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Randomized Trial of Cytoreductive Surgery for Relapsed Ovarian Cancer

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ABSTRACT

BACKGROUND

Treatment for patients with recurrent ovarian cancer has been mainly based on systemic therapy. The role of secondary cytoreductive surgery is unclear.

METHODS

We randomly assigned patients with recurrent ovarian cancer who had a first relapse after a platinum-free interval (an interval during which no platinum-based chemotherapy was used) of 6 months or more to undergo secondary cytoreductive surgery and then receive platinum-based chemotherapy or to receive platinum-based chemotherapy alone. Patients were eligible if they presented with a positive Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score, defined as an Eastern Cooperative Oncology Group performance-status score of 0 (on a 5-point scale, with higher scores indicating greater disability), ascites of less than 500 ml, and complete resection at initial surgery. A positive AGO score is used to identify patients in whom a complete resection might be achieved. The primary end point was overall survival. We also assessed quality of life and prognostic factors for survival.

RESULTS

A total of 407 patients underwent randomization: 206 were assigned to cytoreductive surgery and chemotherapy, and 201 to chemotherapy alone. A complete resection was achieved in 75.5% of the patients in the surgery group who underwent the procedure. The median overall survival was 53.7 months in the surgery group and 46.0 months in the no-surgery group (hazard ratio for death, 0.75; 95% confidence interval, 0.59 to 0.96; P=0.02). Patients with a complete resection had the most favorable outcome, with a median overall survival of 61.9 months. A benefit from surgery was seen in all analyses in subgroups according to prognostic factors. Quality-of-life measures through 1 year of follow-up did not differ between the two groups, and we observed no perioperative mortality within 30 days after surgery.

CONCLUSIONS

In women with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone. (Funded by the AGO Study Group and others; DESKTOP III ClinicalTrials.gov number, NCT01166737.)

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*A list of the investigators in the DESKTOP III trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The mainstay of treatment for women with advanced ovarian cancer has been primary surgery with the goal of complete macroscopic resection of all tumor, followed by carboplatin and paclitaxel combination chemotherapy.[1] More recently, additional systemic therapy with bevacizumab or a poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor has been associated with superior progression-free survival.[2-7] The standard of care in relapsed ovarian cancer has mainly been systemic treatment. So far, only a few trials have shown level 1 evidence of a significant overall survival benefit with the use of systemic therapy in relapsed ovarian cancer.[8,9] Two other trials have shown a clinically relevant survival benefit with systemic therapy, but statistical significance was shown only after adjustment or in subgroup analyses.[10,11] The role of surgery in relapsed ovarian cancer has not been well defined.

We initiated the Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP) series when the evidence consisted only of retrospective trials in heterogeneous populations that suggested a benefit of surgery in patients with platinum-sensitive relapsed disease (i.e., patients with a durable response to platinum therapy, defined as ≥6 months without disease progression after the end of platinum therapy).[12] First, we defined the surgical aim associated with a potential survival benefit and determined a score that would indicate predictive factors for complete resection.[13]

The DESKTOP I trial confirmed the beneficial role of complete resection, which surpassed the effect of cytoreduction in upfront surgery.[14] Only complete resection was associated with any long-term benefit in recurrent ovarian cancer. Therefore, a predictive score (the Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] score) that would identify patients in whom a complete resection might be achieved was deemed necessary to select patients for a prospective trial of cytoreductive surgery. These selection criteria should fulfill two goals: the proportion of patients who are exposed to a potentially harmful intervention but do not gain any benefit must be minimized, and the trial evaluating surgery as the method of treatment should not be diluted by a high number of patients in whom complete macroscopic tumor clearance is not successful. Independent predictive factors in multivariate analysis for complete resection in the DESKTOP I trial were complete resection at primary surgery, an Eastern Cooperative Oncology Group performance-status score of 0 (on a 5-point scale, with higher scores indicating greater disability), and ascites of 500 ml or less. The AGO score was defined as positive if all three factors were present.

In the subsequent multicenter, prospective DESKTOP II trial, which consecutively enrolled 516 patients who had had a platinum-sensitive relapse, complete resection was achieved in 76% of 129 patients who had a positive AGO score and underwent surgery for a first relapse. This finding confirmed the value of the AGO score in predicting complete resectability of a tumor.[15] Thereafter, we conducted the prospectively randomized DESKTOP III trial, the results of which are reported here.

