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Practice Guideline

Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology consensus statement

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ABSTRACT

The Korean Society of Gynecologic Oncology (KSGO) had been making an effort to standardize and enhance the quality of domestic uterine corpus cancer treatment by developing updated clinical practice guidelines in 2021. The KSGO revised the guidelines based on a literature search using 4 key elements: Population, Intervention, Comparison, and Outcome framework. These elements include the evaluation of the efficacy and safety of immune checkpoint inhibitor treatment in recurrent/advanced endometrial cancer patients who have failed platinum-based chemotherapy, as well as the effect of combined treatment with trastuzumab in patients with HER2/neu-positive endometrial cancer. Additionally, the guideline assessed the efficacy and safety of omitting lymph node dissection in low-risk endometrial cancer patients, investigated the effect of sentinel lymph node mapping in early-stage endometrial cancer surgery, addressed the outcome of chemoradiation therapy as a postoperative treatment in patients with advanced (stage III–IVA) endometrial cancer, and explored the impact of initial treatment with immune checkpoint inhibitors on survival in patients with advanced or recurrent endometrial cancer patients.

Keywords: Endometrial neoplasm; Survival; Immune checkpoint inhibitor; Trastuzumab; Surgery; Sentinel lymph node

Synopsis

The committee of uterine corpus cancer of the Korean Society of Gynecologic Oncology developed updated guideline for treatments of uterine corpus cancer patients. Evidences of recommendation according to each key question were evaluated using systematic review and meta-analysis.

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INTRODUCTION

Endometrial cancer diagnoses have increased worldwide in recent years, with the highest incidence rates in North America and Europe [1], and the rates are also continue rising in Korea, as we can see from the annual percent change of 3.5% from 2009 to 2015 [2]. The purpose of developing a clinical practice guideline for uterine corpus cancer by the Korean Society of Gynecologic Oncology (KSGO) is to standardize and enhance the level of domestic endometrial cancer treatment and to improve the survival rates of patients with endometrial cancer in Korea. The Committee on Uterine Corpus Cancer of the KSGO has previously provided and updated practical guidelines for uterine corpus cancer in 2006, 2010, 2016, and 2021.

The guidelines seek to establish a set of standardized protocols for detecting and treating primary/recurrent endometrial cancer including a delineation of indications for primary treatments such as surgery, chemotherapy, chemoradiation therapy, and immunotherapy. Through these guidelines, the KSGO aims to support the healthcare professionals with the latest evidence and provide a resource for making the most appropriate clinical decisions.

METHODS

1. Developing the recommendations

Key questions in this practice guideline were developed by focusing on the latest notable findings and important issues in endometrial cancer. Priority was given to the importance of key questions, disease burden, and variations in treatment. Members of the uterine corpus cancer committee and the other gynecologic cancer committees brainstormed and reviewed the list of key questions in the existing practice guideline of 2021. This new practice guideline was finalized through a vote by the recommendation of the gynecologic cancer committees at a meeting to confirm the key questions (**Data S1**). This practice guideline is developed de novo, following a systematic review of each key question. Initially, Population, Intervention, Comparison, and Outcome (PICO) items were defined and specified for each key question. Subsequently, literature search, selection, and exclusion processes were conducted based on these criteria. Finally, meta-analyses and systematic reviews were performed on the included literature to generate evidence for establishing the direction and strength of recommendations.

2. The strategy of literature search

The main keywords for the PICO items of each key question were converted into search terms (MeSH, free text, and Emtree) of each database to create a search formula. Databases included in the literature search were Medline, Embase, Cochrane CENTRAL, KoreaMed, and KMbase, and only literature written in Korean and English were included in the search (**Data S2**). Animal studies and systematic review articles were excluded from the search. Afterwards, search results from multiple databases were combined to exclude duplicates.

3. Selection criteria

Two researchers independently conducted literature selection and exclusion based on the specified criteria for each key question. Any discrepancies between the investigators were resolved through discussion. To prevent the inclusion of redundant information from studies with overlapping patient groups, only studies with the most comprehensive data were chosen (**Data S3**).

