ASGO 2021 BANGKOK THAILAND

The 7th Biennial Meeting of Asian Society of Gynecologic Oncology

ASGO Asian Society of Gynecologic Oncology

November 25-27, 2021 THAILAND
Virtual Conference

"All accepted abstracts will be published in the JGO"

Abstract submission:
Open on June 1, 2021 - August 15, 2021
Abstract acceptance notification by:
September 15, 2021

Early Registration
Open : June 21, 2021
Close : September 30, 2021

Contact us: asgo2021@gmail.com

Online Registration: www.asgo2021.org

J Gynecol Oncol. 2021 Jul;32(4):e53
https://doi.org/10.3802/jgo.2021.32.e53
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Review Article

Major clinical research advances in gynecologic cancer in 2020

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Received: May 3, 2021
Revised: May 16, 2021
Accepted: May 17, 2021

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ABSTRACT

In 2020 series, we summarized the major clinical research advances in gynecologic oncology with providing representative figures of the most influential study for 1 of each 3 gynecologic cancers: cervix, ovary, and uterine corpus. Review for cervical cancer covered targeted agents and immune checkpoint inhibitors, adjuvant radiation therapy or concurrent/sequential chemoradiation therapy after radical hysterectomy in early cervical cancer, radical surgery in early cervical cancer; and prevention and screening. Ovarian cancer research included studies of various combinations of poly (ADP-ribose) polymerase inhibitors with chemotherapy, immune checkpoint inhibitors, and/or vascular endothelial growth factor inhibitors according to the clinical setting. For uterine corpus cancer, molecular classification upon which the decision of adjuvant treatments might be based, World Health Organization recommendation of 2-tier grading system (low grade vs. high grade), sentinel lymph node assessment and ovarian preservation in clinically early-stage endometrial cancer were reviewed. Molecular targeted agents including immune checkpoint inhibitors which showed promising anti-tumor activities in advanced/recurrent endometrial cancer were also included in this review.

Keywords: Immunotherapy; Molecular Targeted Therapy; Poly(ADP-Ribose) Polymerase; Adjuvant Chemotherapy; Adjuvant Radiotherapy; Cytoreduction Surgical Procedures

INTRODUCTION

The major advances in clinical research for cervical cancer during 2020 can be summarized into 4 parts: 1) targeted agents and immune checkpoint inhibitors; 2) adjuvant radiation therapy (RT) or concurrent chemoradiation therapy (CCRT) after radical hysterectomy in early cervical cancer; 3) radical surgery in early cervical cancer; and 4) prevention and screening for cervical cancer.

In ovarian cancer, poly (ADP-ribose) polymerase inhibitors (PARPi) have continued to dominate the landscape of practice-changing randomized clinical trials after 4 phase III trials

Table 1. Summary of clinical trials for ovarian cancer

Category	Phase III	Phase II	Ongoing
First-line and maintenance	JAVELIN100 (CTx+avelumab) IMagyn0-50 (CTx+bev+atezolimumab)		DUO-O (CTx+bev+ola+durvalumab) FIRST (CTx+nira+dostarlimab±bev) KEYLINK-001 (CTx+ola+pembrolizumab±bev)
First-line maintenance	PAOLA-1 ancillary (ola+bev)*	OVARIO (nira+bev)*	ATHENA (rucaparib+nivolumab)
Neoadjuvant therapy			TRU-D, iPRIME, INeOV, NEO
Platinum-sensitive recurrence	NRG-GY004 (ola+cediranib) SOLO3 (ola)*	MEDIOLA (ola+durvalumab+bev)*	ICON9 (ola+cediranib)
Platinum-resistant recurrence		NCT02595892 (berzosertib+gemcitabine)	NRG-GY005 (ola+cediranib)
PARPi-resistance	SOLO2 ancillary (ola)	EVOLVE (ola+cediranib)	OREO (ola)

CTx, chemotherapy; Bev, bevacizumab; nira, niraparib; ola, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitors.
*Positive results.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: S.D.H., K.J.W.; Methodology: L.Y.Y., C.M.C., P.J.Y., S.D.H., K.J.W.; Project administration: S.D.H., K.J.W.; Supervision: K.J.W.; Writing - original draft: L.Y.Y., C.M.C., P.J.Y., S.D.H.; Writing - review & editing: L.Y.Y., C.M.C., P.J.Y., S.D.H., K.J.W.

evaluating PARPi in the front-line setting have been published (SOLO-1, PRIMA, VELIA, and PAOLA-1) [1-4]. Major clinical researches on combination of PAPRi with chemotherapy (CTx), immune checkpoint inhibitors, and/or vascular endothelial growth factor (VEGF) inhibitors were reviewed according to the clinical setting (**Table 1**).

In endometrial cancer, there have been remarkable research advances which will apply in practice in the near future. Molecular classification was incorporated into one of histologic subtypes of endometrial cancer and gynecologic oncologists should choose the adjuvant treatments based on not only the conventional clinicopathological factors but also this information. In addition to this molecular classification, 2 tier grading system (low grade vs. high grade) of endometrioid adenocarcinoma of endometrium was recommended by the World Health Organization (WHO). In terms of surgical management of endometrial cancer, sentinel lymph node assessment was found to be feasible in clinical stage I endometrial cancer even with high grade and ovarian preservation seems to be safe particularly in clinically early-stage endometrial cancer. In advanced/recurrent endometrial cancer, molecular target agents including immune checkpoint inhibitors showed promising anti-tumor activities in various clinical situations for which Food and Drug Administration (FDA) has approved for its use. Lastly, increased physical activity in endometrial cancer patients was found to be associated with increased survivals in a cohort study.

In this review, for the first time, we picked one of the most influential studies from ovary and uterine corpus cancer, for representative figures.

UTERINE CERVIX

1. Targeted agents and immune checkpoint inhibitors

Phase I/II studies evaluating several types of anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies in recurrent and/or metastatic cervical cancer have been reported. Results of evaluating the immune checkpoint inhibitor alone or in combination with a cytotoxic agent or other targeted agents or dual immune checkpoint inhibitors have been reported.

Preliminary results of balstilimab (anti-PD-1) alone and balstilimab/zalifrelimab (anti-CTLA-4) combination therapy in recurrent and metastatic cervical cancer have been reported in ESMO annual meeting [5]. The authors presented data from 2 phase II trials, of single-agent balstilimab (NCT03104699) and in combination with zalifrelimab (NCT03495882)

in recurrent and metastatic cervical cancer [5]. This was the largest study using immune checkpoint inhibitors in cervical cancer [5]. The objective response rates (ORRs) were 14% and 22% for balstilimab alone and balstilimab/zalifrelimab combination therapy, respectively [5]. Response rates were higher for patients with PD-L1 expression and squamous cell carcinoma [5]. However, responses were also seen in adenocarcinoma patients without PD-L1 expression [5]. Considering that pembrolizumab was approved by FDA for fast tract approval with an ORR of 14% in patients with PD-L1 expression, there results are considered a significant efficacy.

Results of phase I/II trial using tisotumab vedotin in previously treated recurrent or metastatic cervical cancer was reported [6]. Tisotumab vedotin is an antibody-drug conjugate directed to tissue factor. About 51% of patients previously received 2 or more lines of treatment, and 67% of patients received prior bevacizumab + doublet CTx [6]. The ORR was 24% and complete remission was observed in 7% of patients with a manageable safety profile [6].

2. Adjuvant radiation or CCRT after radical hysterectomy in early cervical cancer

The results of a phase III randomized controlled trial comparing standard 4-field pelvic RT with pelvic intensity modulated RT (IMRT) in patients with cervical cancer requiring postoperative RT were reported [7]. The primary endpoint of this study was acute gastrointestinal toxicity reported by patients using a validated patient-reported outcome instrument. Patient-reported adverse events were lower after IMRT compared to standard RT. However, physician-reported adverse events did not differ between the 2 treatment groups. This study showed that clinicians underreported symptomatic gastrointestinal adverse events compared with patients in this disease setting. Thus, the authors concluded that patient-reported symptomatic adverse events are more important to access [7].

