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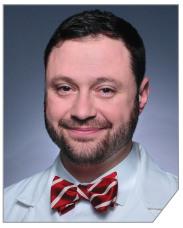

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Highlights from 4 medical and surgical trials on gynecologic cancers and what their results may mean for patient-focused outcomes

Despite the challenges of an ongoing COVID-19 pandemic, researchers in 2021 delivered practice-changing studies in gynecologic oncology. In this cancer Update, we highlight 4 studies that shed light on the surgical and systemic therapies that may improve outcomes for patients with cancers of the ovary, endometrium, and cervix. We review DESKTOP III, a trial that investigated the role of cytoreductive surgery in patients with recurrent ovarian cancer, and SENTOR, a study that evaluated the performance of sentinel lymph node biopsy in patients with high-grade endometrial cancers. Additionally, we examine 2 studies of systemic therapy that reveal the growing role of targeted therapies and immuno-oncology in the treatment of gynecologic malignancies.

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A new era for patients with *BRCA* mutation–associated ovarian cancer

Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22:1721-1731.

Ovarian cancer remains the most lethal gynecologic malignancy due to the frequency of advanced-stage diagnosis and frequent relapse after primary therapy. But for ovarian cancer patients with inherited mutations of the *BRCA1* or *BRCA2* genes, poly(ADP-ribose) polymerase (PARP) inhibitors, a class of oral anticancer medicines that target DNA repair, have ushered in a new era in which the possibility of long-term remission, and even cure, is more likely than at any other time.

Olaparib trial details

The SOLO1 study was a double-blind, placebo-controlled, phase 3 trial that investigated the role of PARP inhibitor maintenance therapy with olaparib in patients with pathologic *BRCA1* or *BRCA2* mutations who responded to platinum-based chemotherapy administered for a newly diagnosed, advanced-stage ovarian cancer.[1] The study enrolled 391 patients, with 260 randomly assigned to receive olaparib

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The updated progression-free survival data from the SOLO1 study provides important and promising evidence that frontline PARP inhibitor maintenance therapy may affect long-term remission in an unprecedented proportion of patients with *BRCA*-related ovarian cancer. Significant, sustained benefit was seen well beyond the end of treatment, and median progression-free survival was an astonishing 3.5 years longer in the olaparib treatment group than among patients who received placebo therapy.

for 24 months and 131 patients randomly assigned to receive placebo tablets. Most patients in the study had a mutation in the *BRCA1* gene (72%), 27% had a *BRCA2* mutation, and 1% had mutations in both genes.

The primary analysis of SOLO1 was published in 2018 and was based on a median follow-up of 3.4 years.[1] That study showed that olaparib maintenance therapy resulted in a large progression-free survival benefit and led to its approval by the US Food and Drug Administration (FDA) as a maintenance therapy for patients with *BRCA*-mutated advanced ovarian cancer who responded to first-line platinum-based chemotherapy.

In 2021, Banerjee and colleagues updated the progression-free survival results for the SOLO1 trial after 5 years of follow-up.[2] In this study, the patients randomly assigned to olaparib maintenance therapy had a persistent and statistically significant progression-free survival benefit, with the median progression-free survival reaching 56 months among the olaparib group compared with 13.8 months in the placebo group (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.25–0.43).[2] Olaparib maintenance therapy resulted in more clinically significant adverse events, including anemia and neutropenia. Serious adverse events occurred in 55 (21%) of the olaparib-treated patients and 17 (13%) of the placebo-treated patients, but no treatment-related adverse events were fatal

FAST TRACK

In the SOLO1 trial, patients randomly assigned to olaparib maintenance therapy had a persistent and statistically significant progression-free survival benefit, with the median progression-free survival reaching 56 months among the olaparib group compared with 13.8 months in the placebo group

Cytoreductive surgery for recurrent ovarian cancer improves survival in well-selected patients

Harter P, Sehouli J, Vergote I, et al; DESKTOP III Investigators. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. N Engl J Med. 2021;385:2123-2131.