4. Data extraction, outcomes of interests, and risk of bias

Two researchers independently gathered relevant data from the studies using the checklist corresponding to each key question. Discrepancies between the investigators were addressed through discussion. The primary outcome variable, progression-free survival (PFS), was defined as the duration between randomization and either disease progression or death from any cause. Overall survival (OS), considered a secondary outcome, was defined as the time between randomization and death from any cause. Safety assessment involved the evaluation of adverse outcomes rated as ≥3.

The quality assessment of the included studies was independently conducted by the 2 investigators using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0 version) [3]. Any disparities between investigators were resolved through discussion.

5. Meta-analysis

The meta-analysis was conducted utilizing Review Manager Version 5.4.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark). Significance was attributed to p-values <0.05. Random-effects models were employed for survival analysis, employing the Inverse Variance method. Adverse events were also analyzed using random-effects models through the Mantel–Haenszel method. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were computed for survival outcomes, while odds ratios (ORs) were calculated for adverse events. Heterogeneities among HRs and ORs across studies were evaluated using the I2 statistic and Cochran's Q statistic. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profiles were generated using GRADEpro GDT.

6. Quality of evidence

The GRADE system guidelines were utilized for assessing the quality of evidence related to the outcomes [4]. In the guideline, the levels of evidence quality are delineated as follows: high quality, suggesting that additional research is unlikely to alter the confidence in the estimated effect; moderate quality, indicating that further research is likely to significantly impact confidence in the estimate and may result in a change; low quality, signifying that further research is highly likely to substantially affect confidence in the estimate and is likely to bring about a change; very low quality, indicating minimal confidence in the estimated effect. The GRADE guidelines encompass a systematic evaluation of evidence quality, consideration of the risk–benefit balance, and subsequent assessment of the strengths of recommendations.

7. Strength recommendation

The strengths of recommendations were evaluated according to the risk of bias, inconsistency, indirectness, and imprecision of the literature included in the review. The certainty of the evidence was expressed in 4 levels: high, moderate, low, and very low. According to GRADE guidelines, the strength of a recommendation is characterized by the confidence in whether the positive outcomes of an intervention outweigh its negative consequences. In strong recommendations, nearly all well-informed individuals would opt either for or against the intervention. Conversely, in weak or conditional recommendations, while many informed individuals would choose the recommended course of action, a significant number might not (**Table 1**).

Table 1. Strength of recommendation

For	Strong For
	Weak/Conditional For
Against	Weak/Conditional Against
	Strong Against

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EVIDENCE

1. Key question 1: Does immune checkpoint inhibitor treatment improve survival in patients with advanced or recurrent endometrial cancer, who have failed treatment with platinum-based chemotherapy?

A 830 studies were identified from the literature review on this key question, and one randomized Phase 3 clinical study that met the eligibility criteria [5] was included in the analysis (**Data S3**). This was a study published by Makker et al. [5] in 2022, termed 309–KEYNOTE-775. This study observed the effectiveness and adverse events of the immune checkpoint inhibitor pembrolizumab combined with the angiogenesis inhibitor lenvatinib and conventional chemotherapy (doxorubicin or paclitaxel) for patients with advanced and recurrent endometrial cancer [5]. The risk of bias was low as the study was a large-scale, multi-country, multi-center analysis and was conducted as planned. As a result, confidence in the study result was high.

Results of the risk of the bias assessments are shown in **Data S4**. The OS and the PFS, and adverse events of ≥ grade 3 are shown in **Data S5**.

PFS & OS

Among all 827 patients, the pembrolizumab + lenvatinib group (n=411) had significantly higher PFS (HR=0.56; 95% CI=0.47–0.66) and OS (HR=0.62; 95% CI=0.51–0.75) compared to the chemotherapy group (n=416) (**Data S5**). In a subgroup analysis of MMR-proficient patients, there was a significant difference in PFS between the pembrolizumab + lenvatinib group and the chemotherapy group at 6.6 months and 3.8 months, respectively (HR=0.60; 95% CI=0.50–0.72).

Adverse events ≥ grade 3

Based on the Study 309–KEYNOTE-775, 88.9% of the pembrolizumab + lenvatinib group and 72.7% of the chemotherapy group experienced adverse events at grade 3 or higher, and the difference was statistically significant (OR=2.96; 95% CI=2.02–4.34). The most common adverse event was hypertension (37.9%) in the pembrolizumab + lenvatinib group and neutropenia (25.8%) in the chemotherapy group. In the pembrolizumab + lenvatinib group, dose reduction was 66.5%, dose interruption was 69.2%, and trial-drug discontinuation was 33.0%. In the chemotherapy group, dose reduction was 12.9%, dose interruption was 27.1%, and trial-drug discontinuation was 8.0%. Deaths directly related to the treatment drugs were 5.7% in the pembrolizumab + lenvatinib group and 4.9% in the chemotherapy group.