Methods

Trial Design

Patients who met the eligibility criteria were randomly assigned in a 1:1 ratio to undergo cytoreductive surgery and then receive the physician's choice of platinum-based chemotherapy or to receive the physician's choice of platinum-based chemotherapy alone. The protocol strongly recommended combination therapy, but a single agent was allowed. Randomization was stratified according to center and platinum-free interval (the interval during which no platinum-based chemotherapy was used: no previous chemotherapy, an interval of 6 to 12 months, or an interval of >12 months). We applied a covariate-adaptive randomization procedure according to Rosenberger and Lachin, which combines elements of the minimization approach with a biased coin technique.[16]

The trial was performed according to the European Network for Gynaecological Oncological Trial Groups model A.[17] Trial centers were selected on the basis of experience in ovarian cancer studies and participation in previous surgical trials in this field. Ethical approval was obtained at each participating center, and all patients provided written informed consent. The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. GlaxoSmithKline and

Medac (two of the sponsors of the trial) had no role in the conduct of the trial, the handling of data, or the preparation of the manuscript.

ELIGIBILITY

Patients were eligible if they had relapsed histologically diagnosed epithelial ovarian cancer (clinically defined as a lesion that is palpable or visible or that is visible on ultrasonographic imaging) or relapsed disease radiologically diagnosed at least 6 months after the last course of initial platinum-based chemotherapy (i.e., platinum-sensitive disease) and had a positive AGO score. An elevated cancer antigen 125 level alone was not deemed to be an acceptable entry criterion.

END POINTS AND ASSESSMENTS

The primary end point of overall survival was defined as the time from randomization to death. We also report the following planned secondary end points: quality of life at baseline, 6 months, and 12 months after randomization, as assessed with the use of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30) and the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy (FACT)–General and FACT–Ovarian and its corresponding FACT–Ovarian Symptom Index; progression-free survival (defined as the time from randomization to investigator-assessed disease progression or death, whichever came first); complete resection as a prognostic factor; complications associated with surgery up to 60 days after surgery; and an exploratory analysis of surgical characteristics and applied chemotherapy.

STATISTICAL ANALYSIS

For the primary efficacy comparison, we used a two-sided Wald test from a Cox regression model of overall survival stratified according to platinum-free interval (no previous platinum chemotherapy, an interval of 6 to 12 months, or an interval of >12 months). For all between-group comparisons of overall survival and progression-free survival, we checked the proportional-hazards assumptions by performing Grambsch–Therneau tests, and we omitted hazard ratios if the tests showed evidence of nonproportionality.[18] On the basis of data from the DESKTOP I trial, we assumed that 2-year overall survival would be approximately 66% in the surgery group and 55% in the no-surgery group, and we planned the trial to show a hazard ratio for death of 0.70. A two-stage group sequential design according to the O'Brien–Fleming procedure[19] was applied, which would have allowed the trial to finish earlier with 80% power if the hazard ratio was 0.50. The interim analysis was scheduled after 122 deaths had been reported, testing against a one-sided significance level of 0.003, and the final analysis was scheduled to be performed after 244 deaths had been reported, testing against a one-sided significance level of 0.024.

With a planned accrual period of 3 years and a 3-year follow-up period, and accounting for a potential dropout rate of 10%, we determined that 408 patients would be needed to observe 244 deaths, which would give the trial a power of 80%. At the interim analysis, the between-group difference in overall survival was not significant at the local 0.003 significance level, so follow-up continued. The final primary efficacy analysis was performed on an intention-to-treat basis after 254 deaths had occurred. Analysis of surgical characteristics was performed in patients assigned to the surgery group who underwent the procedure. Quality-of-life questionnaires were scored according to relevant manuals and analyzed with the use of a model-based approach, assuming missingness at random. Detailed methods and results are provided in Fig. S1 in the Supplementary Appendix, available at NEJM.org. Confidence intervals were not adjusted for multiplicity, so inferences drawn may not be reproducible.

