

Incorporating robotic surgery into the management of ovarian cancer after neoadjuvant chemotherapy

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HIGHLIGHTS

- Interval robotic cytoreduction is feasible in ovarian cancer when patients are carefully selected
- The combination of open and robotic surgery results in adequate survival rates
- Robotics greatly reduces length of stay, blood loss, and transfusions in interval cytoreduction

ABSTRACT

Introduction With the rapid uptake of robotic surgery in surgical oncology, its use in the treatment of epithelial ovarian cancers is being evaluated. Complete cytoreduction represents the goal of surgery either at primary cytoreduction or after neoadjuvant chemotherapy in the setting of interval cytoreduction. In selected patients, the extent of disease would enable minimally invasive surgery. The objective of this study was to evaluate the impact of introducing robotic surgery for interval cytoreduction of selected patients with stage III–IV ovarian cancer.

Methods All patients who underwent surgery from November 2008 to 2014 (concurrent time period when robotic and open surgery were used simultaneously) after receiving neoadjuvant chemotherapy for advanced ovarian cancer (stage III–IV) were compared with all consecutive patients who underwent cytoreductive surgery by laparotomy after neoadjuvant chemotherapy between January 2006 and November 2008. Inclusion criteria included an interval cytoreductive surgery by laparotomy or robotic assistance for stage III–IV non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Exclusion criteria included patients treated concurrently for a non-gynecologic cancer, as well as secondary cytoreductive surgeries and diagnostic surgeries without an attempt at tumor reduction. Overall survival, progression-free survival, and peri-operative outcomes were compared for the entire patient cohort with those with advanced ovarian cancer who received neoadjuvant chemotherapy immediately before and after the introduction of robotic surgery.

Results A total of 91 patients were selected to undergo interval cytoreduction either via robotic surgery (n=57) or laparotomy (n=34) after the administration of neoadjuvant chemotherapy. The median age of the cohort was 65 years (range 24–88), 78% had stage III disease, and the median follow-up time was 37 months (5.6–91.4 months). The median survival was 42.8±3.1 months in the period where both robotic surgery and laparotomy were offered compared with 37.9±9.8 months in the time period preceding when only laparotomy was performed

(p=0.6). All patients selected to undergo interval robotic cytoreduction following neoadjuvant chemotherapy had a reduction of cancer antigen 125 by at least 80%, resolution of ascites, and CT findings suggesting the potential to achieve optimal interval cytoreduction. All these patients achieved optimal cytoreduction with <1 cm residual disease, including 82% with no residual disease. The median blood loss was 100 mL (mean 135 mL, range 10–1250 mL), and the median hospital stay was 1 day.

Conclusion Robotic interval cytoreductive surgery is feasible in well-selected patients. Future studies should aim to define ideal patients for minimally invasive cytoreductive surgery.

INTRODUCTION

Cytoreductive surgery as described by Griffiths has been the prevailing paradigm in treating ovarian cancer,¹ including in the era of platinum, taxanes, and precision medicine.² Despite this radical approach, advanced ovarian cancer has poor survival,³ and its treatments have been associated with significant morbidity including physical as well as psycho-emotional impairment.^{4–7}

The use of neoadjuvant chemotherapy followed by interval surgical cytoreduction and adjuvant chemotherapy has become an option for some women with advanced ovarian cancer, offering comparable survival^{8–11} and decreased morbidity^{9–13} compared with upfront cytoreductive surgery. Preliminary studies have laid the groundwork on the feasibility of minimally invasive interval cytoreductive surgery in selected patients after neoadjuvant chemotherapy.^{14–20} Since the Food and Drug Administration's approval of the da Vinci Surgical System for gynecologic procedures in 2005, it has rapidly integrated into the treatment of uterine cancer and, like laparoscopy, has resulted in reduced operative blood loss, lower incidence of post-operative complications, and faster recovery.^{21 22}

Original article

In view of the decreased tumor burden observed in some patients after neoadjuvant chemotherapy, with minimal or no visible residual disease at the time of interval cytoreduction by laparotomy, the objective of the current study was to evaluate how the addition of robotics as a surgical option for selected patients impacted the outcomes of patients who underwent interval cytoreductive surgery for advanced ovarian cancer.

METHODS

From January 2006 to November 2008, all patients who were offered interval cytoreductive surgery for ovarian cancer underwent abdominal surgery via laparotomy. Starting in November 2008, the use of robotic-assisted surgery was offered to selected patients. To evaluate the impact of incorporating robotics into the surgical management of ovarian cancer, all patients who were operated in the period from November 2008 to 2014 (ie, via either laparotomy or robotic surgery) after receiving neoadjuvant chemotherapy for advanced stage disease (stage III–IV) were compared with all consecutive patients who were operated by laparotomy after neoadjuvant chemotherapy between January 2006 and November 2008 (see online supplementary appendix I).

During this latter period, the decision to proceed with robotic surgery rather than laparotomy was made by the gynecologic oncology tumor board following an initial assessment of whether complete cytoreduction could be expected by the robotics approach, including a clinical evaluation and review of CT images prior to and after administration of neoadjuvant chemotherapy with an expert radiologist in abdominal imaging. During this pilot period no absolute criteria were defined, and a conservative approach was taken favoring laparotomy in suspected complex surgical cases, especially requiring bowel resection, leading to a selection of patients with the highest likelihood of successful cytoreduction in the robotics cohort. Complete cytoreduction was defined as no visible residual disease. Details on the robotic procedure are described in online supplementary appendix II.

Patients were evaluated after 1 week for routine post-operative care and to plan for adjuvant chemotherapy. Following the end of adjuvant treatment, patients in remission were followed every 4 months for 2 years, then every 6 months up to 5 years, and yearly thereafter. Physical examination and standard blood tests including cancer antigen 125 (CA125) were ordered routinely, and imaging studies were performed only if indicated either by clinical symptoms or by increasing CA125 levels.

