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Prognosis of synchronous endometrial and ovarian cancer based on the PROMISE molecular system

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To the Editor: Synchronous endometrial and ovarian cancer (SEOC) was found in approximately 5% of endometrial cancer (EC) patients and 10% of ovarian cancer patients.[1] In the case of concurrent coexistence of endometrial and ovarian carcinomas, there are two scenarios: two independent primary tumors (IPTs) or ECs with ovarian metastases, which have different prognoses and treatment response. Previous studies have shown that endometrioid tumors classified as IPTs had a better prognosis than those classified as FIGO stage IIIA endometrial cancers (IIIA-ECs) (86% *vs*. 58% 5-year survival rates).[2]

However, the distinguishing criteria between endometrial carcinoma with ovarian metastasis and synchronous primary tumors have long been debated in the past. The massive parallel sequencing-based clonality analyses found that low-grade endometrioid carcinomas of endometrium and ovary displayed strikingly similar repertoires of somatic mutations and gene copy number alterations. The consistent mutational processes support the dissemination from one site to the other.[3] Another study supports the view that precursor cells of EC spread beyond the uterus to reach the pelvis and eventually evolve into cancer under an increasing mutational burden.[4] As it is difficult to distinguish between IPTs and metastatic cancer (MC) clinically, the concurrent management of SEOC was based on risk stratification. The patients fulfilling the following criteria could be managed without adjuvant treatment after surgery: (1) low-grade endometrioid morphology, (2) no more than superficial myometrial invasion, and (3) absence of lymph vascular space invasion and additional metastases.[5] Otherwise, it should be managed as a high-risk group and receive external beam radiotherapy (EBRT) with concurrent and adjuvant chemotherapy, or six-cycle chemotherapy alone.[5]

In 2013, the Cancer Genome Atlas (TCGA) Research Network categorized EC into four categories based on the tumor mutation burden and copy-number variants: DNA polymerase epsilon mutation (POLE, ultramutated), microsatellite instability (MSI, hypermutated), copy-number low (endometrioid), and copy-number high (serous-like) subtypes. The prognostic and treatment-predictive values of the molecular systems have been confirmed in EC by a large number of publications. To improve its availability in clinical practice, this molecular system was further replaced by the Proactive Molecular Risk Classifier for Endometrial Cancers (ProMisE) system with immunohistochemistry for the presence of mismatch repair (MMR) proteins, *P53* mutation, and sequencing for the presence of POLE exonuclease domain mutations.[6] SEOC shares a similar morphological and molecular feature to EC. So far, no study has assessed its value in reflecting the prognosis and guiding the postoperative treatment of EC. Therefore, we aimed to investigate the molecular system distribution and its predictive value on prognosis in SEOC.

The study has been approved by the Institutional Review Board from the study center (No. 2022-KY-100-01). Informed consent was waived for the retrospective study. All eligible patients were separated into three groups based on the immunohistochemical examination of EC, mismatch repair deficient group (MMRd, alternative of the MSI group), *P53*-abnormal (*P53*abn, alternative of the copy-number high group), and no specific molecular profile (NSMP, alternative of the copy-number low group). The eligibility criteria, data collection, outcome assessment, and statistical analysis are shown in Supplementary Materials, http://links.lww.com/CM9/B947.

Of the 3507 patients with endometrial or ovarian cancer reviewed, 85 cases had SEOC. Of 85 patients, 87.1% (74/85) cases were available for molecular analysis and further divided into three subgroups based on molecular analysis: *P53*abn EC (n = 21, 28.4%), MMRd (n = 17;

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23.0%), and NSMP (*n* = 36; 48.6%) [Supplementary Figure 1, http://links.lww.com/CM9/B947]. The demographic and clinical characteristics of patients in the whole cohort are summarized in Supplementary Table 1, http://links.lww.com/CM9/B947. There is no difference in the ages of the three groups (*P53*abn, MMRd, *vs*. NSMP: 53.25 ± 10.75, 50.59 ± 7.91, *vs*. 52.22 ± 8.01 years, $P = 0.640$). Although no statistically significant difference was reached, the MMRd group tended to have fewer menopause patients (MMRd, *P53*abn, *vs*. NSMP = 29.4%, 50%, *vs*. 55.6%) and more family history of cancer (MMRd, *P53*abn, *vs*. NSMP = 47.1%, 25%, *vs*. 25%). Interestingly, patients in the MMRd group have lower rates of adenomyosis than patients in the *P53*abn and NSMP subgroups (MMRd, *P53*abn, *vs*. NSMP = 11.8%, 47.6%, *vs*. 47.2%, $P = 0.031$). No significant differences were found in the rates of metabolic-related diseases (including diabetes, hypertension, hyperlipemia, and obesity) among these three groups.