RESULTS

PATIENTS AND TREATMENT

A total of 407 patients (206 in the surgery group and 201 in the no-surgery group) were enrolled from September 2010 through March 2015 and were included in the analyses (Fig. 1). The baseline characteristics were well balanced between the two groups. Nearly all the patients had received previous platinum-based chemotherapy at first diagnosis, and 75% of the patients in each group had a platinum-free interval of more than 12 months (Table 1). The median time from randomization to the start of chemotherapy in the no-surgery group was 15 days (interquartile range, 8 to 22). The median time from randomization to surgery in the surgery group was 16

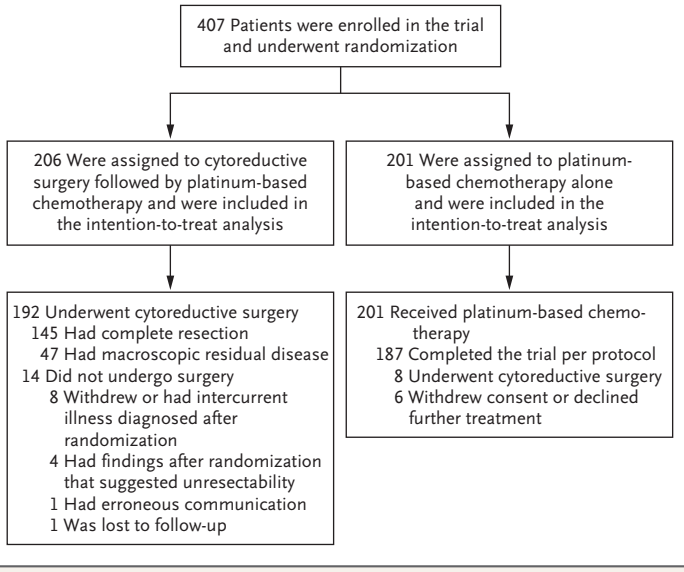

Figure 1. Enrollment, Randomization, and Treatment.

days (interquartile range, 9 to 23), and chemotherapy was started a median of 35 days (interquartile range, 25 to 45 days) after surgery in this group. Of the 206 patients assigned to surgery, 192 (93.2%) underwent the procedure. Reasons for not undergoing the operation were an intercurrent illness that was diagnosed after randomization (8 patients), findings after randomization that suggested unresectability (4 patients), loss to follow-up shortly after randomization (1 patient), and erroneous communication of a randomization result (1 patient) (Fig. 1). A total of 8 patients in the no-surgery group underwent surgery, and another 6 patients withdrew consent or declined further treatment. A total of 32 of 201 patients (15.9%) in the no-surgery group crossed over to surgery because of subsequent relapse.

Macroscopic complete resection was achieved in 75.5% (145 of 192) of the patients who were assigned to surgery and underwent the procedure and in 70.4% (145 of 206) of all patients in the surgery group. There were no deaths within 30 days after surgery, and reoperation was performed in 3.7% (7 of 191 patients). The median operation time was 222 minutes (range, 150 to 300). Additional details regarding surgery and perioperative complications are provided in Table S1.

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

The median follow-up was 69.8 months (interquartile range, 59.8 to 80.4). The median overall survival was 53.7 months (95% confidence interval [CI], 46.8 to 61.6) in the surgery group and 46.0 months (95% CI, 39.5 to 52.6) in the no-surgery group (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.96; P=0.02). The median progression-free survival was 18.4 months (95% CI, 15.7 to 20.8) in the surgery group and 14.0 months (95% CI, 12.7 to 15.4) in the no-surgery group (hazard ratio for progression or death, 0.66; 95% CI, 0.54 to 0.82) (Fig. 2). Among the patients who were assigned to and underwent surgery, the median progression-free survival was 18.5 months (95% CI, 15.9 to 21.0), and the median overall survival was 55.5 months (95% CI, 48.2 to 62.0). Analyses of potential prognostic baseline factors such as age, International Federation of Gynecology and Obstetrics stage at first diagnosis, histologic subtype, treatment history that included previous maintenance therapy, and platinum-free interval (6 to 12 months or >12 months) did not identify a subgroup of patients who did not benefit from surgery (Fig. 3).

OTHER ASSESSMENTS

The role of complete resection as a prognostic factor was analyzed as a secondary end point in the surgery group. Among patients in the surgery group who had complete resection, the median overall survival was 61.9 months (95% CI, 55.3 to 78.9), as compared with 27.7 months (95% CI, 23.5 to 38.7) among patients who did not have complete resection (Fig. S3). This difference remained similar in magnitude when 14 patients who were assigned to surgery but did not undergo the procedure were excluded (data not shown).

