Role of minimally invasive secondary cytoreduction in patients with recurrent ovarian cancer

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ABSTRACT

Objective Retrospective series have shown minimally invasive secondary cytoreductive surgery is a feasible approach in selected cases of recurrent ovarian cancer. However, no predictors of minimally invasive secondary cytoreductive surgery feasibility are currently available. This study aims to identify predictive factors of minimally invasive secondary cytoreductive surgery feasibility and to compare perioperative and survival outcomes in a matched series of recurrent ovarian cancer patients who underwent secondary cytoreduction via an open or minimally invasive surgical approach.

Methods We retrospectively identified all platinum-sensitive recurrent epithelial ovarian cancer patients who underwent minimally invasive or laparotomic secondary cytoreductive surgery between January 2013 and July 2020. Each patient underwent a preoperative positron emission tomography (PET) computerized tomography (CT) scan and diagnostic laparoscopy before secondary cytoreductive surgery. A 1:2 propensity score-matched analysis was performed to balance predictive factors of minimally invasive secondary cytoreductive surgery.

Results Overall, 276 patients were identified (62 minimally invasive and 214 open), and a complete gross resection was achieved in 262 (94.9%) patients. At multivariate analysis, predictive factors for minimally invasive secondary cytoreductive surgery were neoadjuvant chemotherapy at first diagnosis (p=0.007), site of recurrence (p=0.031), and number of lesions (p=0.001). In the 1:2 propensity-matched population (39 minimally invasive and 78 open), complete gross resection was similar for both groups (p=0.082). Early post-operative complications were significantly higher in the laparotomy (33.3%) than in the minimally invasive surgery (10.3%) group (p=0.004). Only one (2.6%) patient experienced a grade >3 early post-operative complication in the minimally invasive surgery group compared with 13 (16.7%) patients in the open cohort (p<0.001). The median follow-up period was 32 months (range: 1–92) in the propensity-matched population. The median post-recurrence survival was 81 months in the minimally invasive surgery group and was not reached in the open group (p=0.11).

Conclusions Patients with single or oligometastatic recurrences can be offered minimally invasive secondary cytoreductive surgery, mainly if localized in the lymph-nodes, and/or if they received neoadjuvant chemotherapy at primary diagnosis. Minimally invasive secondary cytoreductive surgery is associated with favorable perioperative outcomes with no differences in terms of post-recurrence survival with respect to open approach.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have shown the feasibility of minimally invasive secondary cytoreductive surgery for recurrent ovarian cancer, but there are currently no predictors to triage patients towards a minimally invasive approach.

WHAT THIS STUDY ADDS

⇒ Our analysis showed that the neoadjuvant chemotherapy at first diagnosis, site of recurrence, and number of lesions are predictive factors for successful minimally invasive surgery. Propensity matched analysis of the two groups showed no differences in survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To date there are no prospective/randomized clinical studies, therefore we identified predictive criteria for minimally invasive secondary cytoreductive surgery feasibility that can help surgeons to properly plan the surgical approach.

INTRODUCTION

Recurrence in epithelial ovarian cancer occurs in approximately 75% of women within 2 years from first diagnosis, according to stage and primary treatment.[1] The standard treatment of recurrent ovarian cancer includes systemic chemotherapy,[2 3] whereas the role of surgery is still under discussion due to the reported conflicting results.[4–6] Only recently, results from the randomized DESKTOP-III trial have demonstrated an overall survival advantage in patients undergoing secondary cytoreductive surgery followed by chemotherapy, compared with chemotherapy alone, particularly when complete cytoreduction is achieved.[5] In DESKTOP-III, patients suitable for secondary cytoreductive surgery were selected using the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score, achieving a complete tumor cytoreduction in approximately 75% of cases.[5]

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As for upfront and interval surgery, few investigators have assessed the feasibility, and safety of minimally invasive secondary cytoreductive surgery in well-selected patients. This confirms the well-known benefits of the open approach: less blood loss, decreased morbidity, faster recovery, and shorter time to chemotherapy.[7–13] The rate of optimal cytoreduction by minimally invasive secondary cytoreductive surgery is consistent across studies, ranging from 79% to 98%,[7–13] and survival outcomes seem comparable with the open approach.[5–8] However, minimally invasive surgery requires a high level of expertise and skills, especially in this setting of patients, and should be performed in high-volume oncological centers with adequate experience in advanced surgical procedures.

