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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),

**Table 1**
Clinico-pathologic characteristics before tertiary cytoreduction.

| Variable | |
|---|---|
| Age, median [range], years | 55 [20–71] |
| Origin of disease, n (%) | |
| – Ovary | 98 (95.1) |
| – Fallopian tube | 1 (1.0) |
| – Peritoneum | 4 (3.9) |
| FIGO stage at initial diagnosis, n (%) | |
| – I | 12 (11.7) |
| – II | 2 (1.9) |
| – III | 80 (77.7) |
| – IV | 3 (2.9) |
| – Missing | 6 (5.8) |
| Tumor grade, n (%) | |
| – 1 | 3 (2.9) |
| – 2 | 8 (7.8) |
| – 3 | 86 (83.5) |
| – Missing | 6 (5.8) |
| Histology, n (%) | |
| – Adenoca, NOS | 2 (1.9) |
| – Clear cell | 3 (2.9) |
| – Endometrioid | 4 (3.9) |
| – Mixed | 2 (1.9) |
| – Mucinous | 4 (3.9) |
| – Serous | 83 (80.6) |
| – Undifferentiated | 4 (3.9) |
| – Missing | 1 (1.0) |
| Completeness of primary cytoreduction, n (%) | |
| – 0 (no visible residual tumor) | 67 (65.0) |
| – 1 (residual nodules ≤0.25 cm) | 12 (11.7) |
| – 2 (residual nodules >0.25 cm and ≤2.5 cm) | 11 (10.7) |
| – 3 (residual nodules >2.5 cm) | 6 (5.8) |
| – Missing | 7 (6.8) |
| Completeness of secondary cytoreduction, n (%) | |
| – 0 (no visible residual tumor) | 83 (80.6) |
| – 1 (residual nodules ≤0.25 cm) | 9 (8.7) |
| – 2 (residual nodules >0.25 cm and ≤2.5 cm) | 7 (6.8) |
| – 3 (residual nodules >2.5 cm) | 3 (2.9) |
| – Missing | 1 (1.0) |
| Time from the end of initial treatment to first relapse (months), median [range] | 21.5 [6–115] |

FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified.

**Table 2**
Clinico-pathologic characteristics at the time of tertiary cytoreduction.

| Variable | |
|---|---|
| Age, median [range], years | 60 [23–75] |
| Years after primary diagnosis, n (%) | |
| – <2 | 5 (4.8) |
| – ≥2 and <3 | 13 (12.6) |
| – ≥3 | 85 (82.5) |
| Last TFI, n (%) | |
| 6–12 months | 65 (63.1) |
| ≥12 months | 38 (36.9) |
| ECOG performance status, n (%) | |
| – 0 | 76 (73.8) |
| – 1 | 27 (26.2) |
| ASA, n (%) | |
| – 1–2 | 90 (87.4) |
| – 3–4 | 13 (12.6) |
| CA 125 (U/mL) serum levels, n (%) | |
| – <35 | 43 (41.7) |
| – 35–500 | 52 (50.5) |
| – >500 | 8 (7.8) |
| Intraoperative ascites, n (%) | |
| – ≤500 mL | 101 (98) |
| – >500 mL | 2 (2) |
| Sites of recurrence, n (%) | |
| – Abdominal | 86 (83.5) |
| – Distant | 9 (8.7) |
| – Both | 8 (7.8) |
| Abdominal tumor involvement, n (%) | |
| – Intraperitoneal | 55 (58.5) |
| – Retroperitoneal | 21 (22.3) |
| – Both | 18 (19.1) |
| Lesion number, n (%) | |
| – Single | 45 (43.7) |
| – Multiple | 58 (56.3) |
| Size (mm) of largest recurrence, median [range] | 25 [5–120] |
| Completeness of tertiary cytoreduction, n (%) | |
| – 0 (no visible residual tumor) | 71 (68.9) |
| – 1 (residual nodules ≤0.25 cm) | 13 (12.6) |
| – 2 (residual nodules >0.25 cm and ≤2.5 cm) | 4 (3.9) |
| – 3 (residual nodules >2.5 cm) | 15 (14.6) |
| Post-operative complications, n (%) | |
| – G 1–2 | 3 (2.9) |
| – G 3–4 | 10 (9.7) |
| – G 5 | 0 (0) |
| Adjuvant therapy after tertiary cytoreduction, n (%) | |
| – Platinum-based | 54 (52.4) |
| – Non platinum based | 36 (34.9) |
| Follow-up (months) after TCS, median [range] | 39.5 [1–138] |
| Status at last follow-up, n (%) | |
| – NED | 26 (25.2) |
| – AWD | 25 (24.3) |
| – DOD | 40 (38.8) |
| – DID | 5 (4.9) |
| – Missing | 7 (6.8) |