The majority of patients in both groups received at least five cycles of a platinum-containing second-line therapy: 76.7% of the patients in the surgery group and 79.6% in the no-surgery group. A total of 94 patients (47 in each group) received bevacizumab as part of second-line therapy, and only a few patients received a PARP inhibitor during the trial (8 in the surgery group and 12 in the no-surgery group, with some patients participating in double-blind, placebo-controlled trials of PARP inhibition). Kaplan–

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Cytoreductive Surgery (N=206)	No Surgery (N=201)
Median age (IQR) — yr	60.8 (54.2–67.3)	62.2 (54.2–69.9)
FIGO stage at first diagnosis — no. (%)†		
I	24 (11.7)	19 (9.5)
II	20 (9.7)	26 (12.9)
III	145 (70.4)	143 (71.1)
IV	16 (7.8)	13 (6.5)
Missing data	1 (0.5)	0
Tumor histologic type — no. (%)		
High-grade serous	173 (84.0)	155 (77.1)
Low-grade serous	4 (1.9)	6 (3.0)
Clear cell	1 (0.5)	9 (4.5)
Endometrioid	13 (6.3)	16 (8.0)
Mucinous	3 (1.5)	1 (0.5)
Other or mixed	12 (5.8)	14 (7.0)
Previous first-line therapy — no. (%)		
Platinum-based	204 (99.0)	199 (99.0)
Taxane-based	193 (93.7)	180 (89.6)
Antiangiogenic drugs‡	33 (16.0)	31 (15.4)
No previous chemotherapy	3 (1.5)	3 (1.5)
Platinum-free interval§		
6–12 mo — no./total no. (%)	48/203 (23.6)	47/198 (23.7)
>12 mo — no./total no. (%)	155/203 (76.4)	151/198 (76.3)
Median (IQR) — mo	21.1 (12.9–33.6)	18.7 (12.8–32.1)
Tumor marker at baseline		
Median CA-125 level (IQR) — U/ml	61 (28–116)	73 (33–166)
Site of relapse — no. (%)		
Pelvis	125 (60.7)	112 (55.7)
Intraabdominal, above pelvis	103 (50.0)	110 (54.7)
Retroperitoneal	73 (35.4)	73 (36.3)
Parenchymal	26 (12.6)	30 (14.9)
Spleen	13 (6.3)	18 (9.0)
Liver	13 (6.3)	11 (5.5)
Pancreas	0	1 (0.5)
Other	7 (3.4)	5 (2.5)
Abdominal wall	4 (1.9)	3 (1.5)
Thoracic	3 (1.5)	2 (1.0)

* Percentages may not total 100 because of rounding. CA-125 denotes cancer antigen 125, and IQR interquartile range.
† International Federation of Gynecology and Obstetrics (FIGO) stages range from I to IV, with higher stages indicating more advanced cancer.
‡ Patients had received the following antiangiogenic drugs as part of their care or because of participation in a previous trial (some participants may have received placebo rather than the drug): bevacizumab (16 patients in the surgery group and 15 in the no-surgery group), nintedanib or placebo (9 patients in the surgery group and 6 in the no-surgery group), pazopanib (1 patient in the surgery group and 2 in the no-surgery group), pazopanib or placebo (6 patients in the surgery group and 3 in the no-surgery group), sorafenib or placebo (1 patient in the no-surgery group), and trebananib or placebo (1 patient in the surgery group and 4 in the no-surgery group). The drugs had been administered with chemotherapy or as maintenance therapy or both.
§ Data are shown for 203 patients in the surgery group and 198 patients in the no-surgery group who had received previous platinum-based chemotherapy.