There is no guidance defining the ideal candidate for minimally invasive secondary cytoreductive surgery, and no predictors of its feasibility are currently available. Therefore, the choice regarding the minimally invasive approach at secondary cytoreductive surgery is left to the surgeon's discretion. This study aimed to identify predictive factors of minimally invasive secondary cytoreductive surgery feasibility, intended as complete gross resection without conversion. The secondary objective was to compare perioperative and survival outcomes in a matched series of recurrent ovarian cancer patients who underwent secondary cytoreduction via an open or minimally invasive surgical approach.

METHODS

Patients

All recurrent ovarian cancer patients who underwent secondary cytoreductive surgery at our Gynecologic Oncology Unit were retrieved from our prospective REDCap database, starting from January 2013, when we first considered the minimally invasive surgical approach for secondary cytoreductive surgery, until July 2020. All patients signed an informed consent enabling us to collect their data for scientific purposes. The Institutional Review Board approved the study (N 4835/Protocol 0010352/22). We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cohort checklist when writing our report.[14]

Our study included only women with platinum-sensitive recurrent epithelial ovarian cancer. Platinum-sensitivity was defined as recurrence after ≥6 months from the completion of primary chemotherapy. All patients underwent primary or interval debulking surgery followed by platinum-based chemotherapy. None of the women received chemotherapy before secondary cytoreduction. To define recurrence and assess a surgical plan we used physical examination, CA125 serum levels, and radiologic images (positron emission tomography -(PET)/computerized tomography (CT) scans). According to location, the site of recurrence was classified as peritoneal, parenchymal, lymph-nodal, or mixed (in case of more than one anatomical site involvement). Furthermore, the extension of recurrence was classified as single, when only one nodule was identified at PET/CT-scan, "oligometastatic" when up to three nodules were described, "multifocal/diffuse carcinomatosis" when more than three nodules or wide peritoneal spread was observed.[15]

All patients underwent a diagnostic laparoscopy to exclude the presence of miliary carcinomatosis, followed by immediate secondary cytoreduction with a laparoscopic, robotic, or open approach. During the laparoscopic assessment, the criteria that guided the surgeons to continue cytoreduction by minimally invasive surgery were identification of the recurrence, and high chances of performing all surgical procedures to achieve complete gross resection, without conversion to laparotomy. Residual tumor was recorded at the end of the surgery, and complete cytoreduction was defined as no visible residual disease. All surgeons had an annual volume of radical surgeries in advanced ovarian cancer of more than 30 cases both by open approach and minimally invasive surgery.

Inclusion criteria to consider patients for secondary cytoreductive surgery were: absence of ascites and/or diffused carcinomatosis at preoperative workup, the possibility of a complete cytoreduction, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤1. There were no limitations in body mass index (BMI) and American Society of Anesthesiologists score. Exclusion criteria were: no primary or interval debulking surgery, chemotherapy before secondary cytoreduction, borderline ovarian tumors and non-epithelial ovarian cancer histology at primary diagnosis.

We collected the following data: clinical characteristics (age, BMI, International Federation of Obstetrics and Gynecology (FIGO) stage at diagnosis, primary surgical treatment (primary or neoadjuvant chemotherapy). We also collected data on major procedures performed at secondary cytoreductive surgery (rectosigmoid resection, small bowel resection, diaphragmatic peritonectomy/resection, splenectomy, resection of liver metastases, vaginectomy, pelvic and aortic lymphadenectomy). The complexity of surgical procedures was graded according to the surgical complexity score by Aletti et al.[16] Data about post-operative complications occurring within 30 days from surgery were retrieved, and surgical morbidity was classified according to Clavien-Dindo.[17]

The traditional follow-up schedule consisted of a clinical visit at 3–4 month intervals for the first 2 years, at 6 month intervals for the next 3 years, and then annually. A general clinical and gynecological examination (including a transvaginal ultrasonographic scan) and measurement of CA125 serum levels were performed. Imaging diagnostics with CT scan were recommended at 6 month intervals for the first 3 years after surgery. Perioperative complications and survival analysis were performed in a propensity-matched population. For survival, we excluded patients with short follow-up (less than 18 months) if they had no registered event (recurrence or death). Post-recurrence survival was calculated from the date of secondary cytoreductive surgery to death or the last follow-up visit.