Based on the above results, the following was recommended:

> Immune checkpoint inhibitor-based treatment is recommended for patients with advanced or recurrent endometrial cancer who have failed treatment with platinum-based anti-cancer drugs (Strong for).

2. Key question 2: Does combined treatment with trastuzumab improve survival in patients with HER2/neu-positive endometrial cancer?

335 studies were identified from the literature review on this key question, and one randomized phase 2 clinical study [6] that met the eligibility criteria was included in the

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analysis (**Data S3**). The study was a clinical study published by Fader et al. [6] in 2020. The effectiveness and adverse events the combination of trastuzumab with paclitaxel + carboplatin in patients with advanced (stage III–IV) or recurrent serous endometrial cancer were compared with the group of patients who received only paclitaxel + carboplatin [6]. This was a randomized prospective research study, and the analysis was performed as planned. Therefore, it is judged that the risk of bias is low and the confidence in the research results is high.

PFS & OS

Based on the studies included in the analysis, PFS (HR=0.46; 95% CI=0.28–0.76) and OS (HR=0.58; 95% CI=0.34–1.00) were significantly higher in the trastuzumab + paclitaxel + carboplatin group (n=30) compared to the chemotherapy group (n=28). In the sub-analysis results, the median PFS of advanced (stage III–IV) patients (n=41) was 17.7 months in the trastuzumab combination patient group, which was superior to 9.3 months in the non-combination patient group (HR=0.44; 90% CI=0.23–0.83, p=0.015). In patients who relapse, PFS was 9.2 in the trastuzumab combination patient group, which was also superior to 7.0 months in the non-combination patient group (HR=0.12; 90% CI=0.03–0.48; p=0.004). The group with the most significant difference in survival was the advanced patient group, which showed an HR of 0.49 for OS (90% CI=0.25–0.97; p=0.041) (**Data S5**).

Adverse events ≥ grade 3

Based on the studies included in the analysis, fewer adverse events occurred in the trastuzumab combination group (31.3% vs. 46.4%; any grade; OR=0.52; 95% CI=0.18–1.50), but was not statistically significant (p=0.49) (**Data S5**). Adverse events of grade 3 or higher included neutropenia (n=1) and pruritus (n=1) in the trastuzumab combination group, and nausea (n=1), abdominal pain (n=1), and pruritus (n=1) in the non-combination group. However, these were all controllable and did not affect continuous drug administration.

Based on the above results, the following was recommended:

> Chemotherapy combined with trastuzumab is recommended for patients with HER2/neu-positive advanced, recurrent serous endometrial cancer (Strong For).

3. Key question 3: Is there a difference in the recurrence rate if lymph node dissection is omitted in the endometrial cancer staging operation for the low-risk group?

3,611 studies were identified from the literature review on this key question, and 2 randomized clinical studies [7,8] that met the eligibility criteria were included in the analysis (**Data S3**). The studies were conducted by Benedetti Panici et al. [7] and the ASTEC study group in 2008 and 2009, respectively [8]. Both studies were large prospective randomized clinical trials, in particular, the study by the ASTEC study group was conducted at 85 centers located in 4 countries, and the analyses were performed as planned. Therefore, the risk of bias was considered low and there was high confidence in the study results.

PFS & OS

When combining the results of the 2 studies included in the analysis (n=1,922), there was no significant difference in PFS between the group in which pelvic lymph node dissection was performed (n=968) and the group in which pelvic lymph node dissection was omitted (n=954)

(PFS, HR=1.20; 95% CI=0.94–1.53). Therefore, when combining the results of the 2 studies, it was determined that omitting pelvic lymph node dissection does not reduce the recurrence rate in low-risk endometrial cancer. It was also same for OS (HR=1.08; 95% CI=0.81–1.44) (**Data S6** and **S7**).