ASA: American Society of Anesthesiologists; AWD: alive with disease; DID: dead of intercurrent disease; DOD: dead of disease; ECOG: Eastern Cooperative Oncology Group; G: grade; NED: no evidence of disease; TCS: tertiary cytoreductive surgery; TFI: treatment-free interval.

extrahepatic biliary obstruction (1), anastomotic leakage (1), and surgical wound dehiscence (1).

A total of 90 patients (87.3%) have been documented as having received a third-line chemotherapy. In particular, post-TCS treatment with platinum-based chemotherapy was given to 60% of the patients, whereas 40% received other chemotherapy regimens.

At the end of the observation period, 26 patients (27.1%) showed no evidence of disease, 25 (26%) experienced disease progression/further relapse, and 45 patients (46.9%) died.

### 3.1. Predictors of survival and complete tumor resection

Median OS of the entire patient cohort was 39.5 months (95% CI, 31–46.5). Multivariate analysis identified the complete (CC = 0) 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 (Table 4). Kaplan–Meier curves according to significant prognostic factors for survival are presented in Fig. 1. In particular, patients with complete tertiary cytoreduction had a significantly longer survival (median OS: 43 months, 95% CI 31–58) compared to those with any residual tumor (median OS: 33 months, 95% CI 28–46; $p < 0.001$).

Analysis of factors predicting complete surgical cytoreduction is detailed in Table 5. After multivariable adjustment for possible confounders, the presence of a single lesion and a good performance status (ECOG 0) resulted as the only independent predictors of complete surgical cytoreduction (CC = 0). Patients showing both these favourable markers (37, 35.9%) had 94.6% chance of complete cytoreduction (negative predictive value, 45.5%). In particular, the presence of a single lesion was still confirmed as the most significant variable of complete surgical cytoreduction in the subgroup of patients with only abdominal tumor involvement (OR: 12.4, 95% CI 3–50.3, $p < 0.001$), regardless of the intra/retroperitoneal component (intraperitoneal + retroperitoneal, $p < 0.001$; intraperitoneal only, $p = 0.008$; retroperitoneal only, $p = 0.01$).

The backward analysis identified 66 patients with a positive AGO score, 50 of whom had a complete (CC = 0) tertiary cytoreduction (positive predictive value, 75.8%). A total of 37 patients were score negative, of whom 12 fulfilled two of three criteria and 25 fulfilled only one criterion. Among 37 patients with a negative score, however, complete cytoreduction was achieved in 21 (negative predictive value, 43.2%).

**Table 3**
Surgical procedures/organ resections performed at the time of tertiary cytoreduction.

| Surgical procedures/organ resections[a] | N (%) |
|---|---|
| Retroperitoneal lymph node dissection | 39 (37.8) |
| Large bowel resection | 30 (29.1) |
| Peritonectomy | 25 (24.2) |
| Small bowel resection | 15 (14.5) |
| Excision of abdominal-pelvic masses | 12 (11.6) |
| Diaphragmatic resection | 9 (8.7) |
| Splenectomy | 8 (7.7) |
| Colostomy | 6 (5.8) |
| Inguinal lymph node dissection | 5 (4.8) |
| Ileostomy | 4 (3.8) |
| Colpectomy | 3 (2.9) |
| Abdominal anterior wall excision | 2 (1.9) |
| Bladder partial resection | 2 (1.9) |
| Cholecystectomy | 2 (1.9) |
| Hepatic resection | 2 (1.9) |
| Pancreatic tail resection | 2 (1.9) |
| Axillary lymph node dissection | 1 (0.9) |
| Partial gastrectomy | 1 (0.9) |
| Pulmonary lobectomy | 1 (0.9) |
| Resection of brain metastases | 1 (0.9) |

[a] More than one procedure could be performed in the same patient.