Statistical Analysis

Statistical analysis was carried out using Statistical Package for Social Science software, Version 25, and R-Studio 0.98.1091 software. Chi-square or Fisher's exact test was used for the comparison of categorical variables. A logistic regression model in the entire cohort was applied to identify predictive factors of minimally invasive secondary cytoreductive surgery feasibility. We included in the analysis all clinicopathological variables that are regularly evaluated for each patient by the multidisciplinary tumor board, to assess the feasibility and, eventually, the approach of secondary cytoreductive surgery.

Given the non-randomized nature of the study design and the potential allocation biases rising from the retrospective comparison between the groups (minimally invasive surgery vs open), a

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Table 1 Distribution of patients' clinicopathological and surgical characteristics at diagnosis

Variables	All patients n (%)	Group A MIS n (%)	Group B Open n (%)	P value*
All cases	276	62	214	
Median age at first diagnosis years (range)	52 (24–82)	51 (33–82)	52 (24–75)	0.93†
Histology‡				
High-grade serous	211 (79.0)	44 (74.6)	167 (80.3)	0.22
Other	56 (21.0)	15 (25.4)	41 (19.7)	
n.a.	9	3	6	
FIGO stage‡				
I-II	57 (21.3)	10 (17.2)	47 (22.4)	0.26
III-IVB	211 (78.7)	48 (82.8)	163 (77.3)	
n.a.	8	4	4	
BRCA mutations‡				
BRCA wild-type	138 (62.4)	33 (67.3)	105 (61.0)	0.264
BRCA one or two mutation	83 (37.6)	16 (32.7)	67 (39.0)	
n.a.	55	13	42	
First approach				
PDS	202 (73.2)	39 (62.9)	163 (76.2)	**0.030**
NACT	74 (26.8)	23 (37.1)	51 (23.8)	
SCS by Aletti at first surgery				
1	109 (39.5)	27 (43.5)	82 (38.3)	0.46
2	117 (42.4)	27 (43.5)	90 (42.1)	
3	50 (18.1)	8 (12.9)	42 (19.6)	
Residual tumor at first surgery‡				
0	249 (93.6)	52 (91.2)	197 (94.3)	0.29
>0	17 (6.4)	5 (8.8)	12 (5.7)	
n.a.	10	5	5	
First line platinum-based chemotherapy				
No	4 (1.4)	2 (3.2)	2 (0.9)	0.22
Yes	272 (98.6)	60 (96.8)	212 (99.1)	
Bevacizumab maintenance at first therapy‡				
No	187 (68.8)	45 (75.0)	142 (67.0)	0.15
Yes	85 (31.3)	15 (25.0)	70 (33.0)	
n.a.	4	2	2	
Median PFI, months (range)	19 (6–169)	21 (6–169)	19 (6–125)	0.58†

Bold font indicates statistical significance.
*Calculated using the Chi square test or the Fisher's exact test.
†Calculated using the Test U the Mann-Whitney.
‡Rate calculated by the tested population.
n.a, not available; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; PFI, platinum-free interval; SCS, surgical complexity score.

propensity score-matched analysis was applied to balance clinical factors related to perioperative outcomes (survival and intra- and post-operative complications). The MatchIt package in R was used to generate the propensity score matched with a nearest neighbor matching algorithm. A 2:1 ratio was used to increase statistical power. Matching was based on the variables which resulted predictive for minimally invasive secondary cytoreductive surgery at multivariable approach (neoadjuvant chemotherapy at diagnosis, lymph-nodal recurrence, and single/oligometastatic disease).

As the main purpose of the analysis was the impact of each approach on post-recurrence survival, additional clinical variables impacting on ovarian cancer prognosis were included in the

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Table 2 Peri-operative data at secondary cytoreduction surgery