Adverse events ≥ grade 3

In the 2 studies included in the analysis, Benedetti Panici et al. [7] reported a significant difference in postoperative complications, which occurred in 30.7% of the pelvic lymph node dissection group and 13.6% of the non-dissection group (p=0.001). The difference was caused primarily by lymph cysts and lymphedema. According to a study by the ASTEC study group, low short-term postoperative complications were observed in both the pelvic lymph node dissection and non-dissection groups. However, bowel obstruction (3% vs. 1%), deep vein thrombosis (1% vs. 0.1%), lymph cysts (1% vs. 0.3%), and surgical site opening (1% vs. 0.3%) were more common in the dissection group than non-dissection group, which was not statistically significant (**Data S6** and **S7**).

Based on the above results, the following was recommended:

> Pelvic lymph node dissection can be omitted in endometrial cancer staging operation for patients with low risk (Weak/Conditional for).

4. Key question 4: Is there a difference in the recurrence rate between sentinel lymph node mapping and conventional lymph node dissection in early-stage endometrial cancer surgery?

371 studies were identified by the literature review on this key question (**Data S3**). However, there were no studies that met the eligibility criteria. Therefore, it was decided to make a recommendation based on expert opinion. A meta-analysis, based on these recommendations, was conducted on 4 retrospective studies [9-12] related to recurrence and PFS rates, and the results were referred to for judgment. When each study was analyzed through ROBINS-I, various degrees of bias were observed in several domains (**Data S4**). In addition, when all the results of the studies were combined, the risk of bias was very serious, consistency was seriously lacking, and imprecision was also serious, except for indirectness. Therefore, the level of evidence was evaluated as very low.

PFS

When combining the results of the 4 studies included in the analysis (n=847), there was no significant difference in the recurrence rate (OR=0.72; 95% CI=0.45–1.17) and PFS (PFS, HR=0.82; 95% CI=0.63–1.06) between the sentinel lymph node mapping group (n=481) and the conventional lymph node dissection group (n=366). Therefore, when combining the results of the 2 studies, it was determined that there was no difference in the recurrence rate and PFS between sentinel lymph node mapping and conventional lymph node dissection in early endometrial cancer (**Data S6** and **S7**).

Adverse events ≥ grade 3

The 4 studies included in the analysis could not be evaluated in this regard since postoperative complications or adverse events were not described. However, according to a recent review article that compared sentinel lymph node mapping and conventional lymph

node dissection [13], sentinel lymph node mapping can reduce surgery-related complications and long-term complications such as lymph cysts and lymphedema that occur with conventional lymph node dissection. Considering these results, the risk of sentinel lymph node mapping is lower than that of conventional lymph node dissection.

Based on the above results, the following was recommended:

> Sentinel lymph node mapping can be performed during the staging operation for early-stage endometrial cancer (Weak/Conditional for).

5. Key question 5: Does chemoradiotherapy, as a postoperative adjuvant treatment, improve the survival rate compared to chemotherapy in patients with advanced endometrial cancer?

The literature review on this key question identified 749 studies, and one randomized phase 3 clinical study [14] that met the eligibility criteria was included in the analysis (**Data S3**). The study is termed, GOG 258, and was published by Matei et al. [14] in 2019, which compared chemoradiation therapy with chemotherapy as a postoperative treatment for patients with stage III–IVA endometrial cancer. This was a large-scale, multi-country, multicenter study, and the analysis was conducted as planned. Therefore, the risk of bias was considered low, and the study results have moderate certainty (**Data S4**).

PFS

We searched for randomized Phase 3 clinical studies that compared chemoradiation therapy (cisplatin 50 mg/m^2 IV at D1, D 29 with external beam radiation therapy (EBRT) + paclitaxel 175 mg/m^2/carboplatin 5–6 AUC q 3 weeks × 4 cycles) and chemotherapy (paclitaxel 175 mg/m^2 + carboplatin 5–6 AUC q 3 weeks × 6 cycles) as postoperative treatment for patients with advanced (stage III–IVA) endometrial cancer, and the GOG 258 study was the only one selected for analysis. In 736 patients, there was no significant difference in PFS (HR=0.90; 95% CI=0.74–1.09) when treated with chemoradiation therapy compared to chemotherapy. However, 5-year incidence of vaginal recurrence (2% vs. 7%; HR=0.36; 95% CI=0.16–0.82) and the 5-year pelvic or paraaortic lymph node recurrence (11% vs. 20%; HR=0.43; 95% CI=0.28–0.66) showed a significant difference.