**Table 4**
Cox regression analysis of factors predicting mortality.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR [95% CI] | *p*-Value | HR [95% CI] | *p*-Value |
| Age, years | | | | |
| <60 | Reference | 0.01 | Reference | 0.5 |
| ≥60 | 2.2 [1.1–4.2] | | 0.7 [0.2–1.8] | |
| ECOG performance status | | | | |
| 0 | Reference | 0.82 | | |
| 1 | 1 [0.4–2.4] | | | |
| ASA | | | | |
| 1–2 | Reference | 0.5 | | |
| 3–4 | 0.6 [0.1–2.2] | | | |
| FIGO stage at initial diagnosis | | | | |
| I–II | Reference | 0.001 | Reference | 0.01 |
| III–IV | 12.2 [2.8–53.2] | | 4.5 [1.3–15.6] | |
| Tumor grade | | | | |
| 1–2 | Reference | 0.03 | Reference | 0.45 |
| 3 | 2.7 [1–7.1] | | 1.8 [0.3–8.6] | |
| Histological subtype | | | | |
| Serous | Reference | 0.92 | | |
| Others | 0.9 [0.4–2.1] | | | |
| Years after primary diagnosis | | | | |
| ≥3 years | Reference | <0.001 | Reference | 0.04 |
| <3 years | 13.9 [4.6–41.7] | | 3.5 [1–12.8] | |
| Presence of distant metastases | | | | |
| No | Reference | 0.004 | Reference | 0.09 |
| Yes | 4.3 [1.5–11.8] | | 2.8 [0.8–9.6] | |
| Abdominal tumor involvement | | | | |
| Retroperitoneal | Reference | 0.01 | Reference | 0.04 |
| Intraperitoneal ± retroperitoneal | 10.2 [2.5–40.9] | | 3.9 [1.1–15.2] | |
| Lesion number | | | | |
| Single | Reference | 0.01 | Reference | 0.31 |
| Multiple | 2.3 [1.1–4.6] | | 1.6 [0.6–4.1] | |
| Size of largest recurrence | | | | |
| <25 mm | Reference | 0.02 | Reference | 0.15 |
| ≥25 mm | 2.6 [1.1–6.1] | | 2.2 [0.7–6.7] | |
| Ascites | | | | |
| ≤500 mL | Reference | 0.14 | | |
| >500 mL | 0.4 [0.1–1.3] | | | |
| Tumor residuals at primary surgery | | | | |
| No | Reference | 0.14 | | |
| Yes | 0.5 [0.2–1.2] | | | |
| Tumor residuals at secondary surgery | | | | |
| No | Reference | 0.87 | | |
| Yes | 1 [0.4–2.6] | | | |
| Tumor residuals at tertiary surgery | | | | |
| No | Reference | <0.001 | Reference | <0.001 |
| Yes | 4.8 [2.4–9.4] | | 6.7 [2.3–18.8] | |
| Adjuvant therapy after tertiary cytoreduction | | | | |
| Platinum-based | Reference | 0.35 | | |
| Non platinum based | 0.7 [0.3–1.4] | | | |

ASA: American Society of Anesthesiologists; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio.

## 4. Discussion

Even though the role of repetitive surgery has increasingly been investigated during the last decade, there is still a considerable debate on the therapeutic value of secondary/tertiary cytoreduction in the management of recurrent EOC. In particular, need for accuracy and standardization in patient selection for TCS is acknowledged as an unmet goal. Whether the achievement of no postoperative residual tumor is the primary objective of TCS has not yet proven, and the factors predicting complete cytoreduction are still to be identified.

The present analysis, conducted within a gynecologic oncology national cooperative group, underlines the importance of the postoperative residual tumor in determining the survival outcome even in a tertiary elective surgery setting, and has relevant implications in terms of patient selection and their referral to high-volume centres. Our study shows that patients with complete tertiary cytoreduction had a significantly longer survival compared to those with any residual tumor (median OS: 43 months vs. 33 months, $p < 0.001$). After multivariate adjustment, the achievement of postoperative no residual disease was the most potent predictor of survival with an HR of 6.7 [95% CI, 2.3–18.8]. Moreover, a good performance status (ECOG = 0) at the time of TCS and the presence of a single lesion were the only independent predictors of complete surgical cytoreduction.