Variables	All patients n (%)	Group A MIS n (%)	Group 2 Open n (%)	P value*
All cases	276	62	214	
Median age at first recurrence, years (range)	55 (27–84)	55 (36–84)	55 (27–78)	0.80†
Age at first recurrence, years				
<65	211 (76.4)	49 (79.0)	162 (75.7)	0.36
≥ 65	65 (23.6)	13 (21.0)	52 (24.3)	
Median BMI Kg/m^2, (range)	25 (17–41)	25 (17–41)	24 (18–41)	0.53†
BMI, Kg/m^2				
<30	234 (84.8)	52 (83.9)	182 (85.0)	0.48
≥30	42 (15.2)	10 (16.1)	32 (15.0)	
Type of recurrence at PET/CT scan				
Single	88 (31.9)	31 (50.0)	57 (26.6)	**<0.001**
Oligometastatic	79 (28.6)	20 (32.3)	59 (27.6)	
Multifocal/diffused carcinomatosis	109 (39.5)	11 (17.7)	98 (45.8)	
Site of recurrence at PET/CT scan				
Peritoneum	98 (35.5)	24 (38.7)	74 (34.6)	**0.003**
Lymphnodal	100 (36.2)	30 (48.4)	70 (32.7)	
Parenchymal	8 (2.9)	3 (4.8)	5 (2.3)	
Mixed	70 (25.4)	5 (8.1)	65 (30.4)	

Bold font indicates statistical significance
*Calculated using the Chi square test or the Fisher's exact test
†Calculated using the Test U the Mann-Whitney
BMI, body mass index; d-LPS, diagnostic laparoscopy; LPT-SCS, laparotomic secondary cytoreduction surgery; MI-SCS, minimally invasive secondary cytoreduction surgery; PET/CT, positron emission tomography/computerized tomography.

propensity score, such as FIGO stage, age, maintenance treatment and *BRCA* status and platinum-free interval. A standardized difference >0.20 was considered indicative of clinical imbalance. The distribution of categorical variables between groups was compared with Chi squared or Fisher's Exact tests. Multivariate survival analysis was computed with Cox regression and included all variables with p≤0.05 in univariate analysis. Continuous variables were dichotomized. All p-values reported are two-sided and a p<0.05 was considered statistically significant.

Survival was calculated using the Kaplan–Meier method in the propensity score matched cohort. We used the Log-rank test to compare survival between groups. Multivariate analysis for prognostic factors was performed by Cox's proportional hazards regression model. All P values were two-sided, and the p-value was set at 0.05.

RESULTS

Patients' Characteristics

During the study period, 276 patients underwent secondary cytoreductive surgery. Among the overall cohort, 62 (22.5%) patients underwent minimally invasive cytoreductive surgery (group A), while the remaining 214 (77.5%) patients underwent a standard open approach (group B). Preoperative clinico-pathological features of the entire population and the two study groups are reported in Table 1. Most patients (78.7%) presented with FIGO stage III-IV at diagnosis, and the neoadjuvant chemotherapy rate at presentation was higher in group A than in group B (37.1% vs 23.8%, respectively; p=0.03). Overall, the median platinum-free interval was 19 months (range; 6–169) without differences between the two groups (p=0.58).

All patients underwent a preoperative PET/CT scan (Table 2). The single and oligometastatic recurrence rate was higher in group A than in group B (50.0% and 32.3% vs 26.6% and 27.6%, respectively; p<0.001). Regarding the disease pattern, the peritoneal recurrence rate was the same in both groups (38.7% in group A and 34.6% in group B), but the lymph-nodal recurrence rate was higher in group A vs group B (48.4% vs 32.7%, respectively; p=0.003).

The patients in group B underwent more frequent peritonectomies (p=0.001) and bowel resections (p<0.001), with only one patient undergoing bowel resection in group A. Other procedures were equally distributed in the two groups, but the surgical complexity score was significantly higher in the open than in the minimally invasive group (p<0.001) (online supplemental Table 1). No conversions to laparotomies were recorded in the minimally invasive group. Overall, complete gross resection was achieved in 262 (94.9%) patients, with a statistically higher rate of complete gross resection in group A than in group B (100% vs 93.5%, p=0.026).

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Table 3 Logistic regression for prediction of minimally invasive secondary cytoreduction surgery

