS, respectively (1, 8). However Seagle reported that survival was similar between the patients who did not undergo lymphadenectomy and the ones who were detected to have lymph node positivity (23). Today, Gynecologic Cancer Inter-Group does not recommend lymphadenectomy for ESS (10, 23). Lymph node involvement was detected in no patients who underwent lymphadenectomy in our study, supporting the literature.

While ratio of accurate histological diagnosis was reported as 64% for pre-operative endometrial sampling by Bansal, this ratio was 72.7% in our study (17).

Gynecologic Cancer Group trial showed that adjuvant radiotherapy does not prolong overall survival and disease-free survival in Stage 1-2 HG-ESS (24, 25). However hormone receptor positive patients with HG-ESS could be suggested to benefit from hormone therapy (26).

Conclusion

High grade ESSs show different clinical features and prognosis from LG-HSS. Our study showed that HG-ESSs are seen in older ages, progress more aggressively and lead to a poorer survival. Detecting involvement in none of the patients who were performed lymph node dissection leads to suspicion about performing lymphadenectomy in these cases. Serum markers like LDH and CA-125 were seen not to be helpful for discriminating LG-ESS and HG-ESS. Although the rate of an accurate pre-operative histopathological diagnosis is low when compared to epithelial endometrial carcinomas, the accuracy rate of

72.2% found in our study indicates that pre-operative endometrial biopsy has an important place also in endometrial sarcomas. The most appropriate treatment methods could be developed through a more comprehensive perspective together with the accumulating data regarding endometrial sarcomas and thereby unnecessary or insufficient treatments could be avoided and maximum comfort could be provided.

Acknowledgments, Funding: None

Conflict of interest and financial disclosure: The authors declare that there is no conflict of interest and financial relationships.

Author's contributions: HÖŞ, MB; Design of study, Material preparation, data collection and analysis. HÖŞ; Preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. C.G. Trope, V.M. Abeler, G.B. Kristensen. Diagnosis and treatment of sarcoma of the uterus. A review. *Acta Oncol.*, 51 (6) (2012), pp. 694-705
2. Hoang L, Chiang S, Lee CH. Endometrial stromal sarcomas and related neoplasms: new developments and diagnostic considerations. *Pathology*. 2018; 50(2):162–177.
3. Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. 2009;54(3):355–364.
4. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. *J Natl Cancer Inst*. 1986;76(3):399–402.
5. M.R. Hendrickson, F.A. Tavassoli, R.L. Kempson, et al. Mesenchymal tumors and related lesions. F.A. Tavassoli, P. Devilee (Eds.), *World Health Organization Classification of Tumors: Pathology and Genetics - Tumors of the Breast and Female Genital Organs*, International Agency for Research on Cancer, Lyon, France (2003)
6. H. Machida, M.J. Nathenson, T. Takiuchi, C.L. Adams, J. Garcia-Sayre, K. Matsuo. Significance of lymph node metastasis on survival of women with uterine adenosarcoma. *Gynecol. Oncol.*, 144 (2017), pp. 524-530
7. B. Barney, J.D. Tward, T. Skidmore, D.K. Gaffney. Does radiotherapy or lymphadenectomy improve survival in endometrial stromal sarcoma. *Int. J. Gynecol. Cancer*, 19 (7) (2009), pp. 1232-1238
8. J.P. Shah, C.S. Bryant, S. Kumar, R. Ali Fehmi, J.M. Malone Jr., R.T. Morris. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet. Gynecol.*, 112 (5) (2008), pp. 1102-1108
9. H.L. Evans. Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. *Cancer*, 50 (10) (1982), pp. 2170-2182
10. Pautier P, Nam EJ, Provencher DM, et al. Gynecologic Cancer InterGroup (GFIG) consensus review for high-grade undifferentiated sarcomas of the uterus. *Int J Gynecol Cancer*. 2014;24(9 Suppl 3):S73–S77.
11. Benson C, Miah AB. Uterine sarcoma – current perspectives. *Int J Womens Health*. 2017;9:597–606

12. Juang CM, Yen MS, Horng HC, Twu NF, Yu HC, Hsu WL (2006) Potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma. *Eur J Gynaecol Oncol* 27(4):370–374
13. Aviram R, Ochshorn Y, Markovitch O, Fishman A, Cohen I, Altaras MM, Tepper R (2005) Uterine sarcomas versus leiomyomas: gray-scale and Doppler sonographic findings. *J Clin Ultrasound* 33(1):10–13, doi:10.1002/jcu.20075
14. Kido A, Togashi K, Koyama T, Yamaoka T, Fujiwara T, Fujii S (2003) Diffusely enlarged uterus: evaluation with MR imaging. *Radiographics* 23(6):1423–1439
15. F.P. Dijkhuizen, B.W. Mol, H.A. Brolmann, A.P. Heintz The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia. *Cancer* 2000;89:1765
16. T.J. Clark, C.H. Mann, N. Shah, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review *BJOG* 2002;109:313
17. Bansal N, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. *Gynecol Oncol*. 2008 Jul;110(1):43-8
18. Nagai T, Takai Y, Akahori T, Ishida H, Hanaoka T, Uotani T, Sato S, Matsunaga S, Baba K, Seki H. *Springerplus*. 2014 Nov 18;3:678
19. S. Sagae, K. Yamashita, S. Ishioka, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido *Oncology*, 67 (2004), pp. 33-39.
20. Giuntoli RL 2nd, Metzinger DS, DiMarco CS, Cha SS, Sloan JA, Keeney GL, Gostout BS (2003) Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol* 89(3):460–469
21. Patsner B, Mann WJ (1988) Use of serum CA-125 in monitoring patients with uterine sarcoma. A preliminary report. *Cancer* 62(7):1355–1358
22. Li N, Wu LY, Zhang HT, An JS, Li XG, Ma SK. Treatment options in stage I endometrial stromal sarcoma: A retrospective analysis of 53 cases *Gynecol Oncol*. 2008 Feb;108(2):306-11. Epub 2007
23. Seagle BL, Shilpi A, Buchanan S, Goodman C, Shahabi S. Low-grade and high-grade endometrial stromal sarcoma: A National Cancer Database study. *Gynecol Oncol*. 2017 Aug;146(2): 254-262
24. Horng HC, Wen KC, Wang PH, et al. Uterine sarcoma Part II – uterine endometrial stromal sarcoma: the TAG systematic review. *Taiwan J Obstet Gynecol*. 2016;55(4):472–479
25. Reed NS, Mangioni C, Malmström H, et al. 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) *Eur J Cancer*. 2008;44(6):808–818
26. Desar IME, Ottevanger PB, Benson C, van der Graaf WTA. Systemic treatment in adult uterine sarcomas. *Crit Rev Oncol Hematol*. 2018;122:10–20