Adverse events ≥ grade 3

In the GOG 258 study, the incidence of grade 3 or higher complications was 62.9% in the chemoradiation therapy group and 58.4% in the chemotherapy group, which tended to be higher in the chemoradiation group. However, there was no statistical significance (OR=0.83; 95% CI=0.61–1.12). Grade 4 or higher complications were 14% in the chemoradiation group and 30% in the chemotherapy group. The most observed complications of grade 3 or higher in the entire patient group were blood- and bone marrow-related complications, with a statistically significantly higher incidence in chemotherapy (p=0.01).

Based on the above results, the following was recommended:

> Chemoradiotherapy or chemotherapy can be performed after surgery in patients with advanced endometrial cancer (Weak/Conditional for).

6. Key question 6: Does immune checkpoint inhibitors plus chemotherapy improve survival in patients with advanced or first recurrent endometrial cancer?

A total of 2 phase 3 multinational, multicenter, randomized clinical trials were included in the analysis from conducting a literature review on the key question (**Data S3**). These studies are the NRG-GY018 and RUBY clinical studies, which combined paclitaxel + carboplatin with pembrolizumab and dostarlimab, respectively [15,16]. These studies were large-scale, multi-country, multi-center studies, and the analyses were conducted as planned. Therefore, it is considered that the risk of bias is low and there is high confidence in the study results (**Data S4**).

PFS & OS

Based on the results of the 2 clinical studies included in the analysis, patients who received chemotherapy combined with immune checkpoint inhibitors and patients who received conventional chemotherapy for advanced or recurrent endometrial cancer were classified into the mismatch repair-deficient (dMMR) group and mismatch repair-proficient (pMMR) group. When evaluating these 2 groups, PFS in the dMMR group was HR of 0.29 (95% CI=0.20–0.42) in the immune checkpoint inhibitor combination group, showing improved results compared to the conventional chemotherapy group. In the pMMR group, the improvement effect was lower than that of dMMR group, but the immune checkpoint inhibitor combination group showed an improvement in PFS with HR of 0.64 (95% CI=0.46–0.90) compared to the conventional chemotherapy group. In the case of OS, HR in the immune checkpoint inhibitor combination group was improved to 0.30 (95% CI=0.13–0.69) in the dMMR group compared to the conventional chemotherapy group. In addition, HR in the pMMR group was 0.73 (95% CI=0.52–1.02).

Adverse events ≥ grade 3

In the NRG-GY018 clinical study [15], adverse events of grade 3 or higher were reported in the immune checkpoint inhibitor combination group and non-combination group by distinguishing between pMMR and dMMR. In the RUBY clinical study, adverse events of grade 3 or higher were reported in the immune checkpoint inhibitor combination group and non-combination group in all patients (all population). Among all patients in the dMMR and pMMR groups, the immune checkpoint inhibitor combination group had OR=1.93 (95% CI=1.12–3.33), OR=1.48 (95% CI=1.06–2.07), and OR=1.61 (95% CI=1.11–2.35), respectively, showing a significant increase in adverse events compared to the non-combination group. In the NRG-GY018 clinical study, the most common adverse event of grade 3 or higher in the dMMR group was anemia (19.3%) in the immune checkpoint inhibitor combination group and neutropenia (17.0%) in the non-combination group. In the pMMR group, neutropenia was the most common adverse event in both the immune checkpoint inhibitor combination group and the non-combination group (18.5% vs. 12.0%). In the RUBY clinical study, the most common adverse event of grade 3 or higher was anemia (14.9% vs. 16.3%). Deaths directly related to immune checkpoint inhibitors include 5 cases (vs. 0 case) in the immune checkpoint inhibitor combination and non-combination groups of the RUBY clinical study, and 1 case (vs.2 cases) in the dMMR group and 6 cases (vs. 2 cases) in the pMMR group of the NRG-GY018 clinical study. However, based on the study results, most adverse events were considered controllable and at a level where treatment could be continued.

Based on the above results, the following was recommended:

> Immune checkpoint inhibitors in combination with chemotherapy as first-line therapy are recommended in patients with primary advanced or first recurrent endometrial cancer (Weak/Conditional for).

