CA 125 for surgico-pathological stage 1 endometrial cancer

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Endometrial cancer (EC) has become one of rapidly increasing women's cancers, contributing to the most common gynecologic organ cancer, particularly for those women living in high- and middle-income countries.[1,2] Conventionally, since abnormal vaginal bleeding is the most common clinical presentation in women, which triggers these women to search for medical care, resulting in high possibility of an early diagnosis of EC and following immediate and prompt effective and possible curable therapy, contributing to excellent prognosis of EC women, in comparison with other two common types of gynecological cancers (cervical cancer and epithelial ovarian cancer [EOC]).[2–4] A recent Taiwan's publication showed that women with clinical stage 1 EC had over 90% of overall survival (OS) rate, regardless whether these women were treated with either minimally invasive surgery (MIS, 99.4% in the 5-year OS rate, and 98.5% in the 10-year OS rate) or conventional exploratory laparotomy (94.9% in the 5-year OS rate, and 92.5% in the 10-year OS rate),[5] although Endometrial Cancer Staging Subcommittee, the International Federation of Gynaecology and Obstetrics (FIGO) Women's Cancer Committee for FIGO staging of endometrial cancer: 2023 recommends that MIS is a preferred procedure for EC.[6] However, a small number of the early-stage EC patients will recur later and it is relatively fluctuated in management of these recurrent diseases because of very low response rate and most of patients will die of their diseases finally. Therefore, an effective predictive model to offer the better therapeutic guidance (indicators directing the need of postoperative adjuvant therapy, such as systemic toxic agent therapy, immunotherapy, and/or radiation therapy) and provide the useful information for outcome is urgently needed, although the following prognostic factors associated with worse outcomes of EC, such as histology (endometrioid type [type I] and none-endometrioid type [type II]), cell grading (endometrioid type grade 3 considering as type II), deep myometrial invasion (1A [<50% myometrial invasion] and 1B [≥50% myometrial invasion]), lymphovascular space invasion (LVSI), and FIGO stage (stage 1 and stage ≥2) have been frequently used and well-known in the clinical routine practice.[1,2,7,8] However, all of them are based on "surgery-" and "pathology-" findings. Unlike EOC,[9,10] the biomarkers (serum markers) of EC regardless of checking up before or after operation is still uncertain. In the 2023 November issue of the *Journal of the Chinese Medical Association* (*JCMA*), entitled "The relationship between serum CA-125 level and recurrence in surgical stage I EC patients," which attempted to test the equivocal or uncertain role of serum biomarkers, regardless of evaluation before and after operation in the women with surgico-pathological stage 1 none-carcinosarcoma EC either treated with MIS or treated with conventional exploratory laparotomy.[11]

Wu et al[11] retrospectively analyzed 518 women with surgico-pathological stage 1 non-carcinosarcoma EC underwent either MIS-guided (n = 159, 30.7%) or conventional exploratory laparotomy (laparotomy)-guided (n = 359, 69.3%) complete staging surgery at Taipei Veterans General Hospital between 2010 and 2019. During the median follow-up of 49 months, there were 49 women having recurrence (7.9%), resulting in overall progression-free survival (PFS, recurrence-free survival [RFS]) rate of 92.1% in their cohort study.[11] Since their goal was conducted to attempt to determine whether the serum level of CA 125 (carbohydrate antigen 125), regardless of evaluation before and after operation was associated with outcome in women with surgico-pathological stage 1 none-carcinosarcoma EC or not, therefore, all other conventionally-reported prognostic factors had been included for comparison, which included age (≥65 vs <65), body mass index (BMI), Charlson Comorbidity index (CCI, ≥5 vs <5), histology (endometrioid vs non-endometrioid), cell grading (3 vs 1 and 2), FIGO stage (1A vs 1B), LVSI (presence vs absence), tumor size (≥2 vs <2 cm), peritoneal cytology (positivity vs negativity), and postoperative adjuvant therapy (yes vs no).[11] The results showed that except the positive role of postoperative serum level of CA 125, regardless of cutoff value as 35 or 13.75 U/mL, all other evaluated items, such as age, grading, CCI, histology, LVSI, peritoneal cytology, para-aortic lymphadenectomy (done vs skip), FIGO stage (1A vs 1B), tumor size, surgical method (MIS vs laparotomy), postoperative adjuvant therapy, and preoperative serum level of CA 125 (≥35 vs <35) were not associated with disease recurrence.[11] After adjusting all confounding factors using multivariate analysis model, the authors found that only postoperative serum level using cutoff value of 13.75 was an independent risk factor associated with disease recurrence with hazard ratio (HR) of 2.3 (95% confidence interval [CI], 1.1-5.0).[11] Therefore, the authors concluded that a postoperative serum level of CA 125 evaluated within 6 to 12 months after completing staging surgery may be a promising noninvasive biomarker for predicting recurrence.[11] The current study seemed to offer useful information for our routine clinical practice to identify the women having a high possibility of recurrence of their surgico-pathological stage 1 none-carcinosarcoma EC after complete treatment. It is worthy of further discussion.