A phase III trial comparing sequential chemoradiation vs. radiation alone or concurrent chemoradiation in adjuvant treatment after radical hysterectomy for stage IB1–IIA2 cervical cancer (STARS study, NCT00806117) has been reported in ASCO annual meeting [8,9]. In the intention-to-treat population, sequential chemoradiation was associated with a higher 3-year disease-free survival than radiation alone (90% vs. 82%; hazard ratio [HR]=0.52; 95% confidence interval [CI]=0.35–0.76) and concurrent chemoradiation (90% vs. 85%; HR=0.65; 95% CI=0.44–0.96). Sequential chemoradiation was also associated with a higher 5-year overall survival (OS) than radiation alone (92% vs. 88%; HR=0.58; 95% CI=0.35–0.95). However, there were no differences in disease-free and overall survival between concurrent chemoradiation or radiation alone.

3. Radical surgery in early cervical cancer

After the publication of the LACC trial results, the quality-of-life outcome of the LACC trial was reported separately [10]. In this study, postoperative quality of life was similar between open and minimally invasive radical hysterectomy groups [10]. In addition, a retrospective study and a meta-analysis which comparing open vs. minimally invasive radical hysterectomy were published. The outcomes were similar with those of LACC trial [11,12].

One of the reasons for the poor oncologic outcome of the minimally invasive radical hysterectomy group in the LACC trial was the failure to complete the learning curve for minimally invasive radical hysterectomy. An observational cohort study was reported to show

https://doi.org/10.3802/jgo.2021.32.e53

the effect of the completion of a learning curve on postoperative survival outcomes in robotic radical hysterectomy [13]. In this study, the learning phase of robotic radical hysterectomy in early-stage cervical cancer was at least 61 procedures, with higher survival rates in the women treated thereafter. Another reason for the poor oncologic outcome in the minimally invasive radical hysterectomy group in the LACC trial was the absence of a maneuver to prevent intraperitoneal seeding and tumor injury caused by uterine manipulation. A European, multicenter, retrospective, observational cohort study (SUCCOR study) investigated the association between protective surgical maneuver and the risk of relapse after minimally invasive radical hysterectomy [14]. In this study, avoiding the uterine manipulator and using maneuvers to avoid tumor spread at the time of colpotomy in minimally invasive surgery was associated with similar outcomes to open surgery [14].

An international, multicenter, retrospective cohort study evaluating whether the performance of radical hysterectomy improves oncological outcome in patients with intraoperative detection of lymph node involvement compared to CCRT (ABRAX study) was reported [15]. There were no differences in disease-free and overall survival between abandoned vs. completed radical hysterectomy followed by definitive CCRT in patients with intraoperative detection of lymph node positivity [15].

4. Prevention and screening for cervical cancer

While many studies have shown that human papillomavirus (HPV) vaccines reduce the risk of cervical intraepithelial neoplasia, few studies have shown whether it reduces the risk of invasive cervical cancer. Research has been reported that HPV vaccination reduces the incidence of cervical cancer at the population level [16]. In this study, the incidence rate ratio of the vaccinated population was 0.37 (95% CI=0.21–0.57) compared with the unvaccinated population after adjusting for all covariates. The incidence rate ratio was 0.12 (95% CI=0.00–0.34) for women vaccinated before the age of 17 years and 0.47 (95% CI=0.27–0.75) for women vaccinated between 17 to 30 years [16].

OVARY

1. First-line therapy and maintenance

The phase III JAVELIN Ovarian 100 trial [17] evaluated avelumab (PD-L1 inhibitor) in combination with and/or following CTx vs. CTx alone in patients with newly diagnosed stage III–IV epithelial ovarian cancer. HR for progression-free survival (PFS) in avelumab arms vs. CTx alone group were 1.43 (95% CI=1.051–1.946) for CTx → avelumab (n=332) and 1.14 (95% CI=0.832–1.565) for CTx+avelumab → avelumab (n=331). Median PFS was 16.8 months (95% CI=13.5–NE) for CTx → avelumab, 18.1 months (95% CI=14.8–NE) for CTx+ avelumab → avelumab, and NE (95% CI=18.2–NE) for control group (n=335). In both avelumab arms, PFS was not improved vs. control, prespecified futility boundaries were crossed, and the trial was stopped.

The phase III IMagyn050/GOG 3015/ENGOT-Ov39 trial assessed the bevacizumab-containing therapy with or without atezolizumab (PD-L1 inhibitor) for newly diagnosed stage III-IV ovarian cancer [18]. Eligible patients were randomized 1:1 to atezolizumab 1,200 mg or placebo cycles 1–22, with paclitaxel 175 mg/m^2 + carboplatin AUC6 cycles 1–6 + bevacizumab 15 mg/kg cycles 2–22 with 3 weeks interval. There was no statistically significant PFS improvement in either, the intention to treat population (median 18.4 months with placebo

https://doi.org/10.3802/jgo.2021.32.e53

vs. 19.5 months with atezolizumab; HR=0.92; 95% CI=0.79–1.07) or the PD-L1+ population (median 18.5 vs. 20.8 months; HR=0.80; 95% CI=0.65–0.99).

As in these 2 studies, the results of the addition PD-L1 inhibitors are disappointing, several trials including DOU-O [19], FIRST/ENGOT-Ov44 [20], KEYLYNK-001/ENGOT-Ov43 [21] investigated that first-line therapy of CTx in combination with immune checkpoint inhibitors, PARPi and/or bevacizumab and maintenance treatment in newly diagnosed advanced ovarian cancer patients are ongoing.

2. First-line maintenance

The phase II OVARIO trial [22] evaluated the maintenance therapy of niraparib with bevacizumab in advanced ovarian cancer following first-line platinum-based CTx with bevacizumab. All patients (n=105) underwent tissue testing for homologous recombination deficiency (HRD). Bevacizumab was injected 15 mg/kg every 3 weeks up to 15 months, and niraparib, 300 or 200 mg once daily was started within 12 weeks of completing first-line treatment and continued for 3 years or until progression. Preliminary data suggest that niraparib maintenance in combination with bevacizumab is efficacious in the overall population and across all biomarker subgroups (75% of patients remained progression free at 12-months analysis), consistent with the continuum of clinical benefit observed with niraparib single maintenance therapy in the PRIMA trial [2].

The phase III PAOLA-1/ENGOT-ov25 trial evaluated the addition of maintenance olaparib to bevacizumab in women with advanced ovarian cancer who were in response after first-line platinum-based CTx with bevacizumab [4]. Results of sub-group analysis were presented at IGCS 2020 [23]. The median PFS increased from 14.7 months with bevacizumab alone to 20.3 months with the combination maintenance of olaparib plus bevacizumab (HR=0.60; 95% CI=0.49–0.74) in higher-risk patients (International Federation of Gynaecology and Obstetrics [FIGO] stage III with residual tumor at upfront surgery or neoadjuvant CTx, or FIGO stage IV; n=266) and from 22.9 months to 39.3 months (HR=0.46; 95% CI=0.30–0.72) in lower-risk group (FIGO stage III with complete resection at upfront surgery; n=121). The effect of olaparib plus bevacizumab provided the greatest PFS benefit over placebo plus bevacizumab in higher- and lower-risk patients who were HRD positive or who had a tumor *BRCA* mutation.

In patients newly diagnosed with advanced OC, the 5-year follow up data from the SOLO 1 trial [24] demonstrated continued benefit derived from 2 years of maintenance olaparib in patients with *BRCA* mutation: 48.3% of those who received olaparib (n=260) remained progression free at 5 years, compared with 20.5% of patients who received placebo (n=131). The median PFS was 56.0 months in olaparib maintenance group and 13.8 months in placebo (HR=0.33; 95% CI=0.25–0.43). Almost half of patients in complete response (CR) after first-line CTx remained free from relapse 5 years later.