In the DESKTOP III trial, Harter and colleagues contribute results to the ongoing discourse surrounding treatment options for patients with recurrent, platinum-sensitive ovarian cancer.[3] Systemic therapies continue to be the mainstay of treatment in this setting; however, several groups have attempted to evaluate the role of secondary cytoreductive surgery in this setting.[4,5]

Specific inclusion criteria employed

The DESKTOP III investigators randomly assigned 407 patients with platinum-sensitive recurrent ovarian cancer to secondary cytoreductive surgery followed by platinum-based chemotherapy (n = 206) or platinum-based chemotherapy alone (n = 201).[3] An essential aspect of the study's design was the use of specific inclusion criteria known to identify patients with a high likelihood of complete resection at the time of secondary cytoreduction.[6,7] Patients were eligible only if they had at least a 6-month remission following platinum-based chemotherapy, had a complete resection at their previous surgery, had no restriction on physical activity, and had ascites of no more than 500 mL.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

The DESKTOP III trial provides compelling evidence that secondary cytoreductive surgery improves overall and progression-free survival among well-selected patients with recurrent, platinum-sensitive ovarian cancer. These results differ from those of a recently reported Gynecologic Oncology Group (GOG) trial that failed to detect a survival benefit for secondary cytoreductive surgery among patients with platinum-sensitive recurrent ovarian cancer.[5] Key differences, which might explain the studies' seemingly contradictory results, were that the GOG study had fewer specific eligibility criteria than the DESKTOP III trial, and that bevacizumab was administered much more frequently in the GOG study. It is therefore reasonable to discuss the possible benefits of secondary cytoreductive surgery with patients who meet DESKTOP III eligibility criteria, with a focus toward shared decision making and a candid discussion of the potential risks and benefits of secondary cytoreduction.

Surgery group had superior overall and progression-free survival

After a median follow-up of approximately 70 months, patients randomly assigned to surgery had superior overall survival (53.7 months) compared with those assigned to chemotherapy alone (46.0 months; HR, 0.75; 95% CI, 0.59–0.96).[3] Progression-free survival also was improved among patients who underwent surgery (median 18.4 vs 12.7 months; HR, 0.66; 95% CI, 0.54–0.82). Subgroup analyses did not identify any subset of patients who did not benefit from surgery. Whether a complete resection was achieved at secondary cytoreduction was highly prognostic: Patients who had a complete resection had a median overall survival of 61.9 months compared with 27.7 months in patients with residual disease. There were no deaths within 90 days of surgery.

FAST TRACK

Results of the DESKTOP III trial showed that after a median follow-up of 70 months, patients randomly assigned to surgery had superior overall survival (53.7 months) compared with those assigned to chemotherapy alone (46.0 months; HR, 0.75; 95% CI, 0.59-0.96)

Immunotherapy enters first-line treatment regimen for advanced cervical cancer

Colombo N, Dubot C, Lorusso D, et al; KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385:1856-1867.

Persistent, recurrent, and metastatic cervical cancer carries a very poor prognosis: Most patients progress less than a year after starting treatment, and fewer than half survive for 2 years. First-line treatment in this setting has been platinum-based chemotherapy, often given with bevacizumab, a humanized monoclonal antibody that inhibits tumor growth by blocking angiogenesis.[8] Pembrolizumab, an immune checkpoint inhibitor, targets cancer cells by blocking their ability to evade the immune system, and it is FDA approved and widely administered to patients with advanced cervical cancer who progress after first-line treatment.[9]

Addition of pembrolizumab extended survival

In the KEYNOTE-826 trial, Colombo and colleagues investigated the efficacy of incorporating an immune checkpoint inhibitor into the first-line treatment regimen for patients with persistent, recurrent, and metastatic cervical cancer.[10] Researchers in this double-blinded, phase 3, randomized controlled trial assigned 617 patients to receive pembrolizumab or placebo concurrently with the investigator's choice platinum-based chemotherapy. Bevacizumab was administered at the discretion of the treating oncologist.

The proportion of patients who survived at least 2 years following randomization was significantly higher among those assigned to pembrolizumab compared with placebo (53% vs 42%; HR, 0.67, 95% CI, 0.54–0.84).[10] Similarly, median progression-free survival

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

In light of the significant improvements in overall and progression-free survival demonstrated in the KEYNOTE-826 trial, in October 2021, the FDA approved the use of frontline pembrolizumab alongside platinum-based chemotherapy, with or without bevacizumab, for treatment of patients with persistent, recurrent, or metastatic cervical cancers that express PD-L1.

was superior among patients who received pembrolizumab compared with those who received placebo (10.4 months vs 8.2 months; HR, 0.65; 95% CI, 0.53–0.79). The role of bevacizumab in conjunction with pembrolizumab and platinum-based chemotherapy was not elucidated in this study because bevacizumab administration was not randomly assigned.

