Reviewer 1: Minor revision

GENERAL COMMENTS:

I congratulate the authors on presenting a clear and well-articulated manuscript of primary research findings in the area of gynecology-oncology, which is, most certainly, of interest to both health professionals and researchers working in this field.

The authors clearly argue the relevancy of the paper (limited knowledge base), acknowledge the major limitation of the study (very small sample size), explain the reasons for the limitation (rare disease) and offer potential solutions for future studies (multi-center studies).

A general concern is regarding the originality of the work. While I think the work is original and will recommend it for publication, I don’t know if the originality is clear to the reader. The authors argue that “most of the data regarding clinical and pathological variables that may predict prognosis and the benefits of adjuvant therapy are based on small retrospective studies”. First, I would encourage authors to reference some of these papers for their readers.

Second, the authors reference Chan, Kawar, Shin et al (2008) Br J Cancer in their discussion, who considered the same potential prognostic factors, with the exception of tumour hormone receptor status, for ESS survival among 800+ participants in the U.S. There are some important differences between the studies that I think the authors could acknowledge. Besides the fact that the current study is smaller and represents less of the general U.S. population, there are some important strengths of the current study that could be highlighted. First, the current study includes much more recent follow-up (Chan et al. included diagnosis up until 2003, while the current study includes diagnoses up until 2012). Secondly, Chan et al. report on disease-specific survival, which have some inherent limitations. There is benefit to having information about overall survival and progression-free survival for ESS patients available.

I recommend this manuscript be published, with few minor comments provided for the authors and editors consideration. My specific comments are detailed below.

SPECIFIC COMMENTS:

Abstract:

This is nicely written and adequately informative.

Introduction:

Fourth paragraph: I would recommend referring to Chan et al., 2008 and explaining how your current study can add further.

Materials and Methods:
Paragraph 1: what city/town, country was this study conducted in? Please specify for international readers.

Paragraph 1: what ethical approval and, if required, consent process did you go through to obtain approval to conduct this study? Please specify.

Paragraph 1 and 3: you included patients diagnosed January 1990 – April 2012, when was follow-up ceased, when was vital status obtained, what was your censor date?

Paragraph 1: please clarify what is meant by “earliest reported weight and height”. I would assume the record closest to diagnosis would be more ideal. Or did the patients not have medical records prior diagnosis (such as for other cancers, investigations, etc)?

Paragraph 2: I would not use the term “abnormally distributed”, I would say “Not normally distributed”.

Paragraph 2: I recommend reporting in inter-quartile range (IQR) with medians, rather than range - gives a better idea of the distribution.

Results:

Paragraph 1: what information was typically missing?

Paragraph 1: where those excluded different, on key variables, to those included, and/or do you think the exclusions could have resulted in any significant selection bias?

Paragraph 1: This may be my naivety being from outside the U.S. but what is “Caucasian” a category of? Please define this variable in the methods - what is means, how it was measured (how did the register ascertain this information - did patients self-report it or did clinicians report it), what other categories were reported.

Paragraph 4: I find the following sentence confusing; “Median PFS was 49 (range 24-99) months and OS was 238 months (range 56 months to alive at time of analysis).” I understand that while you censored patients at the end of the study period you may find it misleading to report a maximum survival time. However, you are reporting an average, which I assume is based on all patients, not just those who died? Also, you report a maximum of the progression-free survival – and I assume some patients never had recurrence?

You are dealing with a 22 year study period. Some participants may have a very long follow-up period (22 years) and some may have very short follow-up periods (I assume follow-up ended on April, 2012, which means some people may have contributed only days to the study?). Therefore, giving the average survival time can be misleading. I think I would find it most meaningful for you to report the % who survived 1 year and 5 years post diagnosis.

Paragraph 4: I understand it is not possible with small numbers to look at time trends, but I think some attempt to account for the time of diagnosis is warranted, given you are dealing with a 22 year study period and survival outcomes may have changed overtime. Some attempt to address this would be good - perhaps adjusting for diagnosis in 5 year blocks?

Discussion:

Paragraph 2: Good point re: comorbidity and functional status.

Last paragraph: Did you not include all ESS cases diagnosed since 1990 at the one cancer center, in your study? Explain the limitation re nonrandom design
Last paragraph: I would add further discussion on the limitations — small numbers also mean you were not able to look at time trends, and recruitment from one center limits the generalisability of findings.

General: The discussion is otherwise clear and comprehensive

Conclusion

The authors draw reasonable conclusions, have made sensible interpretations from the results, and provide useful suggestions for further research to improve the knowledge base.

Tables:

Table 1

• Indicate you are reporting age using median, range/IQR.
• Indicate you are measuring your categorical variables using n (%) (include %).
• Make your category labels meaningful (e.g. does smoking history refer to current smokers, ever smoked, ex-smokers, never smoked, etc), and include other categories of variables if warranted (e.g. other categories of — what I assume is — ethnicity).