3. Platinum-sensitive recurrence

A phase III NRG-GY004 study compared olaparib monotherapy or the combination of cediranib (VEGF inhibitor) and olaparib to standard platinum-based CTx in platinum sensitive recurrent ovarian cancer [25]. The HR for PFS was 0.856 (95% CI=0.66–1.11; p=0.077) between cediranib plus olaparib (n=189) and standard of care (SOC) (n=187) and 1.20 (95% CI=0.93–1.54) between olaparib (n=189) and SOC, with median PFS of 10.3, 8.2, and 10.4 months for SOC, olaparib, and cediranib plus olaparib, respectively. Response rates

https://doi.org/10.3802/jgo.2021.32.e53

were 71.3% (SOC), 52.4% (olaparib), and 69.4% (cediranib plus olaparib). Patients receiving cediranib plus olaparib (vs. SOC) had more frequent ≥ grade 3 adverse events including gastrointestinal (30.1% vs. 8.4%), hypertension (31.7% vs. 1.8%), and fatigue (17.5% vs. 1.8%). Cediranib plus olaparib demonstrated similar activity to SOC in recurrent platinum sensitive ovarian cancer, however, did not meet the primary endpoint of improved PFS.

The phase II MEDIOLA study [26] evaluated combining of olaparib plus durvalumab (doublet cohort, n=32) and olaparib, durvalumab plus bevacizumab (triplet cohort, n=31) in patients with non-germline *BRCA*-mutated platinum sensitive relapsed ovarian cancer. The triplet combination therapy showed promising efficacy for women with germline *BRCA* wild type platinum sensitive recurrent ovarian cancer, with 77.4% (90% CI=61.7–88.9) disease control rate at 24 weeks (vs. 28.1% [90% CI=15.5–43.9] in doublet cohort) and median PFS of 14.7 months (95% CI=10.0–18.1) compared with 5.5 months (95% CI=3.6–7.5) in doublet cohort. The most common grade ≥3 adverse events in doublet cohort were anemia (22%), lipase increased (6%) and anemia (13%), hypertension (13%), fatigue (6%) in triplet cohort. The combination of olaparib, durvalumab and bevacizumab showed promising efficacy as treatment in the absence of CTx for women with germline *BRCA* wild type platinum-sensitive relapsed advanced ovarian cancer.

A phase III SOLO3 trial evaluated the efficacy of olaparib vs. non-platinum CTx (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan) in patients with germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based CTx [27]. The primary end point was ORR assessed by blinded independent central review. ORR and PFS were significantly higher with olaparib (n=151) than with non-platinum CTx (n=72) (72.2% vs. 51.4%; odds ratio [OR]=2.53; 95% CI=1.40–4.58; p=0.002 and 13.4 vs. 9.2 months; HR=0.62; 95% CI=0.43–0.91; p=0.013, respectively). According to these results, "CTx -free" treatment with olaparib is a reasonable option for women with a *BRCA* mutation and platinum-sensitive relapsed ovarian cancer.

4. Platinum-resistant recurrence

A phase II trial has shown significantly prolonged PFS with the addition of the ATR kinase inhibitor 'berzosertib' to gemcitabine in women with recurrent platinum-resistant high-grade serous ovarian cancer [28]. Eighty-eight patients were assessed for eligibility, of whom 70 were randomly assigned to treatment with gemcitabine alone (36 patients) or gemcitabine plus berzosertib (34 patients). Gemcitabine (1,000 mg/m^2) was injected on day 1 and day 8, or gemcitabine plus berzosertib (210 mg/m^2) was intravenously injected on day 2 and day 9 of a 21-day cycle until disease progression or intolerable toxicity. Median PFS was 22.9 weeks (90% CI=17.9–72.0) in the berzosertib/gemcitabine group vs. 14.7 weeks (90% CI=9.7–36.7) in the gemcitabine group (HR=0.57; 90% CI=0.33–0.98; p=0.044). Median PFS was 27.7 vs. 9.0 weeks (HR=0.29; p=0.0087) among patients with a platinum-free interval of <3 months. The benefit of the combination was greatest in patients with a platinum-free interval of <3 months. The most common treatment-related grade ≥3 adverse events were decreased neutrophil count (39% in the gemcitabine group vs. 47% in the combination group) and decreased platelet count (6% vs. 24%). This study shows a benefit of adding berzosertib to gemcitabine in platinum-resistant high-grade serous ovarian cancer.

5. PARPi-resistance

The phase II EVOLVE trial investigated combining cediranib with olaparib for ovarian cancer after progression on a PARPi [29]. Women with high-grade serous ovarian cancer were

https://doi.org/10.3802/jgo.2021.32.e53

enrolled into 1 of 3 cohorts: platinum sensitive after PARPi; platinum resistant after PARPi; or progression on standard CTx after progression on PARPi. Among 34 heavily pretreated patients, objective responses were observed in 0 of 11 (0%) platinum-sensitive patients, 2 of 10 (20%) platinum-resistant patients, and 1 of 13 (8%) in the progressed patients. Sixteen-week PFS rates were 55%, 50%, and 39%, respectively. The most common grade ≥3 adverse events were diarrhea (12%) and anemia (9%). Acquired genomic alterations at PARPi progression were reversion mutations in *BRCA1, BRCA2*, or *RAD51B* (19%); *CCNE1* amplification (16%); and *ABCB1* upregulation (15%). The activity of cediranib–olaparib varied according to the PARPi resistance mechanism.

The SOLO2/ENGOT Ov-21 ancillary study [30] demonstrated the efficacy of subsequent CTx for patients with *BRCA* mutated platinum-sensitive recurrent epithelial ovarian cancer progressing on olaparib or placebo. A post-hoc analysis of time to second progression (TTSP) calculated from the date of progression after olaparib maintenance to next progression or death as a surrogate of first post-olaparib treatment PFS. TTSP was longer in the placebo (n=69) compared to the olaparib (n=78) arm: 11.1 vs. 7.0 months (HR=1.93; 95% CI=1.35–2.76). TTSP was 14.3 vs. 7.0 months with platinum-based CTx and 8.3 vs. 5.5 months with non-platinum CTx in the placebo and olaparib arm respectively. In this SOLO2 post-hoc comparison, some degree of resistance to standard subsequent CTx is noted in the olaparib arm. The best post-olaparib management should be studied in prospective manner.

6. Secondary cytoreductive surgery (2nd CRS) in platinum-sensitive recurrent ovarian cancer

Two randomized phase III trials in platinum-sensitive recurrent ovarian cancer affirmed the role of 2nd CRS. The AGO DESKTOP III/ENGOT-Ov20 trial [31] enrolled 407 patients with platinum-sensitive recurrent ovarian cancer and a positive AGO score as defined by an Eastern Cooperative Oncology Group status of 0, an ascites volume of ≤500 mL and complete resection (R0) at initial CRS who were then randomized to receive either second-line CTx or 2nd CRS followed by CTx. 2nd CRS led to a significant improvement in OS (53.7 months with surgery and 46.2 months without surgery; HR=0.76; 95% CI=0.59–0.97; p=0.03) exclusively among those patients in whom performed R0 2nd CRS (**Fig. 1**). For subgroup analysis of this study, patients were divided into 3 subgroups: 1) control arm, 2) surgical arm without R0, and 3) surgical arm with R0 [32]. Time to first subsequent therapy (TFST) in the surgical arm was significantly longer compared to the non-surgical arm (21.3 vs. 16.0 months; p<0.001). TFST in group 1 vs. 2 vs. 3 was 16.0 vs. 16.1 vs. 26.3 months, respectively (HR=0.53; 95% CI=0.42–0.68; p<0.001). TFST is prolonged substantially by R0.

The SOC1/SGOG-Ov2 trial [33] used the iMODEL score [34] combined with PET-CT to select patients predicted to undergo R0 surgery, and demonstrated that 2nd CRS followed by CTx improved PFS relative to the PFS after CTx alone (17.4 vs. 11.9 months; HR=0.58; 95% CI=0.45–0.74; p<0.001).