Anemia and neutropenia were the most common adverse events and were more frequent in the pembrolizumab group, but there were no new safety concerns related to concurrent use of pembrolizumab with cytotoxic chemotherapy and bevacizumab. Importantly, subgroup analysis results suggested that pembrolizumab was effective only in patients whose tumors expressed PD-L1 (programmed death ligand 1), a biomarker of pembrolizumab sensitivity in cervical cancer.

Endometrial cancer surgical staging: Is sentinel lymph node biopsy a viable option for high-risk histologies?

FAST TRACK

Median progression-free survival among patients who received pembrolizumab in the KEYNOTE-826 trial was superior compared with those who received placebo—10.4 months vs 8.2 months; HR, 0.65; 95% CI, 0.53-0.79

Cusimano MC, Vicus D, Pulman K, et al. Assessment of sentinel lymph node biopsy vs lymphadenectomy for intermediate- and high-grade endometrial cancer staging. JAMA Surg. 2021;156:157-164.

The use of intraoperative sentinel lymph node mapping and biopsy to identify lymph node metastases among patients undergoing surgical staging for endometrial cancer has become increasingly common. Lymph node status is an important prognostic factor, and it guides adjuvant treatment decisions in endometrial cancer. However, traditional pelvic and paraaortic lymphadenectomy is associated with increased risk of lower-extremity lymphedema, postoperative complications, and intraoperative injury.

Sentinel lymph node biopsy seeks to identify lymph node metastases while minimizing surgical morbidity by identifying and excising only lymph nodes that directly receive lymphatic drainage from the uterus. The combination of a fluorescent dye (indocyanine green) and near infrared cameras have led to the broad adoption of sentinel lymph node biopsy in endometrial cancer staging surgery. This practice is supported by prospective studies that demonstrate the high diagnostic accuracy of this approach.[11,12] However, because most patients included in prior studies had low-grade endometrial cancer, the utility of sentinel lymph node biopsy in cases of high-grade histology has been less clear.

Sentinel lymph node biopsy vs lymphadenectomy for staging

In the SENTOR trial, Cusimano and colleagues examined the diagnostic accuracy of sentinel lymph node mapping and biopsy, using indocyanine green, in patients with intermediate- or high-grade early-stage endometrial cancer.[13]

All eligible patients (N = 156) underwent traditional or robot-assisted laparoscopic hysterectomy with sentinel lymph node biopsy. Subsequently, patients with grade 2 endometrioid carcinoma underwent bilateral pelvic lymphadenectomy, and those with high-grade histology (grade 3

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

The high sensitivity and negative predictive value of sentinel lymph node biopsy in the intermediate- and high-grade cohort included in the SENTOR trial are concordant with prior studies that predominantly included patients with low-grade endometrial cancer. These findings suggest that sentinel lymph node mapping and biopsy is a reasonable option for surgical staging, not only for patients with low-grade endometrial cancer but also for those with intermediate- and high-grade disease.

endometrioid, serous, carcinosarcoma, clear cell, undifferentiated or dedifferentiated, and mixed high grade) underwent bilateral pelvic and para-aortic lymphadenectomy. The investigators evaluated the diagnostic characteristics of sentinel lymph node biopsy, treating complete lymphadenectomy as the gold standard.

Of the 156 patients enrolled, the median age was 65.5 and median body mass index was 27.5; 126 patients (81%) had high-grade histology. The sentinel lymph node biopsy had a sensitivity of 96% (95% CI, 81%–100%), identifying 26 of the 27 patients with nodal metastases. The false-negative rate was 4% (95% CI, 0%–9%) and the negative predictive value was 99% (95% CI, 96%–100%). Intraoperative adverse events occurred in 5 patients (3%), but none occurred during the sentinel lymph node biopsy. ●

FAST TRACK

According to results of the SENTOR trial, in patients with intermediate- or high-grade early-stage endometrial cancer, the sentinel lymph node biopsy had a sensitivity of 96% (95% CI, 81%-100%), identifying 26 of the 27 patients with nodal metastases

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