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Expert Opinion

Why was GOG-0213 a negative trial?

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An ongoing question in the field of gynecologic oncology has been whether or not secondary cytoreductive surgery (SCS) followed by platinum-based chemotherapy increases overall survival (OS) in patients with platinum-sensitive recurrent ovarian cancer. Several retrospective studies have been published on this topic. Bristow et al. published a meta-analysis showing that complete cytoreductive surgery is the strongest independent factor for survival, demonstrating that with every 10% increase in complete cytoreduction, there was an associated 3 months' increase in median survival [1]. To this end, three large, multicenter, randomized, phase 3 trials—the DESKTOP III (NCT01166737), GOG-0213 (NCT00565851) and the SOC-1 trial (NCT01611766)—were designed to evaluate SCS followed by platinum-based chemotherapy in these patients.

Findings from the DESKTOP III trial were recently presented and demonstrated an improved median OS benefit of 7.5 months in the SCS followed by chemotherapy group compared with the chemotherapy-alone group (53.7 vs. 46.2 months, respectively). Looking further into the data, complete macroscopic resection resulted in a median OS benefit of approximately 15 months (60.7 vs. 46.2 months, respectively) [2]. On the other hand, data from the GOG-0213 study did not show an improvement in median OS with SCS followed by chemotherapy compared with chemotherapy alone (50.6 vs. 64.7 months, respectively) [3]. Even when comparing only patients who achieved complete gross resection (CGR) to those who did not undergo SCS, there was still no median OS advantage (56.0 vs. 64.7 months, respectively) [3]. Both the GOG-0213 and DESKTOP III trials, however, did show a progression-free survival (PFS) benefit in the surgery versus no-surgery arms (18.9 versus 16.2 months in GOG-0213 and 18.4 versus 14.0 months in DESKTOP III, respectively) [2,3]. Median OS data from the SOC-1 trial are still immature; however, median PFS was 17.4 months in the surgery arm and 11.9 months in the no-surgery arm [4].

These findings have left gynecologic oncologists wondering why the data from GOG-0213 did not show an OS benefit with SCS, as they did with DESKTOP III. We looked at similarities and differences in trial design and reported outcomes to address this question. Median platinum-free interval, which is a well-established, important prognostic factor for patients with recurrent disease, was similar between the 2 studies (20.4 months in GOG-0213 and 21.1 months in DESKTOP III) [2,3]. Patients in the SOC-1 trial, however, had a median platinum-free interval of 16 months, suggesting the trial enrolled more higher-risk

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Author Contributions

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patients [4]. Rates of serous histology were similar, ranging from 81%–86.8% across the three studies [2,4,5]. The most important common feature across the three trials was the similar achieved CGR rates, ranging from 67%–76.7% [2-4]. Researchers from the GOG-0213 and DESKTOP III concluded that there was no OS benefit with SCS if complete resection could not be achieved.

BRCA mutation status was not provided in either trial, nor was the additional treatment with poly (ADP-ribose) polymerase inhibitor (PARPi) in GOG-0213. In DESKTOP III and SOC-1, 3.9% and 10.1%, respectively, received PARPi maintenance therapy [2,4]. Knowledge of mutational status is important, considering the many available novel treatment options that can have a potential impact on prognosis. For example, maintenance therapy with the PARPi olaparib in patients with platinum-sensitive recurrent ovarian cancer and *BRCA* mutation improved median OS by 12.9 months in the SOLO2 trial [6].

Furthermore, there were marked differences in study design between GOG-0213 and DESKTOP III. Most importantly, there were no defined patient eligibility criteria for surgery in the GOG-0213 trial; eligibility was based on the surgeon's preference. There were no uniform selection criteria or method-defined surgical technique across the participating centers. The only requirements for GOG-0213 enrollment was platinum-sensitive recurrent ovarian cancer with the possibility of achieving a CGR and good medical condition, with acceptable kidney, liver and bone marrow function, as well as a GOG performance status score of 0–2 [3]. The decision to perform surgery was at the surgeon's discretion. On the other hand, the DESKTOP III and SOC-1 trials had strictly defined criteria. In the DESKTOP III trial, Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score was used to carefully select patients for SCS. The AGO score was validated by the DESKTOP II trial to be predictive for complete macroscopic resection, and it included: i) good performance status, ii) ascites less than 500 mL, and iii) CGR at primary debulking surgery [7]. iMODEL score combined with positron emission tomography-computed tomography (PET-CT) imaging was used to predict the possibility of CGR in the SOC-1 trial [4]. The iMODEL is based on six parameters: FIGO stage, progression-free interval, CA-125 levels, Eastern Cooperative Oncology Group (ECOG) performance status, residual disease after primary surgery, and ascites at recurrence [8]. The latter three variables of the iMODEL are concordant with the prospectively validated AGO score. The iMODEL variables were categorized into low risk and high risk, resulting in CGR rates of 53.4% in the low-risk group and 20.1% in the high-risk group [8].