Patients of the *P53*abn group had a higher rate of non-endometroid types than other groups (*P53*abn, MMRd, *vs*. NSMP group = 3.3%, 0 *vs*. 5.6%, $P = 0.003$). Consistently, the rates of high grade (grade 3) differentiation were also higher in the *P53*abn group than in the MMRd or NSMP group (*P53*abn, MMRd, *vs*. NSMP = 52.4%, 29.4%, *vs*. 16.7%, $P = 0.170$). Postoperative pathology showed that patients of the *P53*abn group have a higher rate of lymph node metastasis rates (*P53*abn, MMRd, *vs*. NSMP = 33.3%, 29.4%, *vs*. 8.3%, $P = 0.038$). Although no statistical difference was reached, patients of the *P53*abn group tend to have higher rates of deep myometrial invasion (*P53*abn, MMRd, *vs*. NSMP = 47.6%, 35.3%, *vs*. 25%, $P = 0.217$), and cervical stromal invasion rates (*P53*abn, MMRd, *vs*. NSMP = 33.3%, 17.6%, *vs*. 19.4%, $P = 0.439$). No significant differences were found in the other tumor information (including parametrial involvement, microcystic, elongated and fragmented (MELF) infiltrating, and malignant peritoneal cytology) among the three subgroups. The postoperative treatment (chemoradiation *vs*. chemotherapy) was well-balanced among different molecular subgroups.

The median follow-up time of the total cohort was 33.2 months (range 13.4–51.5). The number of lost follow-up patients in the *P53*abn, dMMR, and NSMP groups was 1 (4.76%), 0, and 2 (5.56%) , respectively. And the recurrence rates in the patients of the *P53*abn, MMRd, and NSMP groups were 6 (28.6%), 1 (5.9%), and 0, respectively. The 3-year and 5-year progression-free survival (PFS) was 82.23% (95% confidence interval [CI]: 56.08–94.34%) and 65.55% (95% CI: 34.13–84.70%) for patients in the *P53*abn group. Both 3-year and 5-year PFS of the MMRd and NSMP groups were 93.33% (95% CI: 61.26–99.03%) for only one recurrence, respectively. Patients with *P53*abn showed a higher risk of recurrence with NSMP (hazard ratio [HR]: 5.09 [95% CI: 1.12–23.19], $P = 0.029$). Compared to patients with MMRd, patients with *P53*abn did not show a higher risk of recurrence (HR: 2.72 [95% CI: 0.56–13.26], $P = 0.289$). There was no significant difference in the recurrence-free survival between the MMRd and NSMP groups [Figure 1A]. Of the six recurrences in the *P53*abn group, three occurred in the pelvis, one in non-pelvic sites, and the locations of two recurrences were unknown. Both the recurrence of the MMRd group and that of the NSMP group were in the pelvis. The 3-year and 5-year rates of overall survival (OS) were 88.54% (95% CI: 61.39–97.01%) and 72.44% (95% CI: 41.24–88.93%) for women with *P53*abn. The 3-year and 5-year rates of OS were the same in the MMRd group: 90% (95% CI: 47.30–98.53%), and no death occurred in the NSMP group. Similar to PFS, patients with *P53*abn also showed a higher risk of death than patients with NSMP (HR: 7.31 [95% CI: 1.22–43.83], $P = 0.032$). No statictically significant differences were found in the risk of death between patients with *P53*abn and MMRd (HR: 2.37 [95% CI: 0.46–12.15], $P = 0.353$) and patients with MMRd and NSMP (HR: 18.2 [95% CI: 0.29–1123], $P = 0.168$) [Figure 1B].

To better predict the survival outcomes of the patients with high-risk factors, we established the prognostic modality with Cox-nomogram.[7] The modality was developed based on *P53* mutation and another four independent prognostic factors identified with least absolute

