Title
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Permalink
https://escholarship.org/uc/item/2hm6j0z8

Journal
British journal of cancer, 99(8)

ISSN
0007-0920

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Publication Date
2008-10-01

DOI
10.1038/sj.bjc.6604527

Peer reviewed
Endometrial stromal sarcoma: a population-based analysis

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To determine independent prognostic factors for the survival of patients with endometrial stromal sarcoma (ESS), data were abstracted from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute from 1988 to 2003. Kaplan–Meier and Cox proportional hazards models were used for analyses. Of 831 women diagnosed with ESS, the median age was 52 years (range: 17–96 years). In total, 59.9% had stage I, 5.1% stage II, 14.9% stage III, and 20.1% had stage IV disease. Overall, 13.0, 36.1, and 34.7% presented with grades 1, 2, and 3, respectively. Patients with stage I–II vs III–IV disease had 5 years DSS of 89.3% vs 50.3% (P<0.001) and those with grades 1, 2, and 3 cancers had survivals of 91.4, 95.4, and 42.1% (P<0.001). In multivariate analysis, older patients, black race, advanced stage, higher grade, lack of primary surgery, and nodal metastasis were independent prognostic factors for poorer survival. In younger women (<50 years) with stage I–II disease, ovarian-sparing procedures did not adversely impact survival (91.9 vs 96.2%; P=0.1). Age, race, primary surgery, stage, and grade are important prognostic factors for ESS. Excellent survival in patients with grade 1 and 2 disease of all stages supports the concept that these tumors are significantly different from grade 3 tumors. Ovarian-sparing surgeries may be considered in younger patients with early-stage disease.

British Journal of Cancer (2008) 99, 1210 – 1215. doi:10.1038/sj.bjc.6604527 www.bjcancer.com
Published online 23 September 2008
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Keywords: endometrial stromal sarcoma; prognostic factors; survival

Endometrial stromal sarcomas (ESSs) are rare tumors of the uterus accounting for 0.2–1% of all uterine malignancies and approximately 6–20% of all uterine sarcomas (Koss et al, 1965; Harlow et al, 1986; Echt et al, 1990; Larson et al, 1990). Given the rarity of ESS, there are limited reports in the literature that have evaluated the prognostic factors of patients with this tumor. On account of significant differences in the clinical behaviour of ESS patients, Norris and Taylor first described the prognostic significance of histologic grade in ESS, and their findings have been subsequently confirmed by others (Norris and Taylor, 1966; Pautier et al, 2000; Leath et al, 2007). Furthermore, as high-grade ESS lack specific differentiation, recent modifications to pathologic classifications of uterine sarcoma have been recommended to rename high-grade ESS as undifferentiated endometrial sarcoma (Jaffe et al, 2001; Moinfar et al, 2007).

Optimal therapy of ESS is not well established. The standard surgical procedure has included a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and radical cytoreductive surgery of extra-uterine disease (Gadducci et al, 1996). Moreover, despite traditional recommendations to include bilateral salpingo-oophorectomy in the primary surgical management of ESS, some investigators have advocated preserving ovarian function, particularly in younger women (Gadducci et al, 1996; Chu et al, 2003; Li et al, 2005; Amant et al, 2007). The role of pelvic and para-aortic lymphadenectomy, and adjuvant therapy with radiation therapy, chemotherapy, or hormonal treatment remains controversial. Most of the earlier studies have been limited by a small number of patients from academic institutions with associated biases (Echt et al, 1990; Haberal et al, 2003; Denschlag et al, 2007; Leath et al, 2007). In addition, there are no large studies that have investigated the potential risk of ovarian preservation in young patients with early-stage disease.

In this large population-based study of 831 patients, we examined the demographic and clinico-pathologic prognostic factors associated with disease-specific survival (DSS) in ESS. In addition, the role of lymphadenectomy, adjuvant radiation therapy, and oophorectomy was analyzed.