Berek et al. first introduced the concept of repetitive cytoreduction, suggesting in recurrent setting as well as in primary surgery, an inverse relationship between residual tumor diameter and survival [15]. This initial observation has been confirmed by subsequent single retrospective studies [3,6,11,16,17], and meta-analysis [2]. In particular, wide survival estimates have been reported after TCS, with medians ranging from 24 to 60.4 months and from 6 to 27.9 months for CC = 0 and CC ≥1, respectively [3,4,6–10]. These wide ranges do suggest a considerable heterogeneity in terms of patient selection. It is to note that most studies evaluating TCS in EOC also included patients who were operated on for palliative purposes [6] and/or recurring with a <6 month TFI [3,6–10]. The only large further multicentre retrospective study on TCS was that published by Fotopoulou et al. [3], and also in this study, 61.8% patients had recurred after a TFI <6 months. As a consequence, the increasing interval to second relapse resulted as the most significant predictor of survival ($p < 0.001$), only followed by the absence of tumor residual at TCS ($p = 0.001$), and platinum at third line chemotherapy ($p = 0.001$) [3].

In our study, only patients with a ≥6 month TFI after completion of first−/second−/third-line therapy were included, and no cases were operated on with palliative intent. Such inclusion criteria defined a selected group of patients undergoing elective TCS and explain why, in our series, patients with CC ≥1 after TCS showed a better survival than that previously reported [3,4,6–10]. Well predefined data

