

Surgery in Recurrent Ovarian Cancer

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Ovarian cancer is one of the most challenging diseases in gynecologic oncology. The presentation of frequent recurrences requires the establishment and further development of therapy standards for this patient group. Surgery is crucial in the therapy of patients with primary ovarian cancer, and the postoperative residual tumor mass is the most relevant clinical prognostic factor. The surgical management of recurrent disease is still subject to an emotional international discussion. Only a few prospective clinical trials focused on the effects of surgery in relapsed ovarian cancer have been published. The available data show improvements in the prognosis due to complete cytoreduction in the setting of recurrence. However, the selection of eligible patients is the essential issue. Therefore, the establishment of reliable predictive factors for complete tumor resection as well as a definition of the group of patients who might profit from this approach remains a field for research. Further randomized trials designed to develop and incorporate operative standards for recurrent ovarian cancer should follow. *Cancer* 2019;125:4598-4601. © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

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INTRODUCTION

Ovarian cancer is one of the most challenging diseases in gynecologic oncology because of the late-stage presentation at the time of primary diagnosis. Surgery and platinum-based chemotherapy are the cornerstones of multimodal treatment in the primary disease setting. The postoperative residual tumor mass is the most relevant clinical factor. Therefore, all activities that assess the quality of surgery should be supported. In this context, several societies, including the European Society of Gynaecological Oncology, have defined quality criteria for surgery. In our presentation, we discussed the need for and importance of surgical quality because overall survival (OS) depends on the quality of surgery and medical interventions. Despite the indisputable role of surgery in the primary disease setting, the surgical management of recurrent disease has remained subject to an emotional international discussion.¹⁻⁵

In principle, the different goals of surgery in relapsed ovarian cancer have to be defined as a prerequisite for a structured dialogue. In this context, palliative surgery with the goal of symptom control (eg, in the case of bowel obstruction) and cytoreductive surgery with the aim of prolonging progression-free survival (PFS) and OS should be distinguished.

Several studies have demonstrated the feasibility and the good clinical outcomes of patients who have undergone surgery with the aim of maximal cytoreduction.¹ Most of these studies have been retrospective and performed at a single center.

Furthermore, selection criteria for patients eligible for surgery are essential, but there are different definitions in the various publications.⁴ Only a few prospective studies have addressed the effect of surgery in relapsed ovarian cancer. Most of them are retrospective and have reported that complete cytoreduction is associated with a better prognosis. Implementing predictive factors for complete tumor resection and defining the group of patients with recurrent disease who might profit from this approach are crucial.

An evaluation of surgery in patients with recurrent ovarian cancer was performed within a multicenter, retrospective study entitled the Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP) by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO).⁶ In this analysis of a total of 267 patients, a subgroup of women who mostly benefitted from secondary cytoreduction was identified. Patients who underwent complete cytoreduction presented with significantly better PFS and OS (median OS, 45.2 months vs 19.7 months for patients with residuals >10 mm; $P < .0001$). In a multivariate analysis, more than 500 mL of ascites in the setting of recurrence and complete primary cytoreduction were found to be independent prognostic factors. The combination of

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these 2 factors with a good performance status constitutes the so-called AGO score. Score-positive patients are those who fulfill all 3 criteria; therefore, a positive score most likely helps to predict complete resection in recurrent ovarian cancer. The subsequent prospective DESKTOP II study validated this AGO score in 516 patients, of whom 51% were classified as AGO score-positive.⁷ The rate of complete macroscopic cytoreduction was 76%, and the mortality rate for surgery was 0.8%.⁷

According to the results of the DESKTOP III study presented at the 2017 annual meeting of the American Society of Clinical Oncology, surgery resulting in complete resection was beneficial for platinum-sensitive patients with their first recurrence and a positive AGO score.⁸ In that study, 407 patients with platinum-sensitive relapsed ovarian cancer were randomly allocated to be treated with chemotherapy alone or surgery plus chemotherapy. The median PFS was 14 months in the chemotherapy-alone arm and 19.6 months in the surgery plus chemotherapy cohort (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.52-0.83; $P < .001$). The median time until the first subsequent therapy was 21 months versus 13.9 months in favor of the surgery arm (HR, 0.61; 95% CI, 0.48-0.77; $P < .001$). Also, the PFS-2 results were favorable in the surgical arm. The 60-day mortality rates were 0% and 0.5% in the surgery arm and the chemotherapy-alone arm, respectively. The rate of relaparotomy was 3.5%.

Recent monocentric analyses have demonstrated that, despite a negative AGO score, patients can still achieve a complete resection with a good clinical outcome when they are treated at an experienced gynecologic center.

In a publication by Muallem et al,⁹ the AGO score was evaluated for 209 patients who underwent secondary surgery in a single-center, retrospective analysis. Seventy of those women had at least 1 negative criterion; 127 women in the AGO score-positive group received complete cytoreduction. Interestingly, 48.5% of the patients with 1 negative criterion also underwent surgery with no residual disease. The PFS was 22 months for the AGO score-positive patients who were tumor-free and 21 months for the AGO-negative patients with complete resection. Morbidity and mortality were also comparable. This study confirmed the validation trials and revealed a chance for eligibility for select score-negative patients.

