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Dr. Wright reports that he is a consultant to Clovis Oncology and Tesaro, Inc, and has received research funding from Merck. Dr. Zhou reports no financial relationships relevant to this article.

Gynecologic malignancies continue to be a major cause of cancer-related mortality. In this article: adjuvant chemotherapy during and after radiation for high-risk endometrial cancers; PARP inhibitors with first-line chemotherapy and as maintenance therapy for ovarian cancer; and secondary cytoreductive surgeries for recurrent ovarian cancer.

Over the past year, major strides have been made in the treatment of gynecologic malignancies. In this Update, we highlight 3 notable studies. The first is a phase 3, multicenter, international, randomized clinical trial that demonstrated a significant improvement in both overall and failure-free survival with the use of adjuvant chemoradiation versus radiotherapy alone in patients with stage III or high-risk uterine cancer. Additionally, we describe the results of 2 phase 3, multicenter, international, randomized clinical trials in ovarian cancer treatment: use of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in combination with platinum and taxane-based chemotherapy followed by the PARP inhibitor as maintenance therapy, and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian cancer.

We provide a brief overview of current treatment strategies, summarize the key findings of these trials, and establish how these findings have changed our management of these gynecologic malignancies.

IN THIS ARTICLE

Adjuvant chemotherapy and radiotherapy improves survival in women with high-risk endometrial cancer

de Boer SM, Powell ME, Mileshkin L, et al; on behalf of the PORTEC Study Group. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;1273-1285.

In the United States, it is estimated that more than 61,000 women were diagnosed with endometrial cancer in 2019.[1] Women with endometrial cancer usually have a favorable prognosis; more than 65% are diagnosed with early-stage disease, which is

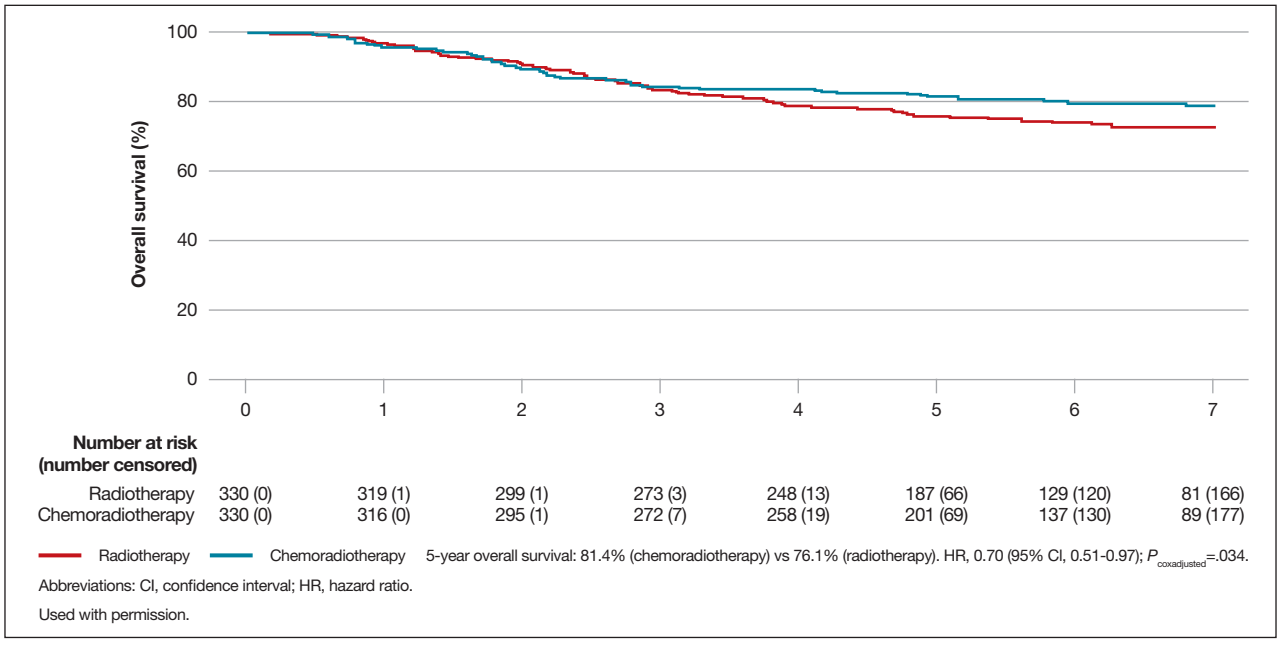

FIGURE Kaplan-Meier curve for overall survival among patients who previously were randomly assigned to chemoradiation (blue line) or radiation alone (red line)[7]