These results are deviated from those of an earlier randomized phase 3 trial, GOG-213 [35], which did not find that 2nd CRS followed by CTx improved OS relative to OS after CTx alone (HR=1.29; 95% CI=0.97–1.72; p=0.08). Together these trials suggest that clinical benefit from 2nd CRS is dependent on achievement of R0 and that the effect may be alleviated by systemic therapy such as bevacizumab (84% use in GOG-213); they also demonstrate the value of implementing careful patient-selection tools, such as the AGO score (DESKTOP III) and iMODEL (SOC1/SGOG-Ov2) (**Table 2**).

https://doi.org/10.3802/jgo.2021.32.e53

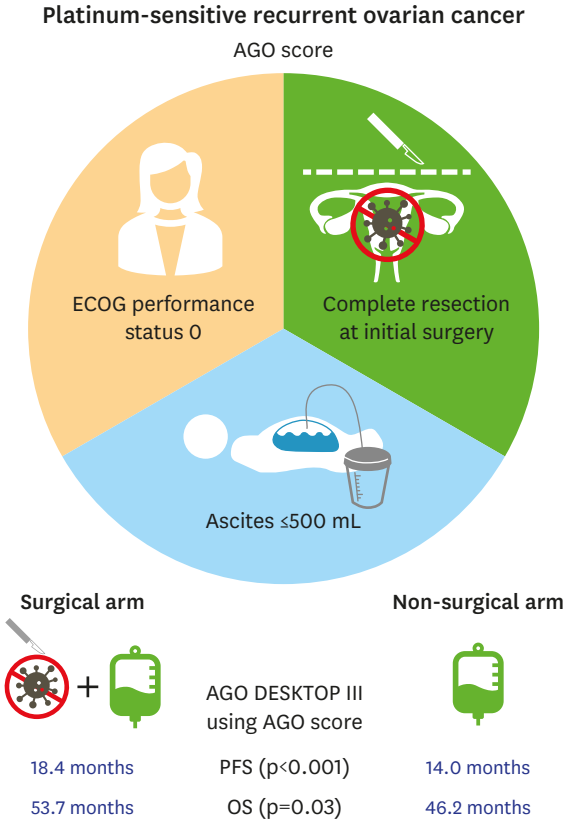

Fig. 1. Results of AGO DESKTOP III/ENGOT-Ov20 study. AGO DESKTOP III trial randomized 407 patients with platinum-sensitive recurrent ovarian cancer and a positive AGO score (defined by an ECOG status of 0, an ascites volume of ≤500 mL and complete resection at initial cytoreductive surgery) to receive either secondary cytoreductive surgery followed by chemotherapy (surgical arm) or second-line chemotherapy alone (non-surgical arm): median OS, 53.7 vs. 46.2 months (HR=0.76; 95% CI=0.59–0.97; p=0.03); median progression-free survival, 18.4 vs. 14.0 months (HR=0.66; 95% CI=0.54–0.82; p<0.001).
AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 2. Comparison of GOG-213, AGO DESKTOP-III, and SOC-1/SGOG-Ov2 trials

Variable	GOG-213 [35]	AGO DESKTOP-III [31]	SOC-1/SGOG-Ov2 [33]
Age (yr)	57	61	54
Study design	Phase 3 randomized	Phase 3 randomized	Phase 3 randomized
Enrolled patients (period)	485 (2007′–2017′)	407 (2010′–2014′)	357 (2012′–2019′)
Selection criteria	TFI >6 mo	TFI >6 mo, AGO score*	TFI >6 mo, iMODEL† + PET-CT
Median PFI (mo)	19.7	19.9	16.1
Cross-over to surgery (control violation)	2%	4%	6%
Complete resection at 2nd CRS	67%	75%	77%
Mortality	0.4% (30-day)	0.5% (90-day)	0% (60-day)
Subsequent surgery in control arm after relapse	NA	11%	37%
2nd line bevacizumab/PARPi use	84%/NA	23%/<5%	1%/10%
Median PFS, surgery vs. no surgery (mo)	18.9 vs. 16.2 (HR=0.82; 95% CI=0.66–1.01)	18.4 vs. 14.0 (HR=0.66; 95% CI=0.54–0.82; p<0.001)	17.4 vs. 11.9 (HR=0.58; 95% CI=0.45–0.74; p<0.001)
Median OS, surgery vs. no surgery (mo)	50.6 vs. 64.7 (HR=1.29; 95% CI=0.97–1.72; p=0.08)	53.7 vs. 46.2 (HR=0.76; 95% CI=0.59–0.97; p=0.03)	Data maturing

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; CI, confidence interval; HR, hazard ratio; NA, non-available; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitors; PET-CT, positron emission tomography-computed tomography; PFI, progression-free interval; PFS, progression-free survival; 2nd CRS, secondary cytoreductive surgery; TFI, treatment-free interval.
*AGO score (Eastern Cooperative Oncology Group performance status 0, ascites ≤500 mL, and complete resection at initial surgery); †iMODEL [34].

https://doi.org/10.3802/jgo.2021.32.e53

JOURNAL OF GYNECOLOGIC ONCOLOGY

UTERINE CORPUS

1. New molecular classification and binary grading

Endometrial cancer usually shows better prognosis compared to other gynecologic malignancies mainly due to its early presentation to clinic [36]. Nevertheless, recurrence rate significantly increases in advanced disease or early disease with high-risk features for recurrence. To reduce the rate of recurrence, various adjuvant treatments have been tested and validated through clinical trials. However, one of limitations in providing these adjuvant therapies, risk stratification to select adjuvant therapy was solely based on pathological findings including grade, lympho-vascular invasion, and cervical stromal invasions, etc. which may be affected by interobserver variabilities [37]. More on that, there is no universal consensus on which pathological definition is optimized for stratifying risk factors for recurrence in endometrial cancer, although low, intermediate, intermediate high, and high-risk groups are generally introduced to use in practice [36].

The Cancer Genome Atlas introduced the molecular classification in endometrial cancer which demonstrated the prominent prognostic role [38]. Four molecular subgroups including p53-abnormal (p53abn), *POLE*-ultramutated (*POLE*mut), mismatch repair-deficient (MMRd), and no specific molecular profile (NSMP) showed distinct prognostic differences providing a significant impact on the treatment of endometrial cancer. Afterwards it has validated through clinical studies that the integration of the molecular classification with conventional clinicopathological findings has improved prognostic accuracy in non-selected cohort or patients with intermediate risk factors [39,40] but not in exclusively high-risk patients. Adjuvant chemoradiotherapy vs. radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3) is a randomized clinical trial investigating the benefit of combined adjuvant CCRT vs. pelvic RT alone for women with high-risk endometrial cancer [41] and it showed a significant benefit in survivals with CCRT over RT alone. Using tissue samples of PORTEC-3, León-Castillo et al. [42] recently reported the prognostic relevance of the molecular classification and sought to find the molecular subgroup which benefit from adjuvant CCRT in this high-risk cohort (**Fig. 2**).

From the view of prognostic value of the molecular classification, patients with p53abn had worst prognosis in contrast to the best survival outcomes of patients with *POLE*mut, otherwise, patients with MMRd or NSMP showed intermediate clinical outcomes. In terms of predictive role of these molecules, patients with p53abn had the highest benefit from CCRT with an absolute benefit of over 20% for 5-year survivals. Patients with *POLE*mut or MMRd showed no benefit and a trend toward benefit from CCRT was observed in patients with NSMP partly due to small number of patients which deemed to be not fully powered to detect differences. The PORTEC-4a trial comparing standard adjuvant brachytherapy in women with intermediate-risk endometrial cancer with individualized adjuvant treatment on the basis of the patients' integrated molecular profile is ongoing [43] and *CTNNB1*mut may become an additional molecular subgroup in NSMP patients according to the results. Although, there is still lack of evidence about the robust or cost-effective methods of detecting mutations of *POLE* or *CTNNB1*, there seems to be no doubt to use the molecular classification in practice.