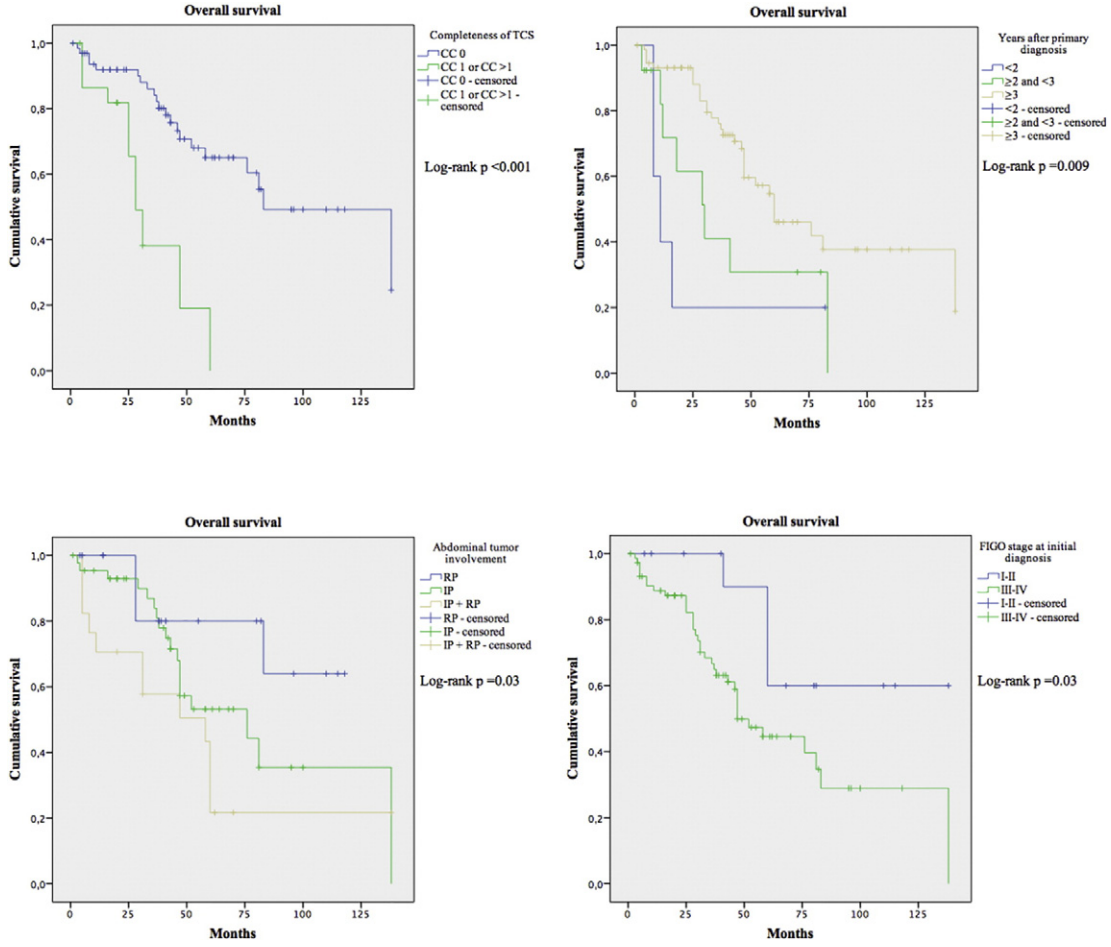


**Fig. 1.** Kaplan–Meier curves according to significant prognostic factors for survival (see Table 4).

collection could have minimized confounders and strengthened associations found in post hoc analysis of data. Complete (CC = 0) cytoreduction resulted the most potent predictor of survival at multivariate analysis, followed by early (I–II) FIGO Stage at initial diagnosis, exclusive retroperitoneal recurrence, and TCS performed over 3 years from primary surgery. These data indicate that completeness of surgical cytoreduction and disease characteristics both have a role in determining the survival outcome also in a tertiary setting. It is reasonable to think that this could be even more actual in the framework of a long surviving population. About 80% of our patients had, in fact, a ≥3 year interval from initial diagnosis, 44% had a single lesion, 27% of which exclusive retroperitoneal. If it can be argued on the impact of TCS per se in patients with such favourable characteristics, our analysis demonstrates a 10 month survival benefit in those with complete cytoreduction compared to those with any residual tumor ($p < 0.001$). Moreover, the value of repetitive surgical efforts in selected EOC is further supported by the DESKTOP III trial results very recently presented. This study prospectively investigated the value of secondary surgical cytoreduction in AGO score-positive recurrent EOC comparing surgery followed by chemotherapy with chemotherapy alone in a randomized setting. Although waiting for more mature data to assess the impact on overall survival, this study showed a significant progression-free survival increase of 5.6 months ($p < 0.001$) for the surgical arm, and of 7.2 months ($p < 0.0001$) for patients achieving complete cytoreduction [18].

Overall, the chance of obtaining a complete surgical cytoreduction depends on patient characteristics but also on tumor spread and quality of surgery [19]. In spite of the considerable efforts made to design models able to reliably predict surgical cytoreductive outcome, such predictability remains an area of controversy and clinical ambiguity. In our study, multivariate analysis showed a good performance status (ECOG = 0) and the presence of a single lesion as the only independent predictors of complete surgical cytoreduction. The association of these two factors was present in about one third of patients (36%), and was able to predict complete cytoreduction in almost 100% (94.6%) of cases.

None of the published studies on TCS included performance status into the analysis [3–10]. Good performance status, however, is one of the three factors building the 'AGO score', together with no residual disease at primary surgery and absence of ascites, to predict feasibility of complete cytoreduction in a secondary setting [11,12]. Such a score has been confirmed to predict a complete cytoreduction in more than two of three patients with platinum sensitive first relapse in a phase III setting [18]. We have assessed for the first time the value of AGO score for prediction of complete cytoreduction in a TCS setting. In this respect, the observed positive predictive value (75.8%) was very consistent with that recently reported in secondary cytoreduction (72.5%) [18].

Looking at a possible score able to identify patients eligible for TCS, it appears that the association of a good performance status plus single lesion recurrence, and the AGO score both showed high predictability rates of complete cytoreduction (PPV 95% and 76%, respectively), which are inversely proportioned with their power of patient selection (36% and 64%, respectively). On the other hand, both had remarkable NPV (45.5% and 43.2%, respectively). This means that almost half of the patients could be completely cytoreduced regardless of the presence of these two clinical profiles, but this could be related with the more favourable disease and patient characteristics. In this respect, it has to be noted that, in our series, >500 mL ascites was detected in only two patients, and tumor residuals at primary and secondary surgery

