



Hormone therapy and low-grade endometrial stromal sarcoma

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Endometrial stromal tumors, accounting for <1% of all uterine tumors (also <3% of all uterine malignancies or ranging from 16% to 21% of all uterine sarcomas) can be divided into the following four categories (based on the World Health Organization-WHO classification): (a) endometrial stromal nodule, (b) low-grade endometrial stromal sarcoma (LG-ESS), (c) high-grade ESS, and (d) uterine undifferentiated sarcoma.¹⁻⁶ The clinical outcome varied greatly among these ESSs, contributing to the importance of the accurate diagnosis. In addition to careful histomorphologic review, sometimes, diagnosis may need special immunohistochemical and molecular testing for further confirmation. Typically, hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) are positive on the tumor cells of LG-ESS, which contributes to the consideration of the therapeutic effect of hormone therapy (HT).^{1,4,6} Based on the experience of the success in using HT for FIGO (International Federation of Gynecology and Obstetrics) IA well-differentiated endometrioid-type endometrial cancer (grade 1 E-EC) in younger women who would like to preserve the reproductive function (uterus preservation),⁷⁻¹⁰ the similar strategy might be applicable in the younger women with LG-ESS. Although more than half of the patients with LG-ESS occur in premenopausal status, the age of the patients seemed to be older than that of those with FIGO IA grade 1 E-EC, with resultant application of the definite surgery, including total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO) with/without complete staging surgery on patients with LG-ESS. Therefore, the role of HT for these patients with LG-ESS is uncertain.^{2,6} We are happy to learn about the current publication from Dr. Comert and colleagues in the May issue of the *Journal of the Chinese Medical Association (JCMA)* to address this controversy.¹¹

The topic is entitled “Hormone therapy following surgery in LG-ESS: Is it related to a decrease in recurrence rate?”.¹¹ The authors retrospectively evaluated the outcome of 37

patients with LG-ESS.¹¹ All patients in their study had underwent definite surgery treatment, including TH and BSO with and without lymphadenectomy (43.2% and 56.8%, respectively).¹¹ Postoperative adjuvant therapy was applied in 62.2% of 37 patients, including three with radiotherapy, seven with chemotherapy, 12 with HT, and one with chemotherapy and HT.¹¹ With the median follow-up period of 96 months, 27% of patients (n = 10) had recurrence, contributing to 72% and 97% of 5-year disease-free survival (DFS) and disease-specific survival (DSS), respectively.¹¹ The authors found that patients having postoperative HT had no recurrence compared with patients treated for surgery alone did (0 vs 38.5%, $p = 0.039$). Based on the above findings, the authors concluded that HT after definite surgery should be considered as an option in all patients with LG-ESS.¹¹ We congratulate the success of publication from the authors, and the current study is interesting and worthy of discussion.

First, as shown by the authors, the cornerstone of the treatment of LG-ESS is surgery (TH and BSO), but optimal extent of surgery especially adding lymphadenectomy is uncertain.^{6,11} The authors used the recommendation of the 2009 FIGO to support the relatively high proportion of the patients who had lymphadenectomy (56.8%, n = 21).¹¹ The 2009 FIGO recommendation supported the need of performing lymphadenectomy in the management of patients with ESS, because of the high rate of lymph node metastases (high rate) and an opportunity to get accurate FIGO stage.¹¹ Herein, the update information should be provided. The 2018 FIGO recommended that TH and BSO is enough for LG-ESS, because much evidence supported that there is not a significant difference in DFS or overall survival in patients treated with and without lymphadenectomy, regardless of disease stage, and suggested that lymphadenectomy does not seem to have a role in the management of women with LG-ESS.¹² Consistent with 2009 FIGO recommendation, 2018 FIGO reconfirmed that BSO should be performed and post-treatment estrogen replacement therapy (ERT) should be discouraged in all patients with LG-ESS.¹² It is very dangerous for patients retaining their ovaries because of nearly 100% recurrence rate.¹² Based on this opinion, there is a certain difference of ovary preservation or estrogen use between LG-ESS and grade 1 E-EC. The former is contraindicated for ovary preservation or post-treatment ERT but the later seems to be acceptable.^{6,12,13}

Second, the authors highly recommended that all patients needed postoperative HT after definite surgery, regardless of stage status. As shown by the authors, is it related to a decrease in recurrence rate? This conclusion might be not mature to be made. Further verification is needed. In addition, the main component of HT for LG-ESS is progestins (often used is megestrol

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acetate). Furthermore, high dose of megestrol acetate is needed. However, the authors totally neglected the potential risks of oral HT. High-dose progestins-related adverse events, such as thromboembolic events, increase in body weight, other deteriorated metabolic problems, etc, might occur during the treatment, with subsequently resultant severe comorbidity and even life-threatening status (myocardial infarction and stroke).¹⁴ One study showed 11.3% of patients treated with chemotherapy and megestrol acetate (this is a progestin used by the authors in the current study.¹¹) had thromboembolic events during treatment compared with none of patients treated with chemotherapy alone did.¹⁴

Third, the recommendation of post-treatment HT after surgery is only limited to certain-type of cancers, such as breast cancer in young women, especially for those breast cancers cases that displayed positive staining for ER and PR.¹⁵ In contrast, for women with LG-ESS, there is no evidence to support the routine use of adjuvant HT as a standard of care after definite complete surgery (TH and BSO).² In fact, some small and retrospective series,² just like the current study by Dr. Comert in the JCMA,¹¹ have showed the benefits of the HT on patients with LG-ESS, but evidence seemed to be low.² It is still unclear why post-treatment HT is not recommended for the treatment of LG-ESS in routine. It is possible that tumor behaviors might not be similar among these hormone-sensitive tumors (LG-ESS, grade 1 E-EC, and breast cancer). LG-ESS is an indolent disease, and clinical outcome is favorable, even though recurrence rate is high.¹⁻⁶ In addition, one of the significant differences is that late recurrence was found in LG-ESS.¹⁻⁶ In addition, LG-ESS is considered as “rare” tumors of uterus and collection of adequate number of patients is nearly impossible. To evaluate the therapeutic benefits of LG-ESS, it needs a multicenter corporation and long time to finish, contributing to difficulty to conduct a prospective randomized study to investigate the benefits and risks of postoperative adjuvant HT in the management of women with LG-ESS.

Fourth, if it is true that postoperative HT should be used for all patients with LG-ESS, the other question is raised. How long the HT should be given? As shown earlier, the disease often recurs very late. It is uncertain how long the progestin used can achieve the adequate protection power. As shown above, case number is limited and follow-up period needs extension to more than 10 years contributing to impossible mission. That is why there is no consensus available yet.

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