As we have learned from previous studies, appropriate patient selection is critical. It is important to consider SCS only in patients in whom a CGR can be achieved in order to avoid the detriments of unnecessary surgery. Different models for prediction have been published. Memorial Sloan Kettering Cancer Center (MSK) published selection criteria for SCS that include disease-free-interval, number of recurrence sites, and the presence of peritoneal carcinomatosis [9]. MSK also performed a comparison analysis of the different models that predict the possibility of CGR with SCS. Patients with first platinum-sensitive recurrent ovarian cancer were included, and the accuracy of the prediction models (MSK criteria, AGO score, and iMODEL score) was assessed. According to the study's findings, the MSK criteria predicted a high CGR rate. The accuracy in prediction was 49% for the AGO score, 86% for MSK criteria, and 88% for the iMODEL [10]. The development of a model that is generalizable, applicable in the clinic, and has a high positive predictive value is necessary.

GOG-0213 data also lacked information on the extent of residual disease after primary debulking surgery and site of recurrence in some patients. Ascites was mentioned as an exclusion criterion [3], but it was not further specified if any ascites or a threshold of a certain amount of ascites was exclusive and how much ascites a patient had at diagnosis. Ascites of more than 500 mL is an exclusion criterion with AGO score.

Furthermore, there is no indication of how many patients in the GOG-0213 non-surgical group crossed over and received surgery at a later time point. The cross-over rate was 11% and 36.9% in DESKTOP III and SOC-1, respectively [4,11]. Cross-over in the GOG-0213 trial could have had an impact on OS in the no-surgery group. Other hypothetical factors that may have impacted overall survival in GOG-0213 could have been that in the United States more lines of chemotherapy are administered in the later stages of disease and the use of palliative surgery for bowel obstructions may be more prevalent than in other parts of the world.

There was also noteworthy variability in race; 49.5% of the patients in the GOG-0213 study were East Asian, whereas only 2.0% of patients in the DESKTOP III trial were East Asian [12]. There is evidence that shows frequency and type of *BRCA* mutation vary by ethnicity and geographical region [13]. Nevertheless, this difference in demographics does not explain the different OS outcomes between GOG-0213 and DESKTOP III.

There was also a stark difference in the rate of additional bevacizumab maintenance therapy across the 3 trials, ranging from 1.1% in the SOC-1 trial to 22.8% in the DESKTOP III trial to 84% in the GOG-0213 trial [2-4]. However, the high rate of treatment with bevacizumab in GOG-0213 compared with DESKTOP III does not explain the negative GOG-0213 trial. The addition of bevacizumab led to a median PFS improvement of 3.4 months (13.8 months with vs. 10.4 months without bevacizumab) [5]. These results confirm the results of the published literature.

The bowel resection rate (35.8% vs. 28%) and stoma creation rate (7.9% vs. 2%) was higher in DESKTOP III than in GOG-2013 [2,3]. These findings suggest that patients in DESKTOP III most likely had a higher tumor burden. GOG-0213 reported a 30-day mortality rate of 0.4%, and DESKTOP III mentioned a 60-day mortality rate of 0% in the surgical group. The re-laparotomy rate differed from 0% in GOG-0213 to 3.7% in DESKTOP III [2,3].

In summary, strict patient eligibility criteria and institutional eligibility criteria may help identify patients who will benefit from SCS. The DESKTOP III study was an exceptionally well-designed study with rigorous patient and institution selection criteria. The results of GOG-0213 confirmed that SCS should not be offered to all patients with platinum-sensitive recurrent ovarian cancer and highlighted the importance of strict patient selection, particularly in comparison with DESKTOP III. This finding is most pronounced when CGR cannot be achieved, as demonstrated by the lowest reported OS in patients left with residual disease after SCS in the GOG-0213 study (37.8 months with incomplete resection, 56 months with CGR, and 64.7 months with chemotherapy alone) [3].

REFERENCES

1. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol 2009;112:265-74.
PUBMED | CROSSREF

2. Du Bois A, 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
3. 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
4. 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
5. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, 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;18:779-91.
PUBMED | CROSSREF
6. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: a phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a *BRCA* mutation. J Clin Oncol 2020;38:6002.
CROSSREF
7. Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer 2011;21:289-95.
PUBMED | CROSSREF
8. 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
9. Chi DS, McCaughty K, Diaz JP, Huh J, Schwabenbauer S, Hummer AJ, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 2006;106:1933-9.
PUBMED | CROSSREF
10. Cowan RA, Eriksson AGZ, Jaber SM, Zhou Q, Iasonos A, Zivanovic O, et al. A comparative analysis of prediction models for complete gross resection in secondary cytoreductive surgery for ovarian cancer. Gynecol Oncol 2017;145:230-5.
PUBMED | CROSSREF
11. Goodman A. The ASCO Post. Two studies report secondary surgery extends survival in recurrent ovarian cancer: benefit seen solely in selected patients treated at specialized centers [Internet]. Huntington, NY: HSP News Service, L.L.C.; 2020 [cited 2020 Nov 10]. Available from: https://ascopost.com/issues/july-10-2020/two-studies-report-secondary-surgery-extends-survival-in-recurrent-ovarian-cancer/.
12. Kim M, Suh DH, Lee KH, Eom KY, Lee JY, Lee YY, et al. Major clinical research advances in gynecologic cancer in 2019. J Gynecol Oncol 2020;31:e48.
PUBMED | CROSSREF
13. Rebbeck TR, Friebel TM, Friedman E, Hamann U, Huo D, Kwong A, et al. Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations. Hum Mutat 2018;39:593-620.
PUBMED | CROSSREF