**Table 5**
Univariate and multivariate analyses of factors predicting complete surgical cytoreduction.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value |
| Age, years | | | | |
| <60 | Reference | 0.002 | Reference | 0.34 |
| ≥60 | 0.3 [0.1–0.7] | | 0.5 [0.1–1.9] | |
| ECOG performance status | | | | |
| 0 | Reference | 0.003 | Reference | 0.009 |
| 1[a] | 0.6 [0.4–0.9] | | 0.2 [0.06–0.6] | |
| ASA | | | | |
| 1–2 | Reference | 0.2 | | |
| 3–4 | 2.7 [0.5–13.2] | | | |
| FIGO stage at initial diagnosis | | | | |
| I–II | Reference | 0.4 | | |
| III–IV[b] | 0.5 [0.1–2.1] | | | |
| Tumor grade | | | | |
| 1–2 | Reference | 0.01 | Reference | 0.56 |
| 3[b] | 1.1 [1–1.3] | | 0.5 [0.08–3.8] | |
| Histological subtype | | | | |
| Serous | Reference | 0.9 | | |
| Others[b] | 1 [0.3–2.9] | | | |
| Years after primary diagnosis | | | | |
| ≥3 years | Reference | 0.76 | | |
| <3 years | 0.6 [0.03–11.9] | | | |
| Presence of distant metastases | | | | |
| Yes | Reference | 0.87 | | |
| No | 1.1 [0.2–4.7] | | | |
| Abdominal tumor involvement | | | | |
| Intraperitoneal ± retroperitoneal | Reference 2.2 [0.6–7.2] | 0.19 | | |
| Retroperitoneal | | | | |
| Lesion number | | | | |
| Multiple | Reference | <0.001 | Reference | <0.001 |
| Single | 11.4 [3.6–36.1] | | 14.2 [4–50.6] | |
| Size of largest recurrence | | | | |
| ≤25 mm | Reference | 0.45 | | |
| >25 mm | 1.5 [0.5–4.3] | | | |
| Ascites | | | | |
| ≤500 mL | Reference | 0.33 | | |
| >500 mL | 1 [0.9–1] | | | |
| Tumor residuals at primary surgery | | | | |
| Yes[b] | Reference | 0.03 | Reference | 0.3 |
| No | 2.5 [1–6] | | 0.5 [0.1–1.7] | |
| Tumor residuals at secondary surgery | | | | |
| Yes[b] | Reference | 0.04 | Reference | 0.62 |
| No | 2.7 [1–7.5] | | 0.7 [0.1–2.8] | |

ASA: American Society of Anesthesiologists; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; OR: odds ratio.

[a] Negatively affecting tumor reduction.

[b] Missing data were added to this group.

correlated with completeness of TCS at univariate ($p = 0.03$ and $p = 0.04$, respectively) without achieving statistical significance at multivariate analysis ($p = 0.3$ and $p = 0.62$, respectively). It has been recommended to include the outcome of previous cytoreductive surgery to select recurrent EOC patients who would be more likely to benefit from repetitive elective surgery [1,20]. It can be argued, however, that candidates for TCS represent a peculiar patient population in which a further natural selection could diminish the impact of factors identified at an earlier stage of disease progression.

In our study, the rate of patients achieving CC = 0 at TCS was 68.9%, with post-operative severe complications occurring in 9.7% and no cases of mortality within 60 days from surgery. Previous studies report complete tertiary cytoreduction rates ranging from 35% to 72.7% with higher rates of severe complications and 30-day operative mortality (ranging from 13% to 31.1%, and from 0 to 5.9%, respectively) [3–10]. In our study, TCS was always performed in high-volume gynecologic oncology referral centres, and the observed surgical outcomes do suggest that sub-specialization and expertise only allow a high chance of complete cytoreduction, hence with potentially improved survival, with an acceptable peri-operative morbidity. In this respect, it has to be considered that the retrospective setting of the study may contribute to underestimate the rate of surgical complications, and to be emphasized once more the need for qualification to perform the usually complex EOC surgery.

In conclusion, our study, although limited by potential bias associated with its retrospective design, is the first large multicentre study on TCS adopting selective inclusion criteria and demonstrates the achievement of postoperative no residual disease as the primary objective of TCS, confirming the prognostic impact of complete surgical cytoreduction even in a tertiary setting. Accurate patient selection is of utmost importance to have the best chance of complete cytoreduction although the value of the clinical scores could be affected by the intrinsic nature of a tumor in long surviving patients. In this perspective, TCS could be offered to selected patients with good clinical conditions for whom a complete surgical cytoreduction is judged reasonably feasible in a high volume gynecologic oncology referral centre. Nevertheless, a prospective international multicentre study seems to be worthwhile in order to better define the clinical boundaries of such elective surgery.

#### Conflict of interest statement

The authors declare that there are no conflicts of interest.

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