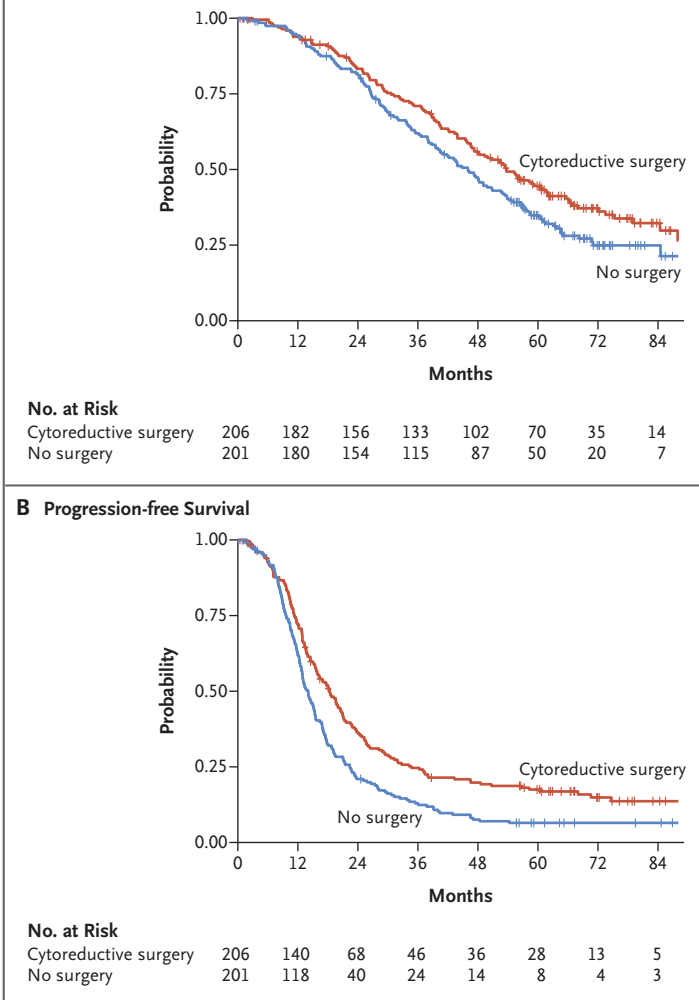

Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival.

Tick marks indicate censored data.

Meier curves of progression-free and overall survival in the subgroup of patients who did not receive bevacizumab as part of second-line therapy are shown in Figure S2. The results of this exploratory subgroup analysis did not indicate any influence of bevacizumab maintenance therapy on survival or on the effect of surgery. The subgroup of patients who received bevacizumab therapy was too small for meaningful analysis.

Results of quality-of-life analyses did not show any between-group differences with respect to global health status, quality of life, or any functional subscale at baseline, visit 1 (at 6 months), or visit 2 (at 12 months). Model-based estimates of the between-group difference in the changes from baseline to 6 months were 9.0 points (95% CI, 1.1 to 17.0) on the insomnia scale and 12.2 points (95% CI, 3.5 to 20.9) on the constipation scale of the QLQ-C30, favoring the no-surgery group (scores on each scale range from 0 to 100, with higher scores indicating worse symptoms). However, at the 6-month evaluation, only 11 of 99 patients (11%) in the no-surgery group, as compared with 32 of 85 patients (38%) in the surgery group, were still receiving chemotherapy. We did not observe any differences regarding these symptoms after the end of chemotherapy treatment at the 12-month evaluation (Fig. S1).

DISCUSSION

Cytoreductive surgery in addition to platinum-based chemotherapy in patients with relapsed ovarian cancer resulted in a benefit with respect to overall survival. Appropriate selection of patients and trial centers was crucial for the success of this trial, and the importance of these selections is reflected in both the high efficacy and low morbidity in the trial. The observed incidence of perioperative complications was lower than the incidence that has been reported among patients with primary ovarian cancer.[20] In the DESKTOP III trial, the number of patients in whom complete resection was achieved was high; therefore, many patients were not exposed to a surgical burden unnecessarily without having any potential benefit, and the power of the trial was not diluted because of a large proportion of patients who did not undergo successful surgery. We anticipated that only complete resection could provide any benefit, and, consequently, a surgical trial could be successful only with a sufficiently large number of patients in whom complete resection is achieved. To enrich the trial population, we had developed a predictive selection tool — the AGO score. This trial confirmed the usefulness of the score, which predicted complete resection in 76% of the patients, a figure much higher than that reported in unselected patients in multicenter trials of systemic therapy in women with primary advanced ovarian cancer (usually 50% or even lower).[21-23]

Four additional randomized trials evaluating the role of surgery in recurrent ovarian cancer are under way worldwide. Unfortunately, two of them (EORTC 55963; ClinicalTrials.gov number, NCT00006356; and Surgery for Ovarian Cancer