DISCUSSION

The recommendations for the treatment of endometrial cancer described in this paper were prepared based on a systematic review and meta-analysis of recently published studies, and changes in treatment protocols. Researchers from a myriad of studies have compared effects and adverse events of the combination therapy of an immune checkpoint inhibitor (pembrolizumab), an angiogenesis inhibitor (lenvatinib), and a cytotoxic chemotherapeutic agent (doxorubicin or paclitaxel) in patients with advanced and recurrent endometrial cancer who failed platinum-based chemotherapy [5]. According to the results of the study 309–KEYNOTE-775, the pembrolizumab + lenvatinib group showed significant increases in PFS and OS compared to the conventional chemotherapy group, and the differences were more noticeable in MMR-proficient patients. Adverse events of grade 3 or higher were still reported during the treatment, but these side effects were controllable and did not reach the threshold at which patients should discontinue the medication. It can be concluded from the outcomes that the overall benefits of immune checkpoint inhibitor-based treatment outweigh the risks in patients with recurrent or metastatic endometrial cancer who have failed platinum-based anti-cancer drugs. Therefore, this guideline proposes application of the immune checkpoint inhibitor-based treatment (pembrolizumab + lenvatinib) for such patients. In a phase I clinical trial, GARNET, which investigated efficacy of the immune checkpoint inhibitor dostarlimab in patients with recurrent endometrial cancer, administration of dostarlimab to patients who had received a maximum of 2 prior treatments for recurrent or advanced disease, after platinum-based doublet therapy, resulted in an overall response rate (ORR) of 45.5% in the dMMR/microsatellite-hihg (MSI-H) group and 15.4% in the pMMR group [17]. The median duration of response (DOR) was not reached in the dMMR/MSI-H group, while it was 19.4 months in the pMMR group. Although there were differences in ORR and DOR based on MMR status, the GARNET study ultimately demonstrated that dostarlimab exhibited favorable antitumor activity in endometrial cancer regardless of the MMR status [17]. This suggests that, in patients with recurrent endometrial cancer who have failed primary platinum therapy, dostarlimab can be considered as a subsequent treatment option along with pembrolizumab.

As reported on publications of 2 randomized controlled trials (RCTs), the combination of an immune checkpoint inhibitor (pembrolizumab or dostarlimab) with the conventional chemotherapy (paclitaxel + carboplatin) led to significant improvements in PFS and OS in advanced and recurrent endometrial cancer [15,16]. It was especially evident in the dMMR group compared to the improvements in the pMMR group. The combination therapy with the immune checkpoint inhibitors causes a considerable increase in side effects; however, in most cases, the level of harm is not life-threatening. A recent phase III DUO-E trial investigated the combination of carboplatin/paclitaxel with maintenance therapy of durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer [18]. Results showed a significant PFS benefit in both the durvalumab arm (HR=0.71; 95% CI=0.57–0.89) and the durvalumab plus olaparib arm (HR=0.55; 95%

CI=0.43–0.69) compared to the control arm [18]. Subgroup analyses indicated PFS benefits in dMMR and pMMR subgroups, as well as in PD-L1–positive subgroups. In conclusion, primary treatment of carboplatin/paclitaxel plus durvalumab with or without olaparib demonstrated a significant and clinically meaningful PFS benefit in advanced or recurrent endometrial cancer patients [18]. Furthermore, the phase 3 AtTEnd trial, involving patients with advanced/recurrent endometrial carcinoma, explored the efficacy of atezolizumab in combination with standard chemotherapy (paclitaxel + carboplatin) [19]. Among the 551 enrolled patients, after a median follow-up of 26.2 months, those dMMR group showed significantly improved PFS (HR=0.36; 95% CI=0.23–0.57) with atezolizumab. A favorable trend in PFS was observed for all participants. Interim analysis indicated potential benefits in ORR of 82.4%, confirming the efficacy of atezolizumab in dMMR patients. Grade 3 or higher adverse events were manageable. This study suggests that adding atezolizumab to standard chemotherapy provides a meaningful PFS benefit, especially in patients with dMMR [19]. The studies aforementioned have moreover corroborated that the benefits outweigh the risks when combining immune checkpoint inhibitors with initial standard chemotherapy. We recommend using immune checkpoint inhibitors (pembrolizumab, dostarlimab, durvalumab or atezolizumab) at the point of initial treatment for advanced or recurrent endometrial cancer patients.