Young endometrial cancer patients who have clinically early stage and strongly desire to preserve fertility, hormonal treatment is known to be a feasible option, however, it was unknown whether the molecular classification provide any role of predicting response to hormonal treatment and Chung et al. [44] recently found better response rate in patients with

https://doi.org/10.3802/jgo.2021.32.e53

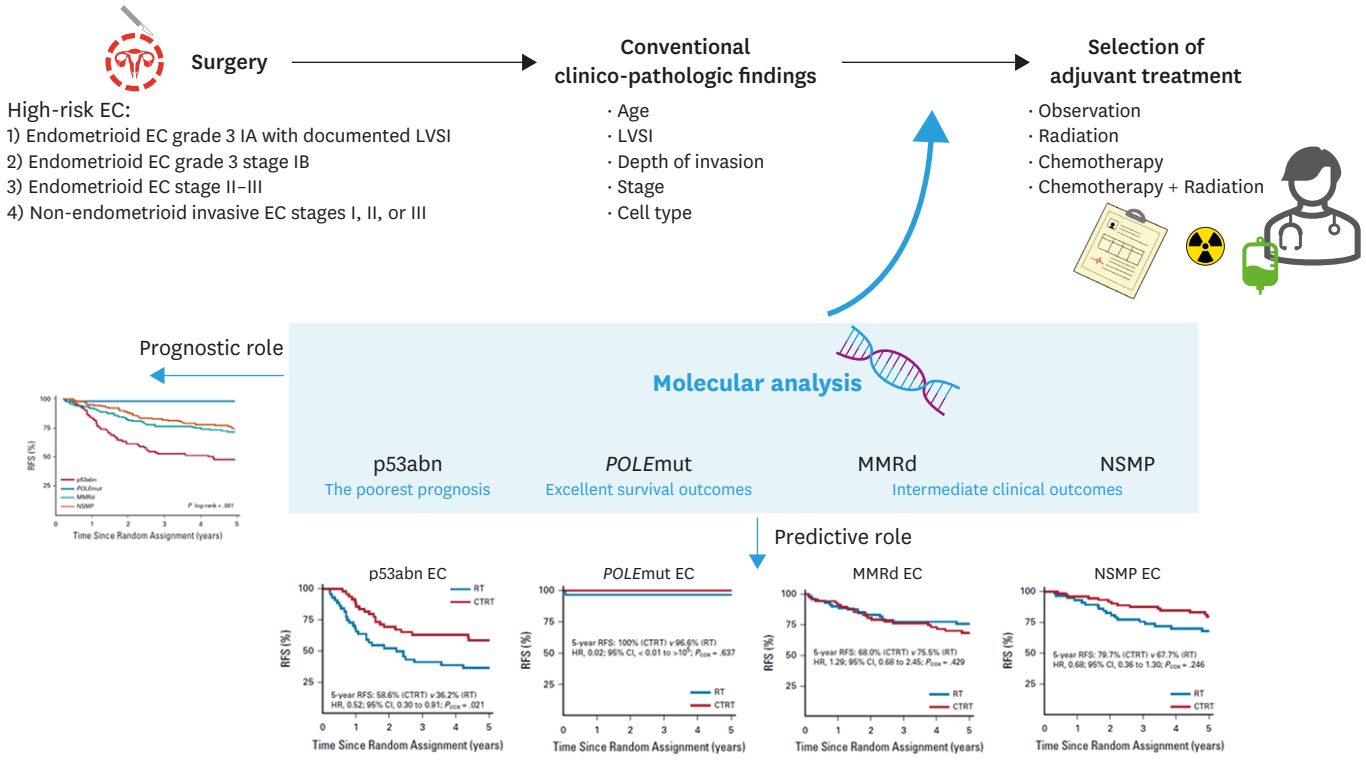

Fig. 2. Role of integration of molecular profiling in high-risk EC. Molecular analysis can increase prognostic accuracy in patients with high-risk EC and patients with p53abn had the highest benefit from adjuvant chemoradiation compared with adjuvant radiation alone. However, no benefit of adding chemotherapy on adjuvant radiation was observed in patients with *POLE*mut or MMRd suggesting its predictive role of expecting response to adjuvant chemotherapy.
CI, confidence interval; CTRT, combined adjuvant chemotherapy and radiotherapy; EC, endometrial cancer; HR, hazard ratio; LVSI, lymph-vascular space invasion; MMRd, mismatch repair-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; *POLE*mut, *POLE*-ultramutated; RFS, recurrence-free survival; RT, radiotherapy.

NSMP compared with MMRd Among 57 patients with clinically stage I and low grade, patients with MMRd had a significantly lower CR/partial response rate than those with NSMP patients in terms of the best overall response (44.4% vs. 82.2%, p=0.018) and CR rate at 6 months (11.1% vs. 53.3%, p=0.010). Based on the results, mismatch repair (MMR) status could be used as a predictive biomarker for selecting patients who could benefit from hormone therapy. And, in the hormonal treatment indications of early endometrial cancer, there was still lack of evidence about whether hormonal treatment can be a safe option for endometrial cancer patients with moderately differentiated tumor grade. A Gynecologic Cancer Inter-Group study observed that CR was achieved in 43.4%, 56.5% and 65.2% of the patients after 6, 9, and 12 months from the initiation of progestin, respectively, achieving 73.9% of an overall CR rate [45]. Although the sample size is very small (23 patients and all were grade 2) the CR rates seem to be identical with the results from previous studies in patients with grade 1. Considering WHO is recommending 2 tier-grading system (grade 1 and 2 as low vs. grade 3 as high), broadened indication for hormonal treatment in endometrial cancer can be discussed with patients who strongly desire for fertility preservation. And, as described above, proactive molecular tests especially for MMR in endometrial biopsy sample may provide the more accurate prognosis enabling early stratification and risk assignment to direct care.

2. Ovarian preservation and sentinel lymph node mapping for early endometrial cancer

During surgical staging, bilateral salpingo-oophorectomy (BSO) and lymph node assessment are routinely recommended for patients with endometrial cancer. However, with low

https://doi.org/10.3802/jgo.2021.32.e53

incidence of ovarian metastasis in clinically early disease, it has been suggested to preserve ovary for selected patients with endometrial cancer amid ongoing debate [46-49]. Shin et al. analyzed the data of 539 patients who were diagnosed with early-stage endometrial cancer and found BSO did not affect survivals of patients (non-BSO; 5-year survival rate 98.6% vs. BSO; 5-year survival rate 93.0%, p=0.089) which is supporting the safety of ovarian preservation in young patients with early-stage endometrial cancer. However, ovarian preservation should not be recommended for patients with family history involving ovarian cancer risk (e.g. *BRCA* mutation, Lynch syndrome, etc.).

Like less radical surgical approach of ovarian preservation for early-stage disease, sentinel lymph node biopsy (SLNB) has also been proposed as a less invasive strategy for nodal assessment for early disease [50,51] and showed acceptable results through 3 important clinical trials [52-54]. In these trials, sensitivity per patients was reported from 84% to 100% and negative predictive value per patient was between 97% and 99.6%. However, its role in patients with high grade tumors remains unclear since the proportion of patients with grade 3 showed 13%, 28%, and 49%, respectively. Cusimano et al. [55] performed a prospective multicenter cohort study comparing SLNB and lymphadenectomy for clinical stage I endometrial cancer with grade 2 endometrioid or high-grade using indocyanine green. Among 156 patients enrolled, 126 (80.7%) patients had grade 3 and SLNB had a sensitivity of 96% and a negative predictive value of 99%for the detection of nodal metastasis demonstrating similar diagnostic accuracy and prognostic ability as lymphadenectomy in patients with high-grade endometrial cancer who are at greatest risk for nodal metastasis [55].

