Should secondary cytoreduction be performed for platinum-sensitive recurrent ovarian cancer?

Such practice should be questioned, according to authors of a phase 3 randomized, controlled trial. In the study, 485 patients with platinum-sensitive recurrent resectable disease who had received 1 previous therapy and had a 6-month or more platinum-free interval (an interval during which no platinum-based chemotherapy was used) were randomly assigned to receive platinum-based chemotherapy or to undergo surgical cytoreduction followed by platinum-based chemotherapy. There were no statistical differences in overall survival, with a trend favoring nonsurgical patients, or progression-free survival, with a trend favoring surgical patients. However, we would recommend using caution in applying the study data to patients with different platinum-free intervals or low-volume disease limited to the pelvis.

FAST TRACK

This is the first RCT to explore the management option of secondary cytoreduction in women with recurrent ovarian cancer

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

EXPERT COMMENTARY

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Ovarian cancer represents the most lethal gynecologic cancer, with an estimated 14,000 deaths in 2019.[1] While the incidence of this disease is low in comparison to uterine cancer, the advanced stage at diagnosis portends poor prognosis. While stage is an independent risk factor for death, it is also a risk for recurrence, with more than 80% of women developing recurrent disease.[2-4] Secondary cytoreduction remains an option for patients in which disease recurs; up until now this management option was driven by retrospective data.[5]

Details of the study

Coleman and colleagues conducted the Gynecologic Oncology Group (GOG) 0213 trial—a

phase 3, multicenter, randomized clinical trial that included 485 women with recurrent ovarian cancer. The surgical objective of the trial was to determine whether secondary cytoreduction in operable, platinum-sensitive (PS) patients improved overall survival (OS).

Patients were eligible to participate in the surgical portion of the trial if they had PS measurable disease and had the intention to achieve complete gross resection. Women with ascites, evidence of extraabdominal disease, and "diffuse carcinomatosis" were excluded. The primary and secondary end points were OS and progression-free survival (PFS), respectively.

Results. There were no statistical differences between the surgery and no surgery groups with regard to median OS (50.6 months vs 64.7 months, respectively; hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.97–1.72) or median PFS (18.9 months vs 16.2 months; HR, 0.82; 95% CI, 0.66 to 1.01). When comparing patients in which complete gross resection was achieved (150 patients vs 245 who did not receive surgery), there was only a statistical difference in PFS in favor of the surgical group (22.4 months vs 16.2 months; HR, 0.62; 95% CI, 0.48–0.80).

Of note, 67% of the patients who received surgery (63% intention-to-treat) were debulked to complete gross resection. There were 33% more patients with extraabdominal disease (10% vs 7% of total patients in each group) and 15% more patients with upper abdominal disease (40% vs 33% of total patients in each group) included in the surgical group. Finally, the median time to chemotherapy was 40 days in the surgery group versus 7 days in the no surgery group.

Study strengths and weaknesses

The authors deserve to be commended for this well-designed and laborious trial, which is the first of its kind. The strength of the study is its randomized design producing level I data.

Study weaknesses include lack of reporting of *BRCA* status and the impact of receiving targeted therapies after the trial was over. It is well established that *BRCA*-mutated patients have an independent survival advantage, even when taking into account platinum sensitivity.[6-8] *BRCA* status of the study population is not specifically addressed in this paper. The authors noted in the first GOG 0213 trial publication, which assessed bevacizumab in the recurrent setting, that *BRCA* status has an impact on patient outcomes. Subsequently, they state that they do not report *BRCA* status because "…its independent effect on response to an anti-angiogenesis agent was unknown," but it clearly would affect survival analysis if unbalanced between groups.[9]

Similarly, in the introduction to their study, Coleman and colleagues list availability of maintenance therapy, for instance poly ADP (adenosine diphosphate–ribose) polymerase (PARP) inhibitors, as rationale for conducting their trial. They subsequently cite this as a possible reason that the median overall survival was 3 times longer than expected. However, they provide no data on which patients received maintenance therapy, which again could have drastically affected survival outcomes.[10] They do report in the supplementary information that, when stratifying those receiving bevacizumab adjuvantly during the trial, the median OS was comparable between the surgical and nonsurgical groups (58.5 months vs 61.7 months).

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

This is the first randomized clinical trial conducted to assess whether secondary surgical cytoreduction is beneficial in PS recurrent ovarian cancer patients. It provides compelling evidence to critically evaluate whether surgical cytoreduction is appropriate in a similar patient population. However, we would recommend using caution applying these data to patients who have different platinum-free intervals or low-volume disease limited to the pelvis.

The trial is not without flaws, as the authors point out in their discussion, but currently, it is the best evidence afforded to gynecologic oncologists. There are multiple trials currently ongoing, including DESTOP-III, which had similar PFS results as GOG 0213. If consensus is reached with these 2 trials, we believe that secondary cytoreduction will be utilized far less often in patients with recurrent ovarian cancer and a long platinum-free interval, thereby changing the current treatment paradigm for these patients.

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The authors discuss the presence of patient selection bias as a weakness in the study. Selection bias is evident in this trial (as in many surgical trials) because patients with a limited volume of disease were selected to participate over those with large-volume disease. It is reasonable to conclude that this study is likely selecting patients with less aggressive tumor biology, not only evident by low-volume disease at recurrence but also by the 20.4-month median platinum-free interval in the surgical group, which certainly affects the trial's validity. Despite being considered PS, the disease biology in a patient with a platinum-free interval of 20.4 months is surely different from the disease biology in a patient with a 6.4-month platinum-free interval; therefore, it is difficult to generalize these data to all PS recurrent ovarian cancer patients. Similarly, other research has suggested strict selection criteria, which was not apparent in this study's methodology.[11] While the number of metastatic sites were relatively equal between the surgery and no surgery groups, there were more patients in the surgical group with extraabdominal disease, which the authors used as an exclusion criterion.

Lastly, the time to treatment commencement in each arm, which was 40 days for the surgical arm and 7 days in the nonsurgical arm, could represent a flaw in this trial. While we expect a difference in duration to account for recovery time, many centers start chemotherapy as soon as 21 days after surgery, which is almost half of the median interval in the surgical group in this trial. While the authors address this by stating that they completed a landmark analysis, no data or information about what time points they used for the analysis are provided. They simply report an interquartile range of 28 to 51 days. It is hard to know what effect this may have had on the outcome. ●

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7-34.
2. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet.* 2003;361:2099-2106.
3. International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet.* 2002;360:505-515.
4. Mullen MM, Kuroki LM, Thaker PH. Novel treatment options in platinum-sensitive recurrent ovarian cancer: a review. *Gynecol Oncol.* 2019;152:416-425.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: ovarian cancer. November 26, 2019. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed December 18, 2019.
6. Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. *Cancer.* 2003;97:2187-2195.
7. Gallagher DJ, Konner JA, Bell-McGuinn KM, et al. Survival in epithelial ovarian cancer: a multivariate analysis incorporating BRCA mutation status and platinum sensitivity. *Ann Oncol.* 2011;22:1127-1132.
8. Sun C, Li N, Ding D, et al. The role of BRCA status on the prognosis of patients with epithelial ovarian cancer: a systematic review of the literature with a meta-analysis. *PLoS One.* 2014;9:e95285.
9. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18:779-791.
10. Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. *N Engl J Med.* 2019;381:1929-1939.
11. Chi DS, McCaughty K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. *Cancer.* 2006;106:1933-1939.