associated with a 95% 5-year survival rate.[1] However, 15% to 20% of patients have disease with high-risk features, including advanced stage (stage II–IV), high tumor grade, lymphovascular space invasion, deep myometrial invasion, or nonendometrioid histologic subtypes (serous or clear cell).[2] The presence of these high-risk disease features is associated with an increased incidence of distant metastases and cancer-related death.

Adjuvant therapy in high-risk endometrial cancer

To date, the optimal adjuvant therapy for patients with high-risk endometrial cancer remains controversial. Prior data from Gynecologic Oncology Group (GOG) protocol 122 demonstrated that chemotherapy significantly improved progression-free survival and overall survival when compared with radiotherapy in patients with advanced-stage endometrial cancer.[3] As such, chemotherapy now is frequently used in this population, often in combination with radiation, although data describing the benefit of chemoradiation are limited.[4] For women with earlier-stage disease with high-risk features, the value of chemotherapy plus radiation is uncertain.[5,6]

Benefit observed with adjuvant chemoradiotherapy

In a multicenter, international, randomized phase 3 trial, known as the PORTEC-3 trial, de Boer and colleagues sought to determine if combined adjuvant chemoradiation improved overall survival (OS) and failure-free survival when compared with external-beam radiation therapy (EBRT) alone in the treatment of women with high-risk endometrial cancer.[7] Women were eligible for the study if they had histologically confirmed stage I, grade 3 endometrioid endometrial cancer with deep invasion and/or lymphovascular space invasion, stage II or III disease, or stage I–III disease with serous or clear cell histology.

Participants were randomly assigned in a 1:1 ratio; 330 women received adjuvant EBRT alone (total dose of 48.6 Gy administered in 27 fractions), and 330 received adjuvant chemotherapy during and after radiation

therapy (CTRT) (2 cycles of cisplatin 50 mg/m^2 IV given on days 1 and 22 of EBRT followed by 4 cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2 IV every 3 weeks).

At a median follow-up of 73 months, treatment with adjuvant CTRT, compared with adjuvant EBRT alone, was associated with a significant improvement in both overall survival (5-year OS: 81.4% vs 76.1%, P = .034 [**FIGURE**]) and failure-free survival (5-year failure-free survival: 76.5% vs 69.1%, P = .016).

The greatest absolute benefit of adjuvant CTRT, compared with EBRT alone, in survival was among women with stage III endometrial cancer (5-year OS: 78.5% vs 68.5%, P = .043) or serous cancers (19% absolute improvement in 5-year OS), or both. Significant differences in 5-year OS and failure-free survival in women with stage I–II cancer were not observed with adjuvant CTRT when compared with adjuvant EBRT alone. At 5 years, significantly more adverse events of grade 2 or worse were reported in the adjuvant CTRT arm.

Results from similar trials

Since the publication of results from the updated analysis of PORTEC-3, results from 2 pertinent trials have been published.[8,9] In the GOG 249 trial, women with stage I–II endometrial cancer with high-risk features were randomly assigned to receive 3 cycles of carboplatin-paclitaxel chemotherapy with vaginal brachytherapy or EBRT.[8] There was no difference in survival, but a significant increase in both pelvic and para-aortic recurrences were seen after the combination of chemotherapy and vaginal brachytherapy.[8]

In GOG 258, women with stage III–IVA endometrial cancer were randomly assigned to receive chemotherapy alone (carboplatin-paclitaxel) or adjuvant chemotherapy after EBRT.[9] No differences in recurrence-free or overall survival were noted, but there was a significant increase in the number of vaginal and pelvic or para-aortic recurrences in patients in the chemotherapy-only arm.[9]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The conflicting data regarding the ideal adjuvant therapy for endometrial cancer suggests that treatment decisions should be individualized. Pelvic EBRT with concurrent adjuvant chemotherapy should be considered in women with stage III endometrial cancer or serous cancers as combination therapy improves survival, although dual modality treatment is associated with increased toxicity. Chemoradiation appears to have less benefit for women with stage I–II cancers with other pathologic risk factors.