MATERIALS AND METHODS

Demographic, clinico-pathologic variables, treatment data, and survival information of women diagnosed with ESS were extracted from the Surveillance, Epidemiology, and End Results (SEER) database of the United States National Cancer Institute for the 15-year period from 1 January 1988 to 31 December 2003. Data are reported from population-based registries that represent approximately 26% of the U.S. population including the states of Utah, Hawaii, Iowa, New Mexico, Connecticut, Alaska Native, and the metropolitan regions of Detroit, San Francisco-Oakland, Seattle-Puget Sound, Atlanta, San Jose-Monterey, Los Angeles, and rural Georgia. The histology code used was 8930 for ESS. Although the database coded grade of disease as 1, 2, 3 and 4, we elected to combine grades 3 and 4 as grade 3 disease given the similarity of the two groups.
Table 1  Demographic and clinico-pathologic characteristics \((n=831)\)

| Characteristics | n | % |
|-----------------|---|---|
| Age at diagnosis (years) | | |
| Median age (range) | 52 (17–96) | |
| \(<52\) years | 432 | 52.0 |
| \(\geq 52\) years | 399 | 48.0 |
| Year of diagnosis | | |
| 1988–1992 | 150 | 18.0 |
| 1993–1997 | 284 | 34.2 |
| 1998–2003 | 397 | 47.8 |
| Race | | |
| White | 553 | 66.5 |
| Black | 114 | 13.7 |
| Hispanic | 82 | 9.9 |
| Asian | 70 | 8.4 |
| Other | 12 | 1.4 |
| Stage | | |
| I | 498 | 59.9 |
| II | 42 | 5.1 |
| III | 124 | 14.9 |
| IV | 167 | 20.1 |
| Grade | | |
| I | 108 | 13.0 |
| 2 | 300 | 36.1 |
| 3 | 288 | 34.7 |
| Unknown | 135 | 16.2 |

Table 2  Treatment characteristics \((n=831)\)

| Characteristics | n | % |
|-----------------|---|---|
| Surgery | | |
| Yes* | 775 | 93.3 |
| No | 56 | 6.7 |
| Lymphadenectomy | | |
| Yes | 282 | 33.9 |
| Positive | 28 | 9.9 |
| Negative | 245 | 86.9 |
| Unknown | 9 | 3.2 |
| No | 543 | 65.3 |
| Unknown | 6 | 0.7 |
| Oophorectomy | | |
| Yes | 483 | 58.1 |
| No | 290 | 34.9 |
| Unknown | 58 | 7.0 |
| Age: <50 years, stage I–II | | |
| Yes | 155 | 64.6 |
| No | 85 | 35.4 |
| Radiation | | |
| Yes | 205 | 24.7 |
| No | 611 | 73.5 |
| Unknown | 15 | 1.8 |

*Primary hysterectomy. *Percent of those undergoing lymphadenectomy. *Percent of those <50 years, stage I–II.

Figure 1  Kaplan–Meier disease-specific survival based on (A) age \((P<0.001)\), (B) race \((P=0.001)\), (C) surgery \((P<0.001)\), (D) stage \((P<0.001)\), (E) grade \((P<0.001)\), (F) nodal metastasis \((P<0.001)\), and (G) oophorectomy in younger women \(<50\) years with stage I–II disease \((P=0.1)\).
Kaplan–Meier models were used to estimate 5-year DSS. Variables examined included age, race, stage, grade, primary surgery, and presence of nodal metastasis, oophorectomy, and adjuvant radiation treatment. All factors that were significant in univariate analyses were tested in the multivariable model. The Cox proportional hazards model was used to identify independent predictors of survival. All P-values reported are two-tailed, and a P-value of less than 0.05 was considered to be statistically significant.

RESULTS

Of 831 women with ESS, the median age at diagnosis was 52 years (range: 17 – 96 years). Demographic characteristics of these patients are presented in Table 1. The majority (59.9%) had stage I disease, 5.1% stage II, 14.9% stage III, and 20.1% had stage IV disease. Grades 1, 2, and 3 comprised 13.0, 36.1, and 34.7% of cases, respectively.

Analysis of surgical treatment found that 775 (93.3%) women underwent a hysterectomy; 282 (33.9%) also had a lymphadenectomy, and 28 (9.9%) women were found to have nodal metastases. Moreover, the rate of lymphadenectomy in those women 50 years and younger vs older than 50 years was 32.2 vs 35.9%, respectively. Oophorectomy was performed in 483 (58.1%) cases. In addition, 24.7% of patients underwent adjuvant radiotherapy. Table 1 provides further details of treatment characteristics. Of patients with grades 1, 2, and 3 disease, 33 (11.7%), 79 (28.0%), and 127 (45.0%) underwent lymph node dissections, of which 2 (6.1%), 7 (8.9%), and 16 (12.6%) had nodal metastases. Lastly, approximately 6.7% of the patients did not undergo primary surgery. Of these 56 patients, the median age was 68.8 years of age compared with only 51 years in those who underwent surgery. In addition, the proportion of advanced stage disease was higher in those without surgery, 82.1 vs 31.6%.