Variables	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.21 (0.60 to 2.40)	0.59		
< 65	1			
≥ 65				
BMI		0.82		
<30	1			
≥30	1.09 (0.50 to 2.37)			
FIGO stage				
I-II	1	0.40		
III-IVB	1.38 (0.65 to 2.94)			
Histology				
High-grade serous	1	0.34		
Other	1.38 (0.70 to 2.73)			
BRCA				
Wild-type	1.31 (0.67 to 2.57)	0.43		
Mutation	1			
First approach				
PDS	1	**0.040**	1	**0.007**
NACT	1.88 (1.03 to 3.44)		2.46 (1.27 to 4.78)	
Residual tumor at first surgery				
0	1	0.41		
>0	1.57 (0.53 to 4.68)			
Bevacizumab maintenance at first therapy				
No	1.47 (0.77 to 2.83)	0.24		
Yes	1			
PFI, months				
<12	1.08 (0.59 to 1.99)	0.79		
>12	1			
Site of recurrence at PET/CT				
Peritoneum	2.83 (1.18 to 6.76)	**0.019**	1.78 (0.69 to 4.60)	0.23
Lymph-node (s)	3.57 (1.52 to 8.36)	**0.003**	2.67 (1.09 to 6.53)	**0.031**
Other	1		1	
Number of lesions at PET/CT				
Single	4.84 (2.26 to 10.37)	**<0.001**	4.17 (1.83 to 9.53)	**0.001**
Oligometastatic (2–3 nodules)	3.02 (1.35 to 6.74)	**0.007**	3.46 (1.48 to 8.07	**0.004**
Multifocal/diffused carcinomatosis	1		1	

Bold font indicates statistical significance.
BMI, body mass index; CI, confidence interval; FIGO, International Federation of Obstetrics and Gynecology; MI-SCS, minimally invasive secondary cytoreduction surgery; NACT, neoadjuvant chemotherapy; OR, overall response; PDS, primary debulking surgery; PET/CT, positron emission tomography/computerized tomography; PFI, platinum-free interval; RT, residual tumour.

Using univariate and multivariate analysis, we analyzed predictors of a successful minimally invasive approach (Table 3). Neoadjuvant chemotherapy at primary diagnosis, peritoneal and lymph-nodal pattern of recurrence and single and oligometastatic disease at preoperative PET/CT scan, were significantly correlated with minimally invasive secondary cytoreductive surgery feasibility. In multivariate analysis, single disease (odds ratio (OR) =4.17, 95% confidence interval (CI): 1.83 to 9.53, p<0.001) and oligometastatic disease at recurrence (OR=3.46, 95% CI: 1.48 to 8.07, p=0.004), neo-adjuvant chemotherapy at primary diagnosis (OR=2.46, 95% CI: 1.27 to 4.78, p=0.007), lymph-nodal site (OR=2.67, 95% CI: 1.09 to 6.53, p=0.031) were confirmed to be independent predictors of minimally invasive secondary cytoreductive surgery.

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Table 4 Perioperative data in propensity matched population

Variables	All patients n (%)	Group A MIS n (%)	Group B Open n (%)	P value*
All cases	117	39	78	–
Age				
< 65	89 (76.1)	31 (79.5)	58 (74.4)	0.36
≥ 65	28 (23.9)	8 (20.5)	20 (25.6)	
First approach				
PDS	66 (56.4)	21 (53.8)	45 (57.7)	0.42
NACT	51 (43.6)	18 (46.2)	33 (42.3)	
PFI, months				
<12	35 (29.9)	13 (33.3)	22 (28.2)	0.36
>12	82 (70.1)	26 (66.7)	56 (71.8)	
Site of recurrence at PET/CT				
Peritoneum	52 (44.4)	15 (38.5)	37 (47.4)	0.33
Lymph-node (s)	46 (39.3)	19 (48.7)	27 (34.6)	
Other	19 (16.2)	5 (12.8)	14 (18.0)	
Number of lesions at PET/CT				
Single	52 (44.4)	18 (46.2)	34 (43.6)	0.92
Oligometastatic (2–3 nodules)	42 (35.9)	13 (33.3)	29 (37.2)	
Multifocal/Diffused Carcinomatosis	23 (19.7)	8 (20.5)	15 (19.2)	
RT at SCS				
0	111 (94.9)	39 (100.0)	72 (92.3)	0.08
> 0	6 (5.1)	0	6 (7.7)	
Number of patients with post-operative Early Complications				
All grades	30 (25.6)	4 (10.3)	26 (33.3)	**0.004**
Grade ≥3	14 (12.0)	1 (2.6)	13 (16.7)	**<0.001**

*Calculated using the Chi square test or the Fisher's exact test
LPT-SCS, laparotomic secondary cytoreduction surgery; MI-SCS, minimally invasive secondary cytoreduction surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; PET/CT, positron emission tomography/computerized tomography; PFI, platinum-free interval; RT, residual tumor; SCS, secondary cytoreduction surgery.