Role for PARP inhibitor plus first-line chemotherapy, and as maintenance therapy, in ovarian cancer treatment

Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403-2415.

Ovarian cancer is the leading cause of gynecologic cancer–related deaths among women in the United States.[10] Treatment consists of cytoreductive surgery combined with platinum and taxane-based chemotherapy.[11] Despite favorable initial responses, more than 80% of patients experience a recurrence, with an 18-month median time to progression.[12] As a result, recent efforts have focused on finding novel therapeutic approaches to improve treatment outcomes and mitigate the risk of disease recurrence.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

For women with newly diagnosed, previously untreated stage III or IV high-grade serous ovarian carcinoma, carboplatin, paclitaxel, and veliparib induction therapy followed by single-agent veliparib maintenance therapy resulted in a significant improvement in median progression-free survival compared with induction chemotherapy alone. However, veliparib use was also associated with a higher incidence of adverse effects that required dose reduction and/or interruption during both the combination and maintenance phases of treatment.

FAST TRACK

A significant improvement was observed in progression-free survival in the veliparib-throughout arm compared with the control arm in 3 cohorts: the BRCA-mutation cohort, the HRD cohort, and the intention-to-treat population

PARP inhibitors are changing the face of treatment

Poly(adenosine diphosphate-ribose) polymerases (PARPs) are a family of enzymes that play a critical role in DNA damage repair. These enzymes promote DNA repair by recruiting proteins involved in repairing single-strand and double-strand DNA breaks and in protecting and restarting stalled DNA replication forks.[13] The predominant mechanisms of action of PARP inhibitors in cells with homologous-recombination deficiency (HRD) include inhibiting repair of single-strand DNA breaks and trapping PARP-DNA complexes at stalled DNA replication forks.[14]

Germline or somatic *BRCA1/2* mutations and genetic alterations resulting in HRD are present in about 20% and 30% of ovarian carcinomas, respectively, and increase the susceptibility of tumors to platinum-based agents and PARP inhibitors.[15,16] Based on multiple clinical trials that demonstrated the efficacy of single-agent PARP in the treatment of recurrent ovarian carcinoma and as maintenance therapy after an initial response to platinum-based therapy, the US Food and Drug Administration approved olaparib, niraparib, and rucaparib for the treatment of high-grade epithelial ovarian cancer.[17-19] Only olaparib is approved for maintenance therapy after initial adjuvant therapy in patients with *BRCA* mutations.[20]

Given the robust response to PARP inhibitors, there has been great interest in using these agents earlier in the disease course in combination with chemotherapy.

Efficacy of veliparib with chemotherapy and as maintenance monotherapy

In a randomized, double-blind, placebo-controlled phase 3 trial, Coleman and colleagues sought to determine the efficacy of the PARP inhibitor veliparib when administered with first-line carboplatin and paclitaxel induction chemotherapy and subsequently continued as maintenance monotherapy.[21]

Women with stage III or IV high-grade epithelial ovarian, fallopian tube, or primary peritoneal carcinoma were eligible for the study. Cytoreductive surgery could be performed prior to the initiation of trial treatment or after 3 cycles of chemotherapy.

Participants were randomized in a 1:1:1 ratio: 371 women received carboplatin and paclitaxel plus placebo followed by placebo maintenance (control arm); 376 received chemotherapy plus veliparib followed by placebo maintenance (veliparib combination-only arm); and 377 received chemotherapy plus veliparib followed by veliparib maintenance therapy (veliparib-throughout arm). Combination chemotherapy consisted of 6 cycles, and maintenance therapy was an additional 30 cycles.

Progression-free survival extended

At a median follow-up of 28 months, investigators observed a significant improvement in progression-free survival in the veliparib-throughout (initial and maintenance therapy) arm compared with the control arm in 3 cohorts: the *BRCA*-mutation cohort, the HRD cohort, and the intention-to-treat population (all participants undergoing randomization).