3. Targeted agents in advanced or recurrent endometrial cancer

Uterine serous carcinoma is highly aggressive among endometrial cancer subtypes. 20%-25% of uterine serous carcinoma shows Her2/Neu amplification [56-58], a receptor tyrosine kinase and the target of the mAb trastuzumab. Fader et al. [59] reported updated survival analysis of randomized phase II trial comparing carboplatin paclitaxel and carboplatin paclitaxel with trastuzumab in advanced or recurrent uterine serous carcinomas that overexpress Her2/Neu. Sixty-one patients were randomized. And OS was significantly higher in the trastuzumab group compared with the control group, with medians of 29.6 months vs. 24.4 months (HR=0.58; 90% CI=0.34–0.99; p=0.046). More on that, the benefit was most significant in those with CTx-naive advanced disease, with survival median not reached in the trastuzumab group vs. 24.4 months in the control group (HR=0.49; 90% CI=0.25–0.97; p=0.041) with similar toxicities.

Palbociclib is an oral selective inhibitor of the CDKs 4 and 6. In estrogen receptor (ER) positive breast cancer, palbociclib combined with letrozole resulted in significantly longer progression free survival than that with letrozole alone [60]. Since ER positive endometrial cancer is also hormone dependent tumor like ER positive breast cancer, combination of palbociclib and letrozole was expected to increase survivals when compared with letrozole alone. Mirza et al. [61] performed a randomized double-blind placebo-controlled phase II trial of palbociclib combined with letrozole in patients with ER positive advanced/recurrent endometrial cancer and, of 77 enrolled patients, it was reported that letrozole plus palbociclib significantly improved progression free survival compared with letrozole alone: median 8.3 vs. 3.0 months, respectively; HR=0.56 (95% CI=0.32–0.98; p=0.041). Grade 3/4 adverse events were significantly higher with letrozole plus palbociclib (anemia 8% vs. 3%; neutropenia 42% vs. 0%) however, patient-reported outcomes were identical [61].

https://doi.org/10.3802/jgo.2021.32.e53

Endometrial cancer has been considered as an ideal target for immunotherapy based on its unique immunological landscape. For example, prevalence of expression of PD-1/PD-L1 is highest (40%–80% in endometrioid, 10%–68% in serous, and 23%–69% in clear) among gynecologic malignancies and high tumor mutational burden results in highly immunogenic tumor with tumor specific neoantigens [38,62,63]. The KEYNOTE-158 study is a multicohort, single-arm, open-label, phase 2 study assessing pembrolizumab (anti-PD-1antibody) monotherapy in patients with recurrent non colorectal cancers with MMRd/MSI-H [64]. During median follow up of 13.4 months, 233 enrolled patients showed ORR was 34.3% (95% CI=28.3–40.8). Endometrial cancer was most common (49/233, 21.0%) with ORR of 57.1% (95% CI=42.2–71.2), which was the best response rate among 27 tumor types in this study. Dostarlimab, another type of anti-PD-1 antibody, showed similar promising results in recurrent or advanced MMRd endometrial cancer [65]. Among 104 women with median follow-up of 11.2 months, ORR was 42.3% (95% CI=30.6–54.6) and 9 patients (12.7%) showed a CR, and 21 patients (29.6%) showed partial response which were durable (median duration of response was not reached). Nivolumab also showed promising anti-tumor activity as ORR of 36% in 13 MMRd endometrial cancer patients [66].

For patients with MMR-proficient/microsatellite-stable (MSS) endometrial cancer, immune checkpoint inhibitor combination with multiple kinase inhibitors showed promising antitumor activity. Lenvatinib, a multiple kinase inhibitor against the VEGF receptor (VEGFR1, VEGFR2, and VEGFR3), was tested as a combination with pembrolizumab in a phase Ib/II study of previously treated endometrial carcinoma [67]. Among enrolled 108 patients with a median follow-up of 18.7 months, 94 patients (87.0%, 94/108) had MSS tumor and ORR at 24 weeks was 36.2% (26.5% to 46.7%). Higher ORR was observed in MSI-high tumors at 63.6% (30.8% to 89.1%), however, small number of patients is limitation (11 patients with MSI-high tumors). Of note, PD-L1 status did not correlate with ORR in this trial. Severe drug induced adverse effects occurred in 83/124 (66.9%) patients. A phase Ib/II study with lenvatinib plus pembrolizumab was performed in selected advanced solid tumors including 23 patients with endometrial cancer [68]. The overall response rate at 24 weeks and overall ORR for endometrial cancer were both 52% (12/23; 95% CI=30.6–73.2) and median duration of response has not reached at the time of analysis. MMR status is unknown in this trial, however, PD-L1 status also did not affect the rate of response.

Cabozantinib, a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and also inhibits AXL and RET, combination with nivolumab demonstrated improved oncological outcomes compared to nivolumab alone in heavily pre-treated women with recurrent endometrial cancer in a randomized phase II study [69]. Among enrolled 76 evaluable patients, only 2 patients were MSI-high. ORR and stable disease were higher in combination arm (25% vs. 16.7% and 44.4% vs. 11.1%, respectively) which were translated into significant clinical benefit favoring combination arm ($p<0.001$). PARP inhibitor, talazoparib, with avelumab also exhibited active antitumor activity in MSS recurrent/persistent endometrial cancer. In 35 patients enrolled, progression free survival at 6 months was 25.8% (95% CI=12.4–41.4) and median progression free survival was 3.65 months (95% CI=2.4–5.4 months) [70]. There are many ongoing trials investigating the efficacy of immunotherapy in combination with other multiple kinase inhibitors or PARPi which will remain to be seen.

4. Physical activity and survivals

It was suggested that active physical activity is associated with improved survival after an endometrial cancer diagnosis in a prospective cohort study by Friedenreich et al [71].

https://doi.org/10.3802/jgo.2021.32.e53

425 women with endometrial cancer were followed up for a median of 14.5 years and the interviewer-administered Lifetime Total Physical Activity Questionnaire recorded pre- and post-diagnosis physical activity. Among occupational, household, and recreational physical activities, higher post-diagnosis recreational physical activity was strongly associated with both improved disease-free survival (HR=0.33; 95% CI=0.17–0.64; p=0.001) and OS (HR=0.33; 95% CI=0.15–0.75; p=0.007). The strongest associations with survival were experienced by women who maintained high levels of recreational physical activity throughout their pre-diagnosis lifetime and into their endometrial cancer survivorship. Based on this study, clinicians should recommend physical activity to patients with newly diagnosed endometrial cancer and survivors to improve quality of life and possibly even survival.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to '2020 team for major clinical research review': Youn Jin Choi (The Catholic University, Seoul), Se ik Kim (Seoul National University, Seoul), Tae Wook Kong (Ajou University, Suwon), Jeong-Won Lee (Sungkyunkwan University, Seoul), and Sung-Jong Lee (The Catholic University, Seoul) for cervical cancer; Hyun Woong Cho & Jin Hwa Hong (Korea University, Seoul), Jung-Yun Lee (Yonsei University, Seoul), Shin-Wha Lee (Ulsan University, Seoul), Eun Ji Nam (Yonsei University, Seoul), and Soo Jin Park (Seoul National University, Seoul) for ovarian cancer; Jin Hwa Hong (Korea University, Seoul), Soo Young Jeong (Hallym University, Seoul), Mi Kyung Kim (Ewha Womans University, Seoul), Maria Lee (Seoul National University, Seoul), Ju Won Roh (CHA University, Goyang) for corpus cancer; Sook Hee Hong (The Catholic University, Seoul) for medical oncology; Hyo Jin Kim (Seoul National University, Seongnam) for pathology; Hyun-Cheol Kang (Seoul National University, Seoul) for radiation oncology.

Special thanks to Bella Lee for illustration.

