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Tertiary cytoreductive surgery in recurrent epithelial ovarian cancer: A multicentre MITO retrospective study

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HIGHLIGHTS

- Complete cytoreduction is the primary objective of TCS in recurrent ovarian cancer.
- Accurate patient selection is of utmost importance.
- TCS could be offered to selected patients with good clinical conditions.

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ABSTRACT

Objectives. To evaluate the impact of tertiary cytoreductive surgery (TCS) on survival in recurrent epithelial ovarian cancer (EOC), and to determine predictors of complete cytoreduction.

Methods. A multi-institutional retrospective study was conducted within the MITO Group on a 5-year observation period.

Results. A total of 103 EOC patients with a ≥6 month treatment-free interval (TFI) undergoing TCS were included. Complete cytoreduction was achieved in 71 patients (68.9%), with severe post-operative complications in 9.7%, and no cases of mortality within 60 days from surgery. Multivariate analysis identified the complete tertiary cytoreduction as the most potent predictor of survival followed by FIGO stage I–II at initial diagnosis, exclusive retroperitoneal recurrence, and TCS performed ≥3 years after primary diagnosis. Patients with complete tertiary cytoreduction had a significantly longer overall survival (median OS: 43 months, 95% CI 31–58) compared to those with residual tumor (median OS: 33 months, 95% CI 28–46; $p < 0.001$). After multivariate adjustment the presence of a single lesion and good (ECOG 0) performance status were the only significant predictors of complete surgical cytoreduction.

Conclusions. This is the only large multicentre study published so far on TCS in EOC with ≥6 month TFI. The achievement of postoperative no residual disease is confirmed as the primary objective also in a TCS setting, with significant survival benefit and acceptable morbidity. Accurate patient selection is of utmost importance to have the best chance of complete cytoreduction.

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1. Introduction

Cytoreductive surgery is the cornerstone of the multimodal therapy in newly diagnosed advanced epithelial ovarian cancer (EOC), and all attempts should be made during primary surgery to achieve complete cytoreduction, as the amount of residual tumor is one of the most important prognostic factors for survival of advanced EOC patients [1].

During the last decade, the role of surgery in recurrent EOC has increasingly been investigated. In fact, the achievement of a complete cytoreduction seems to be of utmost importance also in this setting [2]. The role of secondary/tertiary cytoreductive surgery, however, has not been yet clearly defined. In particular, data on tertiary cytoreductive surgery (TCS), owing to the difficulty of collecting large retrospective series, are even more limited than those in the secondary setting [3–10].

Thus, whether the complete cytoreduction is the primary objective of TCS must be still confirmed, and the factors predicting no postoperative residual tumor identified. Given the high technical difficulty associated with repetitive surgery, accurate patient selection seems, in fact, to be mandatory in order to maximize the likelihood of a complete cytoreduction and minimize the complications potentially derivable from complex surgical procedures. For these purposes, the Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO) endorsed a project among its surgical membership with the aim to retrospectively evaluate EOC patients undergoing TCS.

2. Materials and methods

The present study was designed as a multi-institutional retrospective analysis conducted among MITO affiliate centres. Eleven high-volume gynecologic oncology referral centres enrolled consecutive EOC (including tubal and peritoneal epithelial cancers) patients who underwent TCS for recurrent disease between January 2008 and December 2012.

The primary endpoints for this study were to evaluate the impact of TCS on the overall survival and to determine predictors of complete surgical cytoreduction. The secondary endpoint was to assess the value of a potential score predicting a complete cytoreduction. In particular, the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score derived from DESKTOP I–II [11,12] trials has been evaluated. The "AGO score" was deemed positive if a patient had (i) a good performance status (ECOG 0), (ii) no residual tumor after secondary cytoreductive surgery, and (iii) a clinical diagnosis of <500 mL ascites.

The Institutional Review Boards (IRB) of participating centres approved this study, except for those where analyses of existing data were exempt from formal IRB approval, in the absence of any identifiers linking individuals to the data; all patients included in the present analysis gave written consent to data collection and to the use of personal records for health research.