Table 2

• Include referent groups or specify the referent groups in the footnotes of the table.

Table 3

• I suggesting leaving out “Adjuvant chemotherapy” from the table and adding a footnote only to explain why it was not included in the analysis

Other

• Tables could be formatted into a neater presentation
• I would like to see figures showing the survival curves

Reviewer 2: Declination

Study design

This is a retrospective analysis of the prognostic factors in 37 patients with ESS between January 1990 and April 2012 in one institution.
Advantage: long-term follow-up time for a prognosis study
Disadvantage: small-sized population, not multi-institutional investigation

Novelty
Lack of novelty

Abstract
The statistical method for disease progression or death (multivariate model) is not consistent with the method in results and tables.

Introduction
Lack of the latest information for prognosis analysis

M&M
Small-sized population due to rarity of the studied disease.
Pathological diagnosis was based on pathology reports and was lack of pathological review by pathologists.
ER-positive tumor (14/18, 78%) may not be representative for the whole population.
Stage I (n = 18, 49%), stage II (n = 6, 16%), stage III (n = 3, 8%), stage IV (n = 9, 24%).
LVSI (n = 20, 54%) was not included in statistical analysis (see literature)
Adjuvant therapy (n = 13, 35%) for stage was not mentioned. Five had RT, 2 had chemo (one had ifosfamide; 1 had doxorubicin plus platinum, 4 had HT (Al or megestrol), and 2 had RT plus HT.

Statistics
There is no description regarding the statistical method for disease progression or death. Did authors use Cox proportional hazard model for univariate or multivariate analysis? No multivariate analysis was demonstrated in text or tables as described in the abstract.

Results
In univariate analysis
Age is a marginally poor prognostic factor for death (HR 1.05, 95% CI:1.01-1.09, P = 0.03).
FIGO stage IV versus I for death (HR 4.05, 95% CI:1.11-14.8, P = 0.03)
ER-positive tumor versus ER-negative for death (HR 0.11, 95% CI:0.02-0.69, P = 0.02).
ER-positive tumor versus ER-negative for progression (HR 0.15, 95% CI:0.03-0.77, P = 0.02).
No prognostic role for adjuvant therapy

References
Authors should provide updated literature for supporting your findings. Three references should be included in your article as those follows:

Others
Salpingoooph’e’rectomy (in text, p.5 & 8 and tables) should be salpingoooph’o’rectomy.
Lymphadenectomy in table 1 should be lymphaden’e’ctomy.

Reviewer 3: Major revision
In the present study, Lesly Dossett et al, showed the important clinical and pathologic features for ESS prognosis from a 22-year retrospective study. Moreover, authors suggested available adjuvant therapy should be considered in high-risk patients.

1. In table 1: the author show the median age of ESS patients was 51 years, however the range of age is from 19 to 41.
2. In table 1: the author introduced that 37 evaluable patients were analyzed who have complete records and confirmed ESS diagnosis. However, the total number of Clinical Stage(FIGO) is 36, one missed without any information.
3. In table 1: the notes described "***" while there is not "***" in the table 1.
4. In table 2: why is 1 year increase used in the univariate analysis of age in diagnosis. The total patient number is only 37, then number of every 1 year would be very small.
5. In table 2: the numbers of FIGO stage II vs I, FIGO stage III vs I and FIGO stage IV vs I were all 36, which are not true. The numbers of FIGO I, II, III and IV is 18, 6, 3 and 9 respectively based on the information given in table 1. Then FIGO stage II vs I, FIGO stage III vs I and FIGO stage IV vs I should be 24, 21 and 36 respectively.

Reviewer 4: Major revision
In this interesting retrospective study(over a time frame of 22 years) 37 consecutive patients with ESS are reviewed. PFS and OS are calculated and related to clinical and pathological variables. In a multivariate analyses age, FIGO stage and hormonal receptor status were independent prognostic variables. In a separate analysis any type of adjuvant therapy (hormonal and/or radiotherapy) was an associated with a better PFS
but not OS. In the discussion the authors focus mainly on the adjuvant therapy issue and conclude (both on the basis of literature data and their own data) that adjuvant treatment should be considered in high risk patients.

Minor comments:

1. the authors must clarify better how they retrospectively selected the patients with ESS based on the pathology reports. How do they know for sure that no patients with undifferentiated sarcoma were included?

2. please clarify why the 2009 FIGO endometrial carcinoma staging system was used and not the 2009 FIGO uterine sarcoma staging system?

Major comment:

The authors wrongly conclude that adjuvant therapy might be of benefit for patients with ESS because as a basis for this conclusion they make use of literature data that also include high grade or undifferentiated sarcoma's (like references 21,22,25,26). This must be better discussed.

(end)