The essential components of surgical treatment for EC consist at least a total hysterectomy and bilateral salpingo-oophorectomy

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(TAH + BSO).[1,6] Combination of TAH + BSO and pelvic lymph node and/or para-aortic lymph node dissection called as complete staging surgery is considered the optimally standard therapy for EC,[1,6] although some modifications have become much popular, such as the introduction of sentinel node mapping to balancing the therapeutic benefits to post-treatment adverse events (risks).[1,12] Additionally, the need to perform lymph node dissection for EC patients is still debated. It is well-known when the more lymph nodes are removed, the chance to detect metastatic diseases is increased and the chance to successfully eradicate diseased lesions to finish the optimal "debulking surgery" is also increased. it can offer the useful information to predict the patients' outcome and provide a reasonable guidance postoperative adjuvant therapy.[12] In fact, among the clinical stage 1 EC patients, at least 5% to 15% patients will be up-grated to more advanced stage, contributing to the need of postoperative adjuvant therapy for rescue of these EC patients to minimize the negative impact of unpredictable worse outcome on these clinical stage 1 EC patients.[1,5] In fact, upgraded FIGO stage (from FIGO 1 to FIGO 2-4) is not only the most apparent independent factor contributing to poor prognosis,[1] but also results in the heterogenicity of study population with interfering from the identification of new targeted factors in any study. Advanced FIGO stage is a powerful confounding factor.

Although the authors only enrolled the surgico-pathological stage 1 to minimize the negative impact of FIGO stage on prognosis evaluation, they still failed to identify any conventionally-believed poor prognostic factors, such as FIGO grading 3, type II cancer, FIGO IB, and positivity of LVSI in this study. Although it is hard to give an explanation, the authors still reported their thoughts. First, they mentioned that the adequate and effective postoperative adjuvant therapy was applied frequently in the authors' institute to rescue these EC patients with established worse prognosis.[11] The second reason was secondary to small sample size.[11]

By contrast, without being limited by the aforementioned reasons, the authors found that postoperative serum level of CA 125 was apparently valuable acting as predictive factors. The higher postoperative serum level of CA 125 was and the worse prognosis followed. If the cutoff value was defined as ≥13.75 U/mL or ≥35, both showed the significant value in the predicting outcome, since the former was associated with 3-fold increased risk of recurrence and the latter was more apparent because of its association reaching to a 10-fold increased risk of recurrence.[11] Additionally, the median PFS months were only 13 months in patients with ≥35 U/mL CA 125 compared with the median PFS months were 35.5 months in patients with ≥13.75 U/mL CA 125.[11] Although the authors' findings seemed to be reasonable, it is uncertain how to translate the findings into the routine clinical practice. One of the most critical limitation is how to select an appropriate time to evaluate this serum marker.

Fortunately, the authors had offered the best time to evaluate this biomarker, which was defined 6 to 12 months after surgery.[11] They also provided their thought, this timing can avoid the false elevations of CA 125 secondary to the effect of postoperative adjuvant therapy, particularly for those patients undergoing external bean radiotherapy. However, this timing period is too long, with a period of 6 months. That is to say, it is hard to translate this finding into the clinical routine practice.

By the way, it is hard to believe that only one shot (one test) could be a good predictor for the patients' outcome. Therefore, the question "does the one test at once have a real ability to evaluate the severity of disease status" is raised. Additionally, does the serum level of CA 125 represent the severity of disease in EC patients? Even for EOC patients, it is hard to use one single spot of CA 125 to accurately or precisely predict the outcome. Furthermore, as shown by authors, the preoperative serum level of CA 125 was not correlated with outcome. Therefore, it is hard to get the baseline to evaluate these patients. Moreover, what is the baseline of CA125 after complete therapy in EC patients? Was any nadir of CA 125 in their study? All are worthy of more studies to validate their findings.

Taken together, the uncertainty of monitoring serum level of CA 125 postoperatively in routine for the EC patients is still present. However, the authors' finding is still worthy of our applause, if the further study can further validate it. To limit the study subjects into the real homogeneous population may be a better alternative in response to the aforementioned critique. Another suggestion may encourage the authors to perform subgroup analysis. All are not against the effort of authors.

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