REFERENCES

1. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-505.
PUBMED | CROSSREF
2. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-402.
PUBMED | CROSSREF
3. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 2019;381:2403-15.
PUBMED | CROSSREF
4. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416-28.
PUBMED | CROSSREF
5. O'Malley DM, Oaknin A, Monk BJ, Leary A, Selle F, Alexandre J, et al. Single-agent anti-PD-1 balstilimab or in combination with anti-CTLA-4 zalifrelimab for recurrent/metastatic (R/M) cervical cancer (CC): preliminary results of two independent phase II trials. Ann Oncol 2020;31:S1164-S5.
CROSSREF
6. Hong DS, Concin N, Vergote I, de Bono JS, Slomovitz BM, Drew Y, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. Clin Cancer Res 2020;26:1220-8.
PUBMED | CROSSREF

7. Yeung AR, Pugh SL, Klopp AH, Gil KM, Wenzel L, Westin SN, et al. Improvement in patient-reported outcomes with intensity-modulated radiotherapy (RT) compared with standard RT: a report from the NRG Oncology RTOG 1203 Study. J Clin Oncol 2020;38:1685-92.
PUBMED | CROSSREF
8. Huang H, Feng Y, Wan T, Zhang Y, Cao X, Huang Y, et al. Sequential chemoradiation versus radiation alone or concurrent chemoradiation in adjuvant treatment after radical hysterectomy for stage IB1-IIA2 cervical cancer (STARS Study): a randomized, controlled, open-label, phase III trial. J Clin Oncol 2020;38:6007.
CROSSREF
9. Huang H, Feng YL, Wan T, Zhang YN, Cao XP, Huang YW, et al. Effectiveness of sequential chemoradiation vs concurrent chemoradiation or radiation alone in adjuvant treatment after hysterectomy for cervical cancer: the STARS phase 3 randomized clinical trial. JAMA Oncol 2021;7:361-9.
PUBMED | CROSSREF
10. Frumovitz M, Obermair A, Coleman RL, Pareja R, Lopez A, Ribero R, et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2020;21:851-60.
PUBMED | CROSSREF
11. Uppal S, Gehrig PA, Peng K, Bixel KL, Matsuo K, Vetter MH, et al. Recurrence rates in patients with cervical cancer treated with abdominal versus minimally invasive radical hysterectomy: a multi-institutional retrospective review study. J Clin Oncol 2020;38:1030-40.
PUBMED | CROSSREF
12. Nitecki R, Ramirez PT, Frumovitz M, Krause KJ, Tergas AI, Wright JD, et al. Survival after minimally invasive vs open radical hysterectomy for early-stage cervical cancer: a systematic review and meta-analysis. JAMA Oncol 2020;6:1019-27.
PUBMED | CROSSREF
13. Baeten I, Hoogendam JP, Schreuder H, Jürgenliemk-Schulz IM, Verheijen R, Zweemer RP, et al. The influence of learning curve of robot-assisted laparoscopy on oncological outcomes in early-stage cervical cancer: an observational cohort study. BJOG 2021;128:563-71.
PUBMED | CROSSREF
14. Chiva L, Zanagnolo V, Querleu D, Martin-Calvo N, Arévalo-Serrano J, Căpîlna ME, et al. SUCCOR study: an international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer. Int J Gynecol Cancer 2020;30:1269-77.
PUBMED | CROSSREF
15. Dostalek L, Runnebaum I, Raspagliesi F, Vergote I, Dusek L, Jarkovsky J, et al. Oncologic outcome after completing or abandoning (radical) hysterectomy in patients with cervical cancer and intraoperative detection of lymph node positivity; ABRAX (ABandoning RAd hyst in cerviX cancer). Int J Gynecol Cancer 2020;30:261-4.
PUBMED | CROSSREF
16. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med 2020;383:1340-8.
PUBMED | CROSSREF
17. Ledermann JA, Colombo N, Oza AM, Fujiwara K, Birrer MJ, Randall LM, et al. Avelumab in combination with and/or following chemotherapy vs chemotherapy alone in patients with previously untreated epithelial ovarian cancer: results from the phase 3 javelin ovarian 100 trial. Gynecol Oncol 2020;159:13-4.
CROSSREF
18. Moore KN, Bookman M, Sehouli J, Miller A, Anderson C, Scambia G, et al. Primary results from IMagyn050/GOG 3015/ENGOT-OV39, a double-blind placebo (pbo)-controlled randomised phase III trial of bevacizumab (bev)-containing therapy +/- atezolizumab (atezo) for newly diagnosed stage III/IV ovarian cancer (OC). Ann Oncol 2020;31:S1161-S2.
CROSSREF
19. Harter P, Bidziński M, Colombo N, Floquet A, Pérez MJR, Kim J-W, et al. DUO-O: a randomized phase III trial of durvalumab (durva) in combination with chemotherapy and bevacizumab (bev), followed by maintenance durva, bev and olaparib (olap), in newly diagnosed advanced ovarian cancer patients. J Clin Oncol 2020;37:TPS5598.
CROSSREF
20. Hardy-Bessard A-C, Moore KN, Mirza MR, Asselain B, Redondo A, Pfisterer J, et al. ENGOT-OV44/FIRST study: a randomized, double-blind, adaptive, phase III study of standard of care (SOC) platinum-based therapy ± dostarlimab followed by niraparib ± dostarlimab maintenance as first-line (1L) treatment of stage 3 or 4 ovarian cancer (OC). J Clin Oncol 2020;38:TPS6101.
CROSSREF

21. Vergote I, Sehouli J, Salutari V, Zola P, Madry R, Wenham RM, et al. ENGOT-OV43/KEYLYNK-001: a phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer. J Clin Oncol 2019;37:TPS5603.
CROSSREF
22. Hardesty MM, Krivak T, Wright GS, Hamilton E, Fleming EL, Gupta D, et al. Phase II OVARIO study of niraparib + bevacizumab therapy in advanced ovarian cancer following front-line platinum-based chemotherapy with bevacizumab. Gynecol Oncol 2020;159:3-4.
CROSSREF
23. Harter P, Petran D, Scambia G, Ortega E, Tsibulak I, Nagao S, et al. Efficacy of maintenance olaparib plus bevacizumab by biomarker status in clinical higher- and lower-risk patients with newly diagnosed, advanced ovarian cancer in the PAOLA-1 trial. Int J Gynecol Cancer 2020;30:18.
CROSSREF
24. Banerjee S, Moore KN, Colombo N, Scambia G, Kim B-G, Oaknin A, et al. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. Ann Oncol 2020;31:S613.
CROSSREF
25. Liu JF, Brady MF, Matulonis UA, Miller A, Kohn EC, Swisher EM, et al. A phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer. J Clin Oncol 2020;38;6003.
CROSSREF
26. Drew Y, Penson RT, O'Malley DM, Kim J-W, Zimmermann S, Roxburgh P, et al. Phase II study of olaparib (O) plus durvalumab (D) and bevacizumab (B) (MEDIOLA): Initial results in patients (pts) with non-germline BRCA-mutated (non-gBRCAm) platinum sensitive relapsed (PSR) ovarian cancer (OC). Ann Oncol 2020;31:S615-S6.
CROSSREF
27. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA 3rd, Bidziński M, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol 2020;38:1164-74.
PUBMED | CROSSREF
28. Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, Penson RT, Schumer ST, Doyle LA, et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:957-68.
PUBMED | CROSSREF
29. Lheureux S, Oaknin A, Garg S, Bruce JP, Madariaga A, Dhani NC, et al. EVOLVE: a multicenter open-label single-arm clinical and translational phase ii trial of cediranib plus olaparib for ovarian cancer after PARP inhibition progression. Clin Cancer Res 2020;26:4206-15.
PUBMED | CROSSREF
30. Frenel JS, Kim JW, Berton-Rigaud D, Asher R, Vidal L, Pautier P, et al. Efficacy of subsequent chemotherapy for patients with BRCA1/2 mutated platinum-sensitive recurrent epithelial ovarian cancer (EOC) progressing on olaparib vs placebo: the SOLO2/ENGOT Ov-21 trial. Ann Oncol 2020;31:S615.
CROSSREF
31. Bois AD, Sehouli J, Vergote I, Ferron G, Reuss A, Meier W, et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of AGO DESKTOP III/ENGOT-ov20. J Clin Oncol 2020;38:6000.
CROSSREF
32. Lecuru F, Bois Ad, Sehouli J, Vergote I, Ferron G, Reuss A, et al. AGO DESKTOP III/ENGOT OV20: impact of surgical characteristics and time to first subsequent therapy (TFST). Ann Oncol 2020;31:S617.
CROSSREF
33. Zang R, Zhu J, Shi T, Liu J, Tu D, Yin S, et al. A randomized phase III trial of secondary cytoreductive surgery in later recurrent ovarian cancer: SOC1/SGOG-OV2. J Clin Oncol 2020;38:6001.
CROSSREF
34. Tian WJ, Chi DS, Sehouli J, Tropé CG, Jiang R, Ayhan A, et al. A risk model for secondary cytoreductive surgery in recurrent ovarian cancer: an evidence-based proposal for patient selection. Ann Surg Oncol 2012;19:597-604.
PUBMED | CROSSREF
35. Coleman RL, Spirtos NM, Enserro D, Herzog TJ, Sabbatini P, Armstrong DK, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med 2019;381:1929-39.
PUBMED | CROSSREF

36. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol 2016;27:16-41.
PUBMED | CROSSREF
37. Han G, Sidhu D, Duggan MA, Arseneau J, Cesari M, Clement PB, et al. Reproducibility of histological cell type in high-grade endometrial carcinoma. Mod Pathol 2013;26:1594-604.
PUBMED | CROSSREF
38. Cancer Genome Atlas Research NetworkKandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.
PUBMED | CROSSREF
39. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol 2018;29:1180-8.
PUBMED | CROSSREF
40. Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017;123:802-13.
PUBMED | CROSSREF
41. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:295-309.
PUBMED | CROSSREF
42. León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol 2020;38:3388-97.
PUBMED | CROSSREF
43. van den Heerik AS, Horeweg N, Nout RA, Lutgens LC, van der Steen-Banasik EM, Westerveld GH, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer 2020;30:2002-7.
PUBMED | CROSSREF
44. Chung YS, Woo HY, Lee JY, Park E, Nam EJ, Kim S, et al. Mismatch repair status influences response to fertility-sparing treatment of endometrial cancer. Am J Obstet Gynecol 2021;224:370.e1-370.e13.
PUBMED | CROSSREF
45. Falcone F, Leone Roberti Maggiore U, Di Donato V, Perrone AM, Frigerio L, Bifulco G, et al. Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIG) study. J Gynecol Oncol 2020;31:e74.
PUBMED | CROSSREF
46. Lee TS, Jung JY, Kim JW, Park NH, Song YS, Kang SB, et al. Feasibility of ovarian preservation in patients with early stage endometrial carcinoma. Gynecol Oncol 2007;104:52-7.
PUBMED | CROSSREF
47. Wright JD, Jorge S, Tergas AI, Hou JY, Burke WM, Huang Y, et al. Utilization and outcomes of ovarian conservation in premenopausal women with endometrial cancer. Obstet Gynecol 2016;127:101-8.
PUBMED | CROSSREF
48. Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol 2009;27:1214-9.
PUBMED | CROSSREF
49. Sun C, Chen G, Yang Z, Jiang J, Yang X, Li N, et al. Safety of ovarian preservation in young patients with early-stage endometrial cancer: a retrospective study and meta-analysis. Fertil Steril 2013;100:782-7.
PUBMED | CROSSREF
50. Cormier B, Rozenholc AT, Gotlieb W, Plante M, Giede CCommunities of Practice (CoP) Group of Society of Gynecologic Oncology of Canada (GOC). Sentinel lymph node procedure in endometrial cancer: a systematic review and proposal for standardization of future research. Gynecol Oncol 2015;138:478-85.
PUBMED | CROSSREF
51. Bodurtha Smith AJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol 2017;216:459-476.e10.
PUBMED | CROSSREF
52. Ballester M, Dubernard G, Lécuru F, Heitz D, Mathevet P, Marret H, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011;12:469-76.
PUBMED | CROSSREF

53. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 2017;18:384-92.
PUBMED | CROSSREF
54. Persson J, Salehi S, Bollino M, Lönnerfors C, Falconer H, Geppert B. Pelvic sentinel lymph node detection in high-risk endometrial cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. Eur J Cancer 2019;116:77-85.
PUBMED | CROSSREF
55. Cusimano MC, Vicus D, Pulman K, Maganti M, Bernardini MQ, Bouchard-Fortier G, et al. Assessment of sentinel lymph node biopsy vs lymphadenectomy for intermediate- and high-grade endometrial cancer staging. JAMA Surg 2021;156:157-64.
PUBMED | CROSSREF
56. Santin AD, Bellone S, Gokden M, Palmieri M, Dunn D, Agha J, et al. Overexpression of HER-2/neu in uterine serous papillary cancer. Clin Cancer Res 2002;8:1271-9.
PUBMED
57. Santin AD, Bellone S, Siegel ER, Palmieri M, Thomas M, Cannon MJ, et al. Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): a major prognostic indicator in uterine serous papillary cancer. Am J Obstet Gynecol 2005;192:813-8.
PUBMED | CROSSREF
58. Buza N, Roque DM, Santin AD. HER2/neu in endometrial cancer: a promising therapeutic target with diagnostic challenges. Arch Pathol Lab Med 2014;138:343-50.
PUBMED | CROSSREF
59. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (Stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. Clin Cancer Res 2020;26:3928-35.
PUBMED | CROSSREF
60. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925-36.
PUBMED | CROSSREF
61. Mirza MR, Bjørge L, Marmé F, Christensen RD, Gil-Martin M, Auranen A, et al. A randomised double-blind placebo-controlled phase II trial of palbociclib combined with letrozole (L) in patients (pts) with oestrogen receptor-positive (ER+) advanced/recurrent endometrial cancer (EC): NSGO-PALEO/ENGOT-EN3 trial. Ann Oncol 2020;31:S1160.
CROSSREF
62. Howitt BE, Shukla SA, Sholl LM, Ritterhouse LL, Watkins JC, Rodig S, et al. Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. JAMA Oncol 2015;1:1319-23.
PUBMED | CROSSREF
63. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.
PUBMED | CROSSREF
64. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 Study. J Clin Oncol 2020;38:1-10.
PUBMED | CROSSREF
65. Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol 2020;6:1766-72.
PUBMED | CROSSREF
66. Azad NS, Gray RJ, Overman MJ, Schoenfeld JD, Mitchell EP, Zwiebel JA, et al. Nivolumab is effective in mismatch repair-deficient noncolorectal cancers: results from arm Z1D-A subprotocol of the NCI-MATCH (EAY131) Study. J Clin Oncol 2020;38:214-22.
PUBMED | CROSSREF
67. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol 2020;38:2981-92.
PUBMED | CROSSREF
68. Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, et al. Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. J Clin Oncol 2020;38:1154-63.
PUBMED | CROSSREF

69. Lheureux S, Matei D, Konstantinopoulos PA, Block MS, Jewell A, Gaillard S, et al. A randomized phase II study of cabozantinib and nivolumab versus nivolumab in recurrent endometrial cancer. J Clin Oncol 2020;38:6010.
CROSSREF
70. Konstantinopoulos PA, Gockley AA, Xiong N, Tayob N, Krasner CN, Buss M, et al. Phase II study of PARP inhibitor talazoparib and PD-L1 inhibitor avelumab in patients (pts) with microsatellite stable (MSS) recurrent/persistent endometrial cancer. Ann Oncol 2020;31:S1165.
CROSSREF
71. Friedenreich CM, Cook LS, Wang Q, Kokts-Porietis RL, McNeil J, Ryder-Burbidge C, et al. Prospective cohort study of pre- and postdiagnosis physical activity and endometrial cancer survival. J Clin Oncol 2020;38:4107-17.
PUBMED | CROSSREF