Data were systematically abstracted from medical records, surgery notes were reviewed, and documented according to a standardized database. In particular, data were collected on: patient- (age; performance status according to Eastern Cooperative Oncology Group (ECOG) and American Society of Anesthesiologists (ASA) score at TCS); disease- (origin; histotype and grade; FIGO Stage at initial diagnosis; preoperative CA125 serum level, presence of ascites and tumor dissemination pattern at TCS), and treatment-related characteristics (completeness of primary/secondary/tertiary cytoreduction; postoperative systemic therapies; intra/post-TCS complications/deaths). All data were checked for plausibility and completeness by two authors (SG, FF).

The following patients were considered non-eligible for study inclusion: (i) aged >75 years; (ii) performance status according to ECOG >1; (iii) serological recurrence only (CA 125 serum levels >35 UI/mL); (iv) non-epithelial or borderline tumors; (v) treatment-free interval (TFI) <-6 months after completion of first −/second −/third-line therapy; (vi) patients operated on for strictly palliative purposes; (vii) patients with second malignancies who had been treated by laparotomy or who had a therapy that could interfere with the treatment of relapsed ovarian cancer.

Completeness of surgical cytoreduction was categorized as proposed by Sugarbaker [13]: no visible residual tumor (CC = 0), residual nodules ≤0.25 cm (CC = 1), between 0.26 and 2.5 cm (CC = 2), and >2.5 cm (CC = 3). The site and number of lesions were evaluated clinically (general and gynecologic examinations, CT scan, and PET scan if indicated). Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) were registered as distant metastases. Post-TCS complications were considered within 30 days from hospital discharge, and graded according to the Clavien-Dindo classification [14]. TFI was calculated from the end of one regimen and the start of the next one. Overall survival (OS) was calculated from the date of surgery to either the date of death or the last follow-up. Patient follow-up data were gathered until the end of 2016.

Statistical analysis was performed with SPSS statistical software version 21.0. Categorical and continuous variables were reported as frequency and percentage and as median and range, respectively. The relative importance of variables as independent predictors of OS was analysed with the multivariate Cox proportional hazard regression: to correct for possible confounders, all parameters found to have a $p < 0.10$ at univariate analysis were included into the multivariable Cox regression model; adjusted hazard ratios (HR) and 95% CI for prognostic factors were estimated. Crude and adjusted odds ratios (OR) with corresponding 95% CI for complete tumor resection were obtained using logistic regression analysis. Survival rates were estimated by the Kaplan–Meier method. The log-rank test was used to compare survival curves. Patients known to be still alive or lost to follow-up at the time of analysis were censored at their last follow-up. All p-values were two-sided, and statistical significance was set at $p < 0.05$.

3. Results

A total of 103 recurrent EOC patients, undergoing TCS within the 5-year observation period, were included in the present analysis. Patient, tumor- and treatment-related characteristics before and at the time of TCS are detailed in Tables 1 and 2. Median follow-up times from TCS and from onset of the disease were respectively 39.5 months (range 1–138) and 99 months (range 28–294). Eighty-one percent of patients had advanced disease (FIGO stage III or IV) at initial diagnosis. Complete cytoreduction (CC = 0) was achieved in 65% and 80.6% of the patients after primary and secondary surgery, respectively. Almost all patients had received platinum-based first-line chemotherapy (92.7%). Five patients (4.8%) underwent TCS before completion of the 2nd year after primary diagnosis, 13 (12.6%) between the 2nd and 3rd year, and 85 patients (82.5%) later than 3 years after primary diagnosis.

CA125 levels were preoperatively normal in 41.7% of patients undergoing TCS, ranging from 35 and 500 U/mL in 50.5%, and >500 U/mL in 7.8%. Only two patients presented ascites >500 mL at the time of tertiary surgery.

At TCS, the majority of patients (86; 83.5%) presented with only abdominal tumor involvement, 9 (8.7%) with isolated distant metastases, and the remaining 8 (7.8%) with both abdominal and distant recurrences. Details regarding sites of recurrence, abdominal tumor involvement and lesion number are presented in Table 2. Complete (CC = 0) tertiary cytoreduction was achieved in 71 patients (68.9%), with a further 13 patients (12.6%) showing ≤0.25 cm residual tumor (CC = 1). Surgical procedures/organ resections performed are detailed in Table 3. Post-operative severe (grade 3, 4) complications occurred in 9.7%, with no cases of mortality within 60 days from surgery. In particular, 9 patients (8.7%) experienced complications requiring reoperation for the following reasons: intestinal perforation (2), post-operative bleeding (2), subglissonian hematoma (1), subphrenic abscess (1),

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