Nevertheless, it must be underlined that the AGO score is validated only for a positive enhancement of the patient cohort with optimal surgical outcomes. A negative AGO score (eg, ascites >500 mL) does not exclude the chance of surgery without any postoperative residuals.

Harter et al¹⁰ published data on 217 consecutive patients: 112 were AGO score-positive, and 105 were negative. Complete resection was achieved in 89.3% and 66.7% of the patients, respectively. Patients with complete resection and a positive AGO score showed a median OS of 63.9 months (95% CI, 48.1-79.6 months), whereas the median OS was 48.4 months (95% CI, 30.3-66.5 months) after complete resection and a negative score (log-rank $P = .10$). However, in a multivariate analysis, the only independent prognostic factor was complete resection (HR, 2.450; 95% CI, 1.542-3.891). The AGO score could identify suitable candidates for secondary cytoreductive surgery. However, an independent prognostic value for OS has failed to be proven. Further prospective studies should evaluate the predictive and prognostic impact of the AGO score.

At the 2018 meeting of the American Society of Clinical Oncology, the Gynecologic Oncology Group presented the negative results of its randomized phase 3 trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC) with or without bevacizumab in platinum-sensitive recurrent ovarian cancer with a focus on the role of SSC.¹¹ In this trial, 240 women received SSC plus PBC, and 245 received PBC alone. However, contrary to the DESKTOP data, no use was made of a structured score in patient selection. The HR for death (SSC vs none) was 1.28 (95% CI, 0.92-1.79), which corresponded to median OS times of 53.6 and 65.7 months, respectively. The median PFS was 18.2 months in the surgery arm and 16.5 months in the control arm (HR, 0.88; 95% CI, 0.70-1.11). No new safety signals were observed. Critical points in the interpretation of this study were the very long recruitment period, the high east Asian population percentage, and the fact that 84% of the patients received bevacizumab in addition.¹¹ Therefore, the final evaluation of secondary surgery most likely will be possible only after an OS analysis of the DESKTOP data is available.

Another option is palliative surgery, which leads to relief of the symptoms and enables further systemic treatment. The vast majority of reported studies had a high risk of bias. Selection bias was the main problem because treatment allocation depended on clinician/patient preference, with patients who were managed with surgery tending to be in better overall health. In addition, the heterogeneity of outcomes severely limited the conclusions that could be drawn.¹² Nevertheless, a palliative operation followed by chemotherapy should be discussed with patients as a valuable option.

The quality criteria of the European Society of Gynaecological Oncology have been recently finalized and are recommended for incorporation into institutional or governmental quality-assurance programs in European countries.⁴ Furthermore, they could serve as a basis for certification processes of gynecologic oncology centers. The quality indicators were identified according to scientific evidence and/or expert consensus. A 4-step evaluation process revealed 10 structural, process, or outcome indicators crucial for quality assurance at gynecologic oncology centers. Perioperative management, minimal requirements for surgical and pathology reports, and postoperative complication reporting were described as quality indicators. Among these, the rate of complete surgical resection, the number of surgical procedures performed annually, clinical trial participation, and others were listed. The quality indicators and the corresponding targets provide a quantitative basis for improving care in the surgical management of advanced ovarian cancer.

TERTIARY SURGERY

Complete tumor resection has been identified as the most relevant prognostic factor for improved survival in patients with ovarian cancer. As a result, radicality through a multivisceral approach has increased within the last decades.¹³⁻¹⁶ Although there are data available regarding complete resection in secondary surgery, its prognostic significance in the tertiary setting remains unclear.¹⁷⁻²¹ The data regarding tertiary cytoreductive surgery are limited and are based mainly on single-center, low-cohort experiences.²²⁻²⁷

A series of 135 consecutive patients who underwent tertiary surgery for relapsed ovarian cancer was published in 2011.²⁷ Complete tumor resection was achieved in 53 patients (39.3%). The 30-day operative mortality rate was 6%. Seventy-eight patients (57.8%) died, whereas 52 patients (38.5%) suffered from further relapse within the median follow-up period of 9.6 months (range, 0.1-75 months). The median OS was 19.1 months: 37.8 months for patients without any residual tumor mass, 19.0 months for patients with residual tumors smaller than 1 cm, and 6.9 months for patients with residual tumors larger than 1 cm. Complete tumor resection was identified as the main predictor of survival in this setting. Moreover, tumor involvement of the middle abdomen and peritoneal carcinomatosis were identified as independent predictors of complete tumor resection in the multivariate analysis. Ascites and peritoneal

carcinomatosis, in association with potential resectability, should be investigated in future multicenter, prospective trials.

The high impact of residual tumor on OS and PFS in the tertiary setting of ovarian cancer was reported by Fotopoulou et al.²⁸ High complete resection rates are obtainable at specialized gynecologic oncology centers. Characteristics such as stage, age, and histology, which have been shown to be of significant predictive value in the primary disease setting, do not appear to be of any prognostic significance in the tertiary setting. However, a prospective clinical trial should be performed to confirm definitively the value of tertiary cytoreductive surgery for patients with recurrent ovarian cancer.

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