The 5-year DSS for the entire cohort was 76.2%. The 5-year DSS of younger patients (<52 years) was significantly higher compared with older women (85.9 vs 64.7%, P < 0.001) (Table 2). Blacks had a worse DSS compared with other races (62.5 vs 78.1%; P = 0.001). Those who underwent primary hysterectomy had a significant benefit over those who did not (78.5 vs 42.4%; P < 0.001). Moreover, the 5-year DSS of those with stage I – II disease was 89 vs 50.3% in those with stages III – IV disease (P < 0.001). Those with grades 1, 2, and 3 disease had 5-year DSSs of 91.4, 95.4, and 42.1%, respectively (P < 0.001) (Figure 1).

In the overall study group, there was no difference in 5-year DSS in those who underwent oophorectomy vs ovarian-sparing procedures (P = 0.06) (Table 2). Similarly, in the subset of younger women (<50 years) with stage I – II disease, those who underwent ovarian-sparing procedures had a similar survival compared with those who underwent oophorectomies (96.2 vs 91.1%; P = 0.1). However, the exact number of patients who may have undergone adnexal surgery before their cancer diagnosis is not reported. Furthermore, lymphadenectomy and adjuvant treatment with radiation therapy had no demonstrable impact on overall survival.

Factors found to be significant in univariate analysis were then analyzed using a Cox proportional hazards model to determine independent predictors of DSS. On multivariate analysis, older age

Figure 1  Continued.
at diagnosis, black race, no surgery, advanced stage, and higher grade of disease were all independent predictors for poorer survival (Tables 3 and 4).

**DISCUSSION**

As endometrial stromal sarcomas are rare uterine malignancies, there are limited reports on their clinical behaviour and optimal treatment strategies. Most of these studies involve case reports, and retrospective case series by academic institutions with a small number of patients accrued over long time periods. In addition, others series have included additional histological subtypes of uterine sarcomas. To our knowledge, this analysis is one of the largest studies, including over 800 patients evaluated for prognostic factors important in ESS patients.

Earlier studies on the importance of age in ESS have been inconclusive. Denschlag et al (2007) reported on 28 patients with ESS, and found overall better survival was significantly associated with younger patient age. Similarly, Kokawa et al (2006) showed that younger age was an independent predictor of improved survival in multivariate analysis of 15 cases of ESS. In contrast, Nodal et al (1996) studied 48 patients with ESS and found that age was not significantly correlated to survival. In this study of over 800 patients, patients ≤ 52 years had more than a 20% higher 5-year DSS compared with older patients. Moreover, age, as a continuous variable remained a significant prognostic factor in multivariate analysis.

In this analysis, our data also showed that blacks had a worse DSS compared with all other racial groups after adjusting for other prognostic factors. Racial and ethnic differences in treatment and survival have been previously reported for several gynecologic malignancies, including ovary and uterine cancers (Wingo et al, 1996; Madison et al, 1998; Maxwell et al, 2006; Morris et al, 2006; Chan et al, 2008). In uterine sarcomas, Brooks et al (2004) found a survival difference among racial groups, but this was no longer present after adjusting for treatment differences. In this analysis, we demonstrated that blacks with ESS have a poorer survival after adjusting for surgery and adjuvant radiotherapy. Further studies are warranted to identify the underlying cause for racial differences in survival that cannot simply be explained by treatment disparities.