Propensity-matched Analysis: Peri-operative Complications and Survival Analysis

The perioperative characteristics of the propensity-matched population are described in Table 4. The complete gross resection rate was similar for both groups (100% in minimally invasive surgery and 92.3% in the open group, p=0.082). Both populations were comparable in terms of the number of lesions (p=0.92) and site of recurrence (p=0.33).

Early post-operative complications were significantly higher in the open group (33.3% vs 10.3%; p=0.004). In the minimally invasive surgery group, only one patient experienced an enteroiliac fistula treated with surgery and post-operative intensive care admission for 1 day (grade 4). In the open group, 11 severe post-operative complications (grade >3) were registered: five grade 3A pleural effusions, three grade 3A abdominal collections, one grade 3B hemoperitoneum, one grade 4 necrotizing fasciitis treated with multiple surgeries, one grade 5 peritonitis due to anastomotic leakage.

The median follow-up period was 32 months (range; 1–92) in the overall propensity-matched population, and precisely 31 months (range; 1–91) in group A and 29 months (range 2–92) in group B. The median post-recurrence survival was 81 months in the minimally invasive surgery group and not reached in the open group (p=0.11, Figure 1). The 3 years post-recurrence survival rate was 76% and 84.1% in minimally invasive surgery and open groups, respectively.

DISCUSSION

Summary of Main Results

In our study, patients who underwent neoadjuvant chemotherapy and interval debulking surgery at primary surgery and those with oligometastatic recurrent disease had a higher likelihood of minimally invasive secondary cytoreductive surgery. We also showed no differences in overall survival between the two surgical approaches in the propensity-matched analysis. However, we showed a higher

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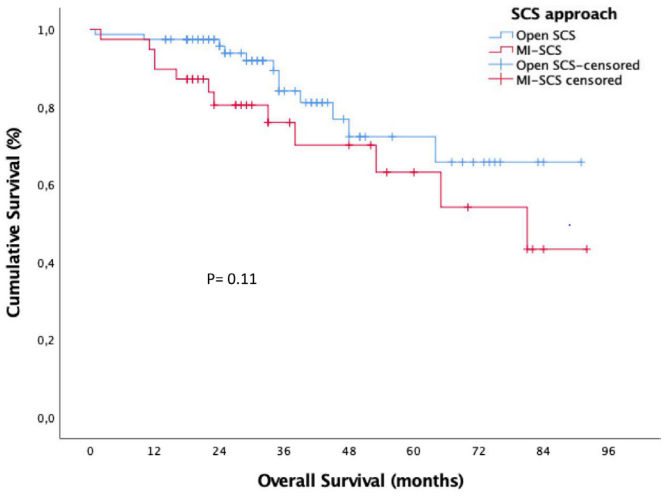

Figure 1 Overall survival of patients undergoing minimally invasive and open secondary cytoreduction surgery in the propensity-matched population.

rate of both overall and severe (grade>3) early complications in the open group.

Results in the Context of Published Literature

Many authors have highlighted the need for more targeted patient selection to achieve complete gross resection at secondary cytoreductive surgery.[10 13] In the literature, candidates for minimally invasive secondary cytoreductive surgery are mainly patients with single-site or localized peritoneal disease, lymph nodes, or isolated parenchymal lesions.[7 9 10 13 18] In this retrospective study, we confirm these characteristics, but also we showed a higher rate of neoadjuvant chemotherapy and interval debulking surgery at first diagnosis (p=0.030) in the minimally invasive surgery group. We may argue that patients undergoing neoadjuvant chemotherapy may receive a less complex surgery at interval debulking surgery, with consequently fewer adhesions and/or a different pattern of recurrence potentially favorable to a minimally invasive approach. Considering that the interval debulking surgery population has significantly increased in recent years, representing up to 42.2% of primary ovarian cancers,[19] the use of minimally invasive secondary cytoreductive surgery could increase accordingly in the coming years.[20]

Only two small retrospective studies directly compared the oncological outcomes between the minimally invasive and open approaches at secondary cytoreductive surgery,[7 8] showing no statistically significant differences in survival rates.[7 8] Eriksson et al reported a 2 year post-recurrence survival of 92.2% and 81.4% in the minimally invasive surgery and open group, respectively (p=0.7).[7] This different trend could be explained with the different clinicopathological data between the minimally invasive surgery and open groups in this retrospective study: higher rate of localized pelvic lesions (50% vs 27%; p=0.04), lower median number of lesions (1 vs 2; p<0.0005) and lower median size of largest lesion (2.45 cm vs 4 cm; p<0.005) in the minimally invasive surgery group compared with open.[7]