In a clinical study published by Fader et al. [6] in 2020, the treatment effect and adverse events of trastuzumab combined with paclitaxel + carboplatin in patients with advanced (stage III–IV), recurrent serous endometrial cancer were compared with the group of patients who were administered only paclitaxel + carboplatin. Based on the study results included in the analysis, the trastuzumab + paclitaxel + carboplatin group showed a significant increase in PFS and OS compared to the paclitaxel + carboplatin group. In addition, adverse events of grade 3 or higher that occurred during the treatment did not significantly increase in the trastuzumab group. All the adverse events were controllable and at a level that allowed the patient to continue treatment. Therefore, the overall benefit of treatment combined with trastuzumab is more significant for patients with HER2/neu-positive recurrent or metastatic endometrial cancer. This guideline recommends treatment combined with trastuzumab for patients with HER2/neu-positive advanced or recurrent serous endometrial cancer.

According to 2 RCTs on staging operations in low-risk endometrial cancer patients, omitting pelvic lymph node dissection does not have a significant negative effect on recurrence, PFS or OS [7,8]. Instead, omitting pelvic lymph node dissection resulted in fewer postoperative complications overall, and the study by Panici et al. showed a statistically significant difference. Therefore, omitting pelvic lymph node dissection in low-risk endometrial cancer staging surgery is considered to have fewer risks. However, there is no statistical benefit in terms of recurrence and PFS.

There was no RCT comparing the survival rates of sentinel lymph node mapping and conventional lymphadenectomy in surgery for early endometrial cancer. We conducted meta-analyses of 4 retrospective studies [9-12] on recurrence and PFS in sentinel or conventional lymphadenectomy groups and found that sentinel lymph node mapping does not have a significant negative effect on recurrence or PFS compared to conventional lymphadenectomy. Instead, a literature review confirmed that sentinel lymph node mapping causes fewer complications than conventional lymphadenectomy where less harm is expected [13]. Therefore, we can claim that sentinel lymph node mapping can be performed in surgery for early-stage endometrial cancer.

In a randomized phase 3 clinical study comparing chemoradiation therapy (cisplatin 50 mg/m^2 IV at D1, D 29 with EBRT + paclitaxel 175 mg/m^2/carboplatin 5–6 AUC q 3 weeks × 4 cycles) and chemotherapy (paclitaxel 175 mg/m^2 + carboplatin 5–6 AUC q 3 weeks × 6 cycles) as postoperative treatment in patients with advanced (stage III–IVA) endometrial cancer, there was no difference in PFS rate when chemoradiation therapy treatment was performed compared to chemotherapy [14].

However, both the 5-year vaginal recurrence rate and the 5-year pelvic and aortic lymph node recurrence rate were significantly lower. In addition, there was no difference in the incidence of moderate severity 3 or higher adverse events between the 2 groups. Although chemoradiation therapy has minimal benefits, there is no difference in side effects [14]. Therefore, The Korean Society for Radiation Oncology suggested that intervention and chemotherapy are the treatments of choice. In addition, with the consent of the attending committee members, this guideline suggests that chemoradiation therapy or chemotherapy can be performed after surgery in patients with advanced (stage III–IVA) endometrial cancer.

The limitations of this treatment guideline are as follows. Since the key questions were structured around the most recent studies and essential issues, only a few large-scale clinical studies were ultimately included. The guidelines will be updated continuously based on future large-scale clinical studies. Meanwhile, since the most of the current treatment guidelines are based on clinical trials conducted on patients in Europe and North America, there were difficulties applying them to domestic patients or Korea's medical environments. Many institutions in Korea are trying to conduct various clinical trials to set up practical guidelines that can be used in real-world setting in Korea. In addition, the recommendations in this guideline will be distributed to all members of KSGO and related associations for use in patient treatment.

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SUPPLEMENTARY MATERIALS

Data S1
The Population, Intervention, Comparison, and Outcome (PICOs) for key questions

Click here to view

Data S2
Search strategy

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Data S3
Flow chart of study selection

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https://doi.org/10.3802/jgo.2024.35.e45

Data S4
Meta-analysis

Click here to view

Data S5
Characteristics of the included studies

Click here to view

Data S6
Risk of bias

Click here to view

Data S7
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidece profiles

Click here to view

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