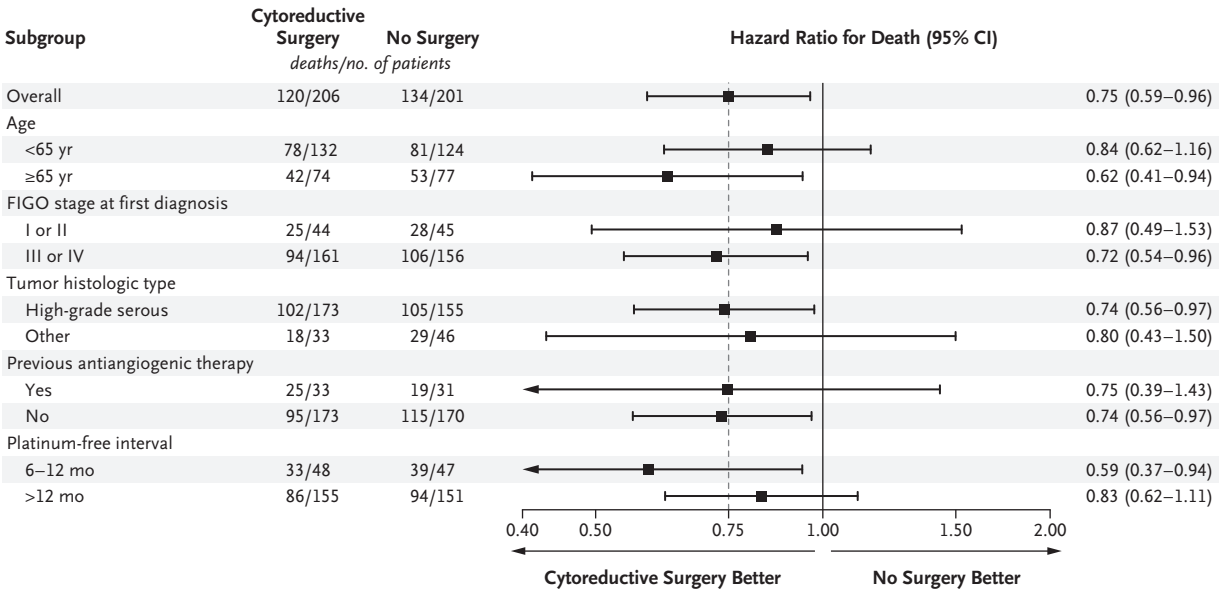

Figure 3. Analyses of Overall Survival According to Prognostic Baseline Factors.

International Federation of Gynecology and Obstetrics (FIGO) stages range from I to IV, with higher stages indicating more advanced cancer; the FIGO stage was missing for one patient in the surgery group. The dashed line indicates a hazard ratio of 0.75.

Recurrence [SOCCER]; Netherlands Trial Register number, NTR3337) were stopped because of low recruitment. The surgical part of the Gynecologic Oncology Group (GOG)–0213 trial completed recruitment, and the results have been published.[24] A total of 485 patients in whom complete resection was deemed feasible by the investigator underwent randomization in that trial. Complete resection was achieved in 67% of the patients assigned to surgery who underwent the procedure. After a futility analysis indicated a low chance of showing a positive trial, the data were locked and analyzed and were published with an updated follow-up. The trial failed to show a survival benefit of adding surgery to systemic treatment.

The Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC-1) trial also completed recruitment: 357 patients were randomly assigned to undergo surgery and then receive chemotherapy or to receive chemotherapy alone.[25] Patients were selected for enrollment if they had potentially resectable disease as predicted with the use of the international model (iMODEL) or if the surgeon determined that resection was possible on the basis of positron-emission tomography and computed tomography. The primary end points were progression-free survival and overall survival. Complete resection was achieved in 77% of patients. The results of progression-free survival, which were reported recently, showed a significant benefit of adding cytoreductive surgery to chemotherapy.[25] As in our trial, the effect was limited to patients in whom a macroscopic complete resection was achieved. Mature data regarding overall survival in this trial are awaited.

Do we have any explanation for the inconsistent results of the DESKTOP III and SOC-1 trials on the one hand and the GOG-0213 trial on the other hand? One observed difference among the trials was that 84% of the patients in the GOG-0213 trial received bevacizumab, whereas 23% in the DESKTOP III trial and 1% in the SOC-1 trial received bevacizumab. Could the activity of bevacizumab have modified the effect of surgery? This question should be discussed cautiously, since DESKTOP III is a pure surgical trial and GOG-0213 used a mixture of chemotherapy and surgery. In the subgroup of patients in the GOG-0213 trial who did not receive maintenance treatment with bevacizumab, the median overall survival was 32.4 months among patients who underwent surgery and 67.0 months among those who did not undergo surgery, suggesting a detrimental effect of performing surgery before chemotherapy is administered.[22] However, this post