In the *BRCA*-mutation cohort, the median progression-free survival was 12.7 months longer in the veliparib-throughout arm than in the control arm. Similarly, in the HRD cohort, the median progression-free survival was 11.4 months longer in the veliparib-throughout arm than in the control group. In the intention-to-treat population, the median progression-free

survival increased from 17.3 to 23.5 months in the veliparib-throughout arm compared with the control arm.

Women who received veliparib experienced increased rates of nausea, anemia, and fatigue and were more likely to require dose reductions and treatment interruptions. Myelodysplastic syndrome was reported in 1 patient (*BRCA1* positive) in the veliparib combination-only arm.

Secondary cytoreductive surgery or chemotherapy alone for platinum-sensitive recurrent ovarian carcinoma?

Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med. 2019;381:1929-1939.

Primary surgical cytoreduction combined with platinum and taxane-based chemotherapy remains the mainstay of ovarian cancer treatment.[11] The role of surgery for women with recurrent ovarian cancer, so-called secondary cytoreduction, remains controversial.[22]

Data have shown that among women who undergo secondary surgery, those with little or no postoperative residual disease benefit the most from a secondary debulking.[23-26] Prior work largely is based on small retrospective reports and is limited by substantial bias in the selection of patients undergoing surgery. Additionally, with the availability of targeted therapies such as bevacizumab and PARP inhibitors as maintenance—medical interventions with a demonstrated benefit in progression-free survival[17-19,27]—the role of secondary cytoreduction in the treatment of ovarian carcinoma needs to be clarified.

Overall survival after secondary cytoreduction followed by chemotherapy

Coleman and colleagues conducted a prospective, multicenter, international, randomized phase 3 trial to assess whether secondary cytoreductive surgery followed by chemotherapy would improve overall survival versus chemotherapy alone among women with resectable platinum-sensitive, recurrent ovarian cancer.[22] Platinum sensitivity was defined as a disease-free interval of at least 6 months after the last cycle of platinum-based chemotherapy.

All women had recurrent epithelial ovarian carcinoma considered to be amenable to complete gross surgical resection by the investigator and a history of complete response to at least 3 cycles of platinum-based chemotherapy as determined by a normal CA-125 value or negative imaging studies (if obtained).

Participants were randomly assigned 1:1, with 240 women assigned to secondary surgical cytoreduction followed by platinum-based chemotherapy, and 245 assigned to chemotherapy alone. The type of adjuvant chemotherapy used (carboplatin-paclitaxel

FAST TRACK

Secondary cytoreduction followed by chemotherapy was not associated with improved overall survival compared with chemotherapy alone in women with platinum-sensitive, recurrent ovarian cancer

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For women with platinum-sensitive, recurrent ovarian cancer, a secondary cytoreductive surgery followed by chemotherapy was not associated with an improvement in overall survival when compared with chemotherapy alone. Secondary cytoreductive surgery should not be used routinely in women with recurrent ovarian cancer.

or carboplatin-gemcitabine) and whether or not bevacizumab was administered were at the investigators' discretion.

Shorter survival, decline in quality of life

Among the participants assigned to and who underwent surgery, complete gross resection was achieved in 67%. Eighty-four percent of the entire study population received platinum-based chemotherapy with bevacizumab followed by bevacizumab maintenance therapy, which was equally distributed between the 2 study arms.

At a median follow-up of 48.1 months, median overall survival was 50.6 months in the surgery arm compared with 64.7 months in the chemotherapy arm, corresponding to a hazard ratio (HR) for death of 1.29 (95% confidence interval [CI], 0.97–1.72; P = .08). This effect was unchanged after adjusting for platinum-free interval, chemotherapy choice, and restricting the analysis to women who had a complete gross resection.

Similarly, the adjusted HR for disease progression or death was 0.82 (95% CI, 0.66–1.01) and corresponded to a median progression-free survival of 18.9 months for the surgery group and 16.2 months for the chemotherapy group. Surgical morbidity was reported in 9% of patients who underwent surgery, and 1 patient (0.4%) died from postoperative complications.

While a significant decline in both quality of life and patient-reported outcomes was reported immediately after surgery, significant differences were not noted between the 2 groups after the initial postoperative recovery period. ●

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