Peer Review File

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Reviewer A

Although endometrial stromal sarcoma is a very rare condition, the topic of this paper is very interesting since fertility-sparing management represents a new frontier of research in pathologies of gynecological interest.

Reply: Thank you for your evaluation and approval of our work, your appreciation gives us confidence and encouragement.

Some considerations:

Comment 1:

I would add some information about the follow up of the cases analyzed. Has a protocol been drawn up for the follow-up? how often were patients subjected to follow-up?

Reply 1:

Thanks to you for your professional comments. Adopt your advice, we supplemented the follow-up protocol in Methods section. The follow-up examinations of all patients were conducted every three months during the first three years after treatment, every six months thereafter. The follow-ups included the recurrence and survival status, and recurrence was defined as new focus was found by imaging and confirmed by pathology.

Changes in the text:

We added the follow-up protocol in Methods section (see Page 3-4, line 64-67).

Comment 2:

Although 4 of the 5 cases analyzed developed relapse despite adjuvant hormonal therapy, Table 3 shows, on a greater number of cases, the probable protective role of adjuvant therapy against relapses. However, a vast heterogeneity of therapies is also highlighted. Further studies are needed to understand the best one, also in terms of methods of administration. Meanwhile, in your research, have you found cases of use of medicated intrauterine devices?

Reply 2:

Thanks to you for your constructive comments. In Table 3, we summarized 14 literatures, including 40 cases of conservative treatment, given that all of these post-hormonal-treatment recurrent cases were stage IA and IB, the effect of adjuvant therapy on recurrence may be related

to tumor stage, tumor size and other factors. Therefore, the role of hormonal treatment in LG-ESS is still far from conclusion.

In our research, we found that megestrol acetate and medroxyprogesterone acetate are the most often used drugs for hormonal treatment, and the latter is most commonly used in our hospital. Considering the rarity and indolent behavior of this tumor, the experience of fertility-sparing management is very limited, so large-scale studies with long-term follow-up are still needed to confirm the results and to further assess the safety and feasibility of conservative excision of uterine mass combined with adjuvant hormonal therapy.

Taking into account that all five patients in our study were young and nulliparous, LNG-IUD were not used in our study. However, a retrospectively study [1] found that two patients were treated with GnRH analogues followed by insertion of LNG-IUD and no recurrence occurred. These results indicate that adding the LNG-IUD to progestins or GnRH analogues may be a promising treatment for patients with no plans to conceive in the short term.

[1] Xie, W. et al. Fertility-sparing surgery for patients with low-grade endometrial stromal sarcoma. Oncotarget 8, 10602-10608, doi:10.18632/oncotarget.12491 (2017).

Changes in the text:

We have modified our text as advised (see Page 9, line 183-186).

Comment 3:

I would recommend to extract, from the data obtained by the SEER database, only those relating to women of childbearing age to obtain more informations regarding patients of your interest. There may be some factors, such as postmenopausal status, that can influence the data obtained. For example I would calculate the survival time, for the different surgical procedure, only in young patients; in this way if it is confirmed, also in this group, that there is no statistical significant differences in survival time between TH+/- BSO and conservative surgery, fertility sparing management will be much more easier to propose as a safe alternative to the standard treatment. Moreover, I would add in Figure 1 also informations about tumor stage at diagnosis for each patient.

Reply 3:

Thanks to you for your professional suggestions. Your suggestions are all valuable and very helpful for making our analysis more persuasive. Taking your advice, we've already added survival analysis among women of childbearing age (Figure 2B), and the results showed that there were no statistical significance observed among TH±BSO, radical hysterectomy, subtotal hysterectomy and local tumor excision (*P*=0.69), which confirmed that local tumor excision did not affect the probability of survival. Also, we added the information about tumor stage and grade in Figure 1. Tumor cell grade was available in 22 patients (79%), 4 being grade 1 (14%) and 18 being grade 2 (64%). But the information about stage was missing for most patients. Among patients who had this record, 8 (29%) patients were stage I, 2 (7%) were stage II, and 1 (4%) was stage IV (Figure 1).

Changes in the text:

We added the survival analysis among women of childbearing age in Results section and Figure 2 (see Page 7, line 133-142). We added the information about tumor stage and grade in in Results section and Figure 1 (see Page 6, line 125-130).

Comment 4:

The median recurrence-free survival time in the 5 cases that you described was of 38 months; I would calculate this parameter even in young patients subjected to conservative treatment extracted from the SEER database. This information is essential to better plan the right time for pregnancy.

Reply 4:

Thanks to you for your constructive comments, the suggestion you made is very professional. But unfortunately, in SEER database, there are no related data about recurrence-free survival time. The SEER database collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the population of the USA. Here, we chose SEER to do analysis mostly because it is an open database, which means that all statistical analysis is repeatable and can provide us some real-world evidence. Although the available information is not comprehensive, the repeatability of the analyses is already a considerable advantage. Moreover, the data are large in scale and are not designed for a particular study. Thus, although this is a retrospective study, selection bias was effectively avoided by big data analysis.

In our series, the median recurrence-free survival time was 38 months, and through literature review, we found that in most studies, the median recurrence-free survival time was between 30 and 40 months. These indicated that once recovered from surgery, patients with fertility requirements could try to pregnant as soon as possible to prevent recurrence. But it's hard to say that pregnancy may contribute to the development of LGESS due to changes in hormone levels during pregnancy, so we should monitor those pregnancies closely.

Next phase, we plan to collect more cases and perform a large-scale study with long-term follow-up, hoping that we can more useful conclusions which can benefit younger nulliparous LG-ESS patients.

Comment 5:

When in the future a greatest number of cases will be collected it will be important to define also the timing to subject patients to standard surgical treatment after pregnancy and before the development of relapse.

Reply 5:

Thanks to you for your constructive comments. You have put forward a very professional suggestion, large-scale studies with long-term follow-up are really needed. What we plan for the next phase of our research is to collect more cases and to look for opportunities to cooperate with more hospitals to conduct a multicenter study. We are planning to focus on the safety and feasibility of conservative excision of uterine mass combined with adjuvant hormonal therapy, and of course, we'll adopt your advice and explore the appropriate time when to start the standard surgical

treatment after pregnancy and before the development of relapse. Once we collect more data, we'll be able to do more accurate analyses and hope to benefit those young nulliparous LG-ESS patients who want to preserve their fertility.