Similar to other reports, our analysis found that stage and grade were important predictors of overall improved survival (Echt et al, 1990; Kokawa et al, 2006; Denschlag et al, 2007). In our analysis, stage I – II patients had a 5-year DSS of 89.3% compared with only 50.3% in stage III – IV disease. Grade has also long been recognized as an important factor in ESS (Norris and Taylor, 1966; Pautier et al, 2000; Haberal et al, 2003; Leath et al, 2007). In over 400 patients with grades 1 and 2 tumors in our study, the 5-year DSS was more than 90% compared with only 42% in those with grade 3 tumors. These findings clearly support the hypothesis that high-grade ESSs have a distinct biologic behaviour. This has also been demonstrated by others (Gadducci et al, 1996; Leath et al, 2007). In fact, there are some investigators who have recommended a change in the classification of high-grade ESS to undifferentiated endometrial sarcoma, as these tumors have distinct pathologic and clinical properties compared with low-grade ESS. The 2003 World Health Organization Classification of tumors employs this new nomenclature, as does the current pathology literature, where the term of ESS is used to describe low-grade stromal sarcomas only (Jaffe et al, 2001; Moinfar et al, 2007).

Although standard therapy for ESS has included hysterectomy and bilateral salpingo-oophorectomy, the additional extent of surgery, especially the role of pelvic and para-aortic lymphadenectomy, remains controversial. In our study, the survival of those who underwent a lymph node dissection was not significantly different compared with those without lymph node dissection (P = 0.351). However, it was interesting to note that nearly 10% of those who underwent lymph node dissection were found to have nodal metastases. Thus, it is important to perform lymphadenecomy in ESS patients for both prognostic and treatment purposes.
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to direct adjuvant therapy. In addition, patients with positive nodal metastasis at the time of lymphadenectomy had significantly poorer survival (35.3%) compared with those that had negative nodes (80.1%). Other reports have also suggested that the rates of lymph node involvement in ESS may be higher than expected (Goff et al, 1993; Reich et al, 2005; Rieposel et al, 2005). Therefore, lymph node dissection clearly provides prognostic information and treatment guidance; however, the potential therapeutic value of lymph node dissection remains to be determined.

Similar to endometrioid uterine cancer, the standard recommendations have included bilateral salpingo-oophorectomy in the primary surgical management of ESS. This study showed that ovarian-sparing surgeries in the subset of younger women (<50 years) with otherwise early-stage disease did not adversely impact survival. Similarly, Li et al (2005) found that ovarian preservation did not affect recurrence or survival in women with stage I low-grade ESS. Similar findings were described by Amant et al (2007) in a multicenter analysis of 34 women with ESS. In stage I–II premenopausal women who underwent hysterectomy with or without bilateral salpingo-oophorectomy, 3 of 12 (25%) and 1 of 6 (17%) recurred, respectively. Although the sample size was too small to draw conclusions, ovarian preservation did not seem to compromise outcomes. These results were also confirmed by others (Gadducci et al, 1996; Chu et al, 2003). In contrast, in a recent analysis of 53 patients, investigators found that ovarian preservation resulted in higher recurrence rates of 9 of 9 patients vs 10 of 44 (P<0.001) in those who had bilateral salpingo-oophorectomy (Li et al, 2008). Although our data suggest that ovarian-sparing surgeries may be considered in younger patients with early-stage disease, it is important to note that the SEER data do not include data on adnexal surgeries before cancer diagnosis. Thus, these limitations may have influenced our results.

The strength of our study is the large number of patients, which permitted subset analyses investigating the role of lymphadenectomy and oophorectomy, as well as other prognostic factors, such as age, race, and grade of disease. Moreover, the SEER database is representative of the general patient population without associated biases of case reports and studies from single academic institutions that span over many years. Several studies have demonstrated the accuracy of pathology from the SEER database (Glaser et al, 2001; Field et al, 2004). There are, however, several limitations of this study, including a lack of information regarding surgeon specialty, residual disease or margin status after primary surgery, hormone receptor status, sites of recurrence, earlier oophorectomy, chemotherapy, hormonal treatment or combined treatments.

In summary, the results of this study of 831 women with ESSs showed that age, race, stage, and grade of disease are important independent prognostic factors for survival. The survival of more than 90% in patients with grades 1 and 2 disease compared with only 42% in those with grade 3 disease supports the concept that low-grade ESSs have a significantly different clinical behaviour from high-grade tumors. The therapeutic role of lymphadenectomy and adjuvant therapy remains unclear. However, our data suggest that ovarian-sparing surgeries may be considered in younger patients with early-stage disease.

ACKNOWLEDGEMENTS

We thank Alexander Sherman for his work in performing additional statistical analyses.

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