hoc observation is based on the results in only a small subgroup that was not prospectively defined. Furthermore, this finding contradicts other clinical studies about the effect of successful surgery when added to chemotherapy in ovarian cancer.[26,27] Although the subgroup of patients who did not receive bevacizumab in the DESKTOP III trial (77% of the trial population) was larger than that in the GOG-0213 trial, our data indicated that there was a benefit in these patients that was similar to that in the analysis of the primary end point in the intention-to-treat population. However, such an analysis in a trial that is not conducted in a blinded manner and not placebo-controlled has substantial bias. Subsequent therapy was not standardized, and the choice of therapy might have been influenced by randomization outcome, residual disease after surgery for relapse, postoperative complications, the patients' wishes, or the preferences of the investigators. Therefore, it is not adequate to conclude that subsequent systemic therapy could compensate for incomplete surgery or no surgery for relapsed disease or that systemic therapy could make successful surgery unnecessary.

Another relevant difference between the DESKTOP III and SOC-1 trials and the GOG-0213 trial is the process of selecting patients and centers. The strict selection process in the current trial was intended to identify a subgroup of patients in whom surgical resection would most likely be successful. Finally, another potential factor is the different selection of centers in the three trials. It is not easy to quantify these factors. A meta-analysis of the DESKTOP III and GOG-0213 trials to better understand the differences is under way.

The results of the current trial showed a benefit of surgery with respect to progression-free and overall survival, with an acceptable incidence of complications and without a detrimental effect on quality of life in patients selected for inclusion on the basis of the AGO score. All patients with a first relapse after a platinum-free interval of at least 6 months may be evaluated to assess whether surgery is an option, and the AGO score may be incorporated into this process. Eligible patients could receive counseling about the options for cytoreductive surgery in centers of gynecologic oncology that have experience in surgery for relapsed ovarian cancer. In contrast, patients who have a high probability of incomplete resection on the basis of disease or clinical characteristics should not be exposed to a potentially harmful surgical treatment.

The results of this trial cannot be extrapolated to interval debulking after chemotherapy or to the treatment of relapse after later lines of treatment. These scenarios deserve further study that should also focus on the potential interaction of surgery with new drugs such as PARP inhibitors or further targeted therapies.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). Ann Oncol 2005;16:Suppl 8:viii7-viii12.
2. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83.
3. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.
4. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-505.
5. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-402.
6. 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;381:2403-15.
7. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416-28.
8. Parmar MKB, 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;361:2099-106.
9. Pfisterer J, Shannon CM, Baumann K, et al. Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial. Lancet Oncol 2020;21:699-709.
10. 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;18:779-91.
11. Poveda A, Floquet A, Ledermann JA, 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. abstract (https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.6002).
12. Harter P, du Bois A. The role of surgery in ovarian cancer with special emphasis on cytoreductive surgery for recurrence. Curr Opin Oncol 2005;17:505-14.
13. Harter P, du Bois A, Hahmann M, et al. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol 2006;13:1702-10.
14. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115:1234-44.
15. Harter P, Sehouli J, Reuss A, 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.
16. Rosenberger WF, Lachin JM. Randomization in clinical trials: theory and practice. New York: John Wiley, 2002.
17. du Bois A, Reuss A, Pujade-Lauraine E, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and industry partners — first update 2015. Int J Gynecol Cancer 2015;25:1328-30.
18. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26. DOI: 10.2307/2337123.
19. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
20. Harter P, Sehouli J, Lorusso D, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med 2019;380:822-32.
21. du Bois A, Kristensen G, Ray-Coquard I, et al. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2016;17:78-89.
22. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. Lancet 2019;394:2084-95.
23. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014;15:396-405.
24. Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med 2019;381:1929-39.
25. Shi T, Zhu J, Feng Y, et al. Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:439-49.
26. Hall M, Savvatis K, Nixon K, et al. Maximal-effort cytoreductive surgery for ovarian cancer patients with a high tumor burden: variations in practice and impact on outcome. Ann Surg Oncol 2019;26:2943-51.
27. Klein DA, Mann AK, Freeman AH, Liao C-I, Kapp DS, Chan JK. Chemotherapy alone for patients 75 years and older with epithelial ovarian cancer — is interval cytoreductive surgery still needed? Am J Obstet Gynecol 2020;222(2):170.e1-170.e11.