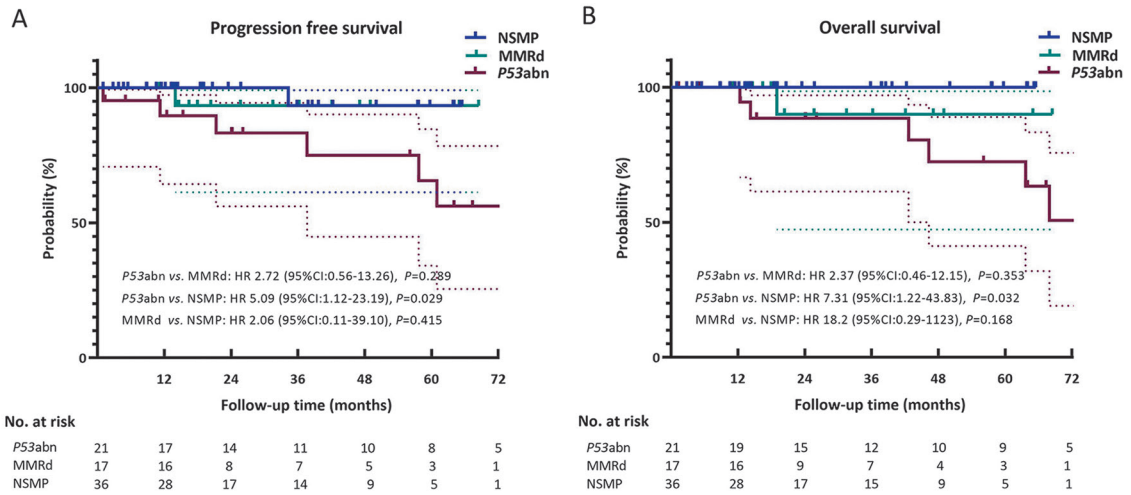

Figure 1: The (A) PFS and (B) OS of patients in different molecular subgroups. HR: Hazard ratio; MMRd: MMR-deficient; NSMP: No specific molecular profile; OS: Overall survival; PFS: Progression-free survival.

shrinkage and selection operator (LASSO) regression (including deep myometrial invasion, ovarian laterals, lymph node metastasis, and Ki-67 scores) [Supplementary Figure 2A, http://links.lww.com/CM9/B947]. The C-index of the modeling was 0.890 (95% CI: 0.774–0.999). To assess the availability of the nomogram, the patients were classified into low-risk (score 0–110) and high-risk groups (score >110) according to the predicted 7-year survival probability of 70%. The 3-year and 5-year OS were 89.06% and 67.86% for the patients in the high-risk group, respectively, while both the 3-year and 5-year OS were 96.97% in the low-risk group. Consistently, the 3-year and 5-year PFS were 87.18% and 25.83%, respectively, for the patients in the high-risk group, while both the 3-year and 5-year PFS were 96.97% in the low-risk group. Compared to the patients in the low-risk group, the hazard ratios of recurrence and death were 13.97 (95% CI: 2.78–70.33) and 12.74 (95% CI: 2.15–75.47) in the high-risk group, respectively [Supplementary Figure 2B–C, http://links.lww.com/CM9/B947].

Also, we further compared different postoperative adjuvant treatment modalities (six cycles of chemotherapy alone *vs*. sequential chemoradiation) in the same molecular subgroups. The adjuvant information was not available in three (14.3%) cases of the *P53*abn group, six (35.3%) cases of the MMRd group, and five (13.9%) cases of the NSMP group due to unknown or incomplete information of adjuvant treatment. In the MMRd group, only two patients received adjuvant chemotherapy alone, and most patients received sequential chemoradiation. Further, 44.4% (16/36) of the patients of the NSMP group received sequential chemoradiation and 36.1% (13/36) of the patients received six cycles of chemotherapy alone, whereas 38.1% (8/21) of the patients in the *P53*abn group received sequential chemoradiation and 47.6% (10/21) of the patients received six cycles of chemotherapy alone. Both long-cycle chemotherapies alone and sequential chemoradiation have overlapping relapse-free and OS rates in the *P53*abn and NSMP groups [see Supplementary Figure 3, http://links.lww.com/CM9/B947].

This study compared the prognosis of SEOC with different molecular signatures and established a prognostic modality based on its molecular signatures. The results showed that SEOC patients with the *P53*abn signature were associated with a significantly worse prognosis than patients with NSMP. Our study did not investigate the POLE mutations for their low occurrences and favorable prognosis. However, this did not affect its application, especially in developing countries without universal promotion. We also compared the sequential chemoradiation and long-cycle chemotherapy in the NSMP and *P53*abn groups. However, no significant differences were found for sample size restriction and more studies are needed to investigate the treatment responses in SEOC patients.

Turashvili *et al*[8] proposed a risk-based stratification in SEOC: a high-risk group comprising non-endometroid EC with ≥50% myometrial invasion irrespective of lymph node status, and a low-risk group consisting of all endometroid EC, as well as lymph node-negative non-endometroid EC with <50% myometrial invasion. The risk-based classification was superior to the original classification of ECs as IPTs *vs*. IIIA-EC for predicting PFS (log-rank test, P <0.001 *vs*. P = 0.07).[8] To better identify the high-risk patients, we established a prognostic modality based on *P53*abn and four other independent prognostic factors. The C-index of the modeling was 0.89, which showed a good discrimination. The 3-year and 5-year PFS was 96.97% in the low-risk groups. The results of our study provide the theoretical basis for predicting the prognosis and decision-maker in the individualized management of this population.

Conflicts of interest

None.

Availability of data and materials

All the data obtained and analyzed during the present study are available from the corresponding authors on reasonable request.

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