In our propensity matched population, we showed no difference in post-recurrence survival when comparing the two groups (3 year post-recurrence survival 84.1% in the open group vs 76% in minimally invasive surgery; p=0.11). Interestingly, the rate of post-recurrence survival is similar to the Eriksson study in the laparotomy group, whereas it is decreased in the minimally invasive secondary cytoreductive surgery group. Finally, our median post-recurrence survival of 73 months in the overall population in comparison to 61.9 months in the complete gross resection population of the DESKTOP III trial could be related to patient selection and/or use of any maintenance/experimental treatment at time of recurrence. Furthermore, in our study, we reported a higher probability of minimally invasive secondary cytoreductive surgery in case of oligometastatic disease (p=0.004) and lymph-node recurrence (p=0.031), which is in line with our previously reported data in recurrent ovarian cancer patients with isolated lymph node relapse and managed by salvage lymphadenectomy (laparotomy=56, 65.9%, and minimally invasive surgery=29, 34.1%), with a 3 year overall survival of 81.9% in the entire series.[13]

Strengths and Weaknesses

This is the largest study comparing minimally invasive and open approaches in platinum-sensitive recurrent ovarian patients undergoing secondary cytoreduction. There are several other strengths to our study. The first was the high homogeneity of the included recurrent ovarian cancer population, namely, we selected only patients with platinum-sensitive recurrent ovarian cancer surgically managed in a single tertiary oncological center with a high rate of complete gross resection in both groups (93.5%–100%). Moreover, PET/CT was applied in all cases, and a dedicated radiologist reviewed preoperative imaging within a multidisciplinary tumor board. Also, a diagnostic laparoscopy was used in all patients before deciding whether and how to proceed with surgery. The additional value of PET/CT scans with respect to standard CT scans still needs to be clarified; currently, its preoperative use is not mandatory in this setting, and the results of this study in this regards should be interpreted with caution.

Second, we performed a diagnostic laparoscopy at secondary cytoreductive surgery in all cases to assess the distribution of disease and convert to an open approach if a complete cytoreduction by a minimally invasive approach did not seem feasible on the surgeon's assessment. Third, we compared the oncological outcomes of the two surgical approaches in a propensity matched analysis to reduce the potential biases due to imbalance of different preoperative oncological characteristics potentially affecting oncological outcomes.

However, we also acknowledge limitations inherent to the study's retrospective nature, the relatively small sample size in the propensity match cohort that could impact the regression model analysis, and the lack of information on *BRCA* mutation data in some patients (55 of 276 patients). Moreover, data on maintenance therapy were not available given that not all patients received maintenance therapy in our institution.

Implications for Practice and Future Research

The lessons learned from the Laparoscopic Approach to Cervical Cancer (LACC) trial,[21] showing a detrimental effect of minimally invasive surgery in early-stage cervical cancer patients, should not be forgotten. The no statistically significant difference of minimally invasive vs open approach presented in our study does not reflect the near 10% difference in post-recurrence

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survival in favor of the open group, as shown by the Kaplan-Meier curves. It might be that the small sample size is not able to detect any statistically significant difference. Therefore, larger prospective studies are needed in this specific population, although we acknowledge the hurdles in performing such trials due to the selection of patients and complex approach. In this context, we consider that the availability of preoperative variables able to identify patients who can benefit from a successful minimally invasive approach is valuable.

CONCLUSIONS

The minimally invasive approach is feasible in selected patients with oligometastatic platinum-sensitive recurrent epithelial ovarian cancer. Also, these women experience a lower rate of early postoperative complications than those undergoing open secondary cytoreductive surgery. Thus far, no statistically significant differences in a propensity-matched population have been observed in terms of post-recurrence survival, but these data are explorative and represent a real-life experience. In general, all recurrent ovarian cancer patients, candidates for secondary cytoreductive surgery, should be treated in a referral high volume cancer center. Moreover, a specific training in minimally invasive surgery (either laparoscopy and/or robotic) should be included. With these characteristics, these results can be considered generalizable. Further confirmation in more extensive series and a multicentric validation are required.

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