The inclusion criteria included an interval cytoreductive surgery by laparotomy or robotic assistance for stage III–IV non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Exclusion criteria included patients treated concurrently for a non-gynecologic cancer, as well as secondary cytoreduction surgeries or diagnostic surgeries without an attempt at cytoreduction. This study was approved by the hospital's Institutional Review Board (approval # CODIM-MBM-CR18-07).

Statistical tests were performed using Fisher's exact test for categorical variables, the Wilcoxon rank sum test for continuous variables, and exact logistic regression for odds ratios (presented as OR±SE). Time-to-event outcomes such as survival and progression-free survival were analyzed using Kaplan–Meier curves, and the

log-rank test for statistical significance. Cox proportional hazard models were used to control for stage (III, IV) and age, with hazard ratios presented as HR±SE. To use the most reproducible time criteria to compare between periods, overall survival was measured from the date of first neoadjuvant chemotherapy treatment to the date of last follow-up or death. Progression-free survival was measured from the date of first treatment to the date of recurrence, death, or last follow-up. Patients who progressed without a disease-free interval were estimated to recur on the day of their last treatment. Recurrences were diagnosed on imaging or physical examination. As part of a sensitivity analysis, the progression-free survival analysis was repeated using the date that patients began or were offered second-line therapy as the date of recurrence. Survival time is presented as median survival ±SE. Statistical analyses were performed using Stata 13.0 (StataCorp). A two-sided significance level of $p < 0.05$ was used throughout the study.

RESULTS

A total of 91 patients were selected to undergo interval cytoreduction either via robotic surgery ($n=57$) or laparotomy ($n=34$) after the administration of neoadjuvant chemotherapy. Surgical outcomes as well as the pattern of recurrence were examined for all patients who underwent interval cytoreduction ($n=34$ via laparotomy and $n=57$ via robotics) since the first robotic surgery for ovarian cancer in November 2008. These were compared with a historical cohort of patients in the immediately preceding period who underwent interval surgery by laparotomy ($n=22$) (online supplementary appendix I). Chemotherapy regimens during both periods were similar and consisted of platinum and taxanes, and no patients were treated with bevacizumab in the first-line setting.

Patient and tumor characteristics for patients before and after the addition of the robotics approach are shown in Table 1. Patients in the robotic surgery era had more grade 3 disease ($p=0.005$). Table 2 describes peri-operative outcomes in the pre-robotic era as well as in the period combining laparotomy and robotics. The latter period had higher rates of optimal cytoreduction rates ($p=0.005$), shorter hospital stays ($p=0.0001$), and reduced intra-operative blood loss ($p=0.001$). Within the robotic era, patients who were transfused were significantly more likely to have undergone a laparotomy than robotic surgery, and this applied to both intra-operative (OR=12.2±8.3, $p < 0.001$) and post-operative (OR=4.9±2.3, $p=0.0007$) transfusions.

Complications were evaluated intra-operatively (bleeding, injuries to the bladder, ureters, bowel, nerves, and blood vessels), as well as postoperatively (fever, infection, abscess formation, cardiac complications, poor glucose control, cerebrovascular morbidity, ileus, lymphocyst formation, pulmonary complications, renal morbidity, septicemia, thromboembolic complications, urinary retention, urinary tract infection, vault complications, wound complications, and post-operative death). There were no significant differences in the above complications between the two time periods (all $p > 0.05$).

During the follow-up period, 19 (86%) patients in the pre-robotic surgery era had a recurrence and 16 (73%) patients died; in the robotic surgery era, 73 (80%) patients had a recurrence and 46 (51%) patients died, including three due to reasons unrelated to their ovarian cancer. Figure 1A and B illustrates the overall and

Table 1 Description of population before and after the use of robotic surgery for ovarian cancer

	Pre-robotic era: laparotomy only (n=22)	Robotic era: laparotomy + robotics (n=91)	P value
Age, mean (SD)	65.4 (9.2)	64.1 (13.5)	0.98
BMI, mean (SD)	27.3 (5.8)	26.7 (6.3)	0.52
ASA			0.41*
1	2 (9.1%)	3 (3.3%)	
2	11 (50.0%)	54 (59.3%)	
3	7 (31.8%)	33 (36.3%)	
Unknown	2 (9.1%)	1 (1.1%)	
Stage			1.00
III	17 (77.3%)	71 (78.0%)	
IV	5 (22.7%)	20 (22.0%)	
Grade			0.005
1	0 (0%)	1 (1.1%)	
2	4 (18.2%)	1 (1.1%)	
3	18 (81.8%)	89 (97.8%)	
Histology			0.37
Serous	19 (86.4%)	79 (86.8%)	
Endometrioid	1 (4.6%)	3 (3.3%)	
Clear cell	0 (0%)	5 (5.5%)	
Carcinosarcoma	0 (0%)	1 (1.1%)	
Adenosquamous	1 (4.6%)	0 (0%)	
Not defined	1 (4.6%)	3 (3.3%)	
Follow-up time (months)			0.56
Mean (SD)	46.0 (29.5)	38.2 (19.1)	
Median (range)	36.2 (9.0–104.3)	37.0 (5.6–91.4)	

Data are presented as n (%) unless stated otherwise.

*Statistical significance excludes unreported/missing data.

ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index (kg/m²).

progression-free survival before and after the use of robotic surgery. The addition of robotic surgery for interval cytoreduction did not adversely affect overall survival (median survival 37.9 months (pre-robotic era) vs 42.8 months (robotic era), $p=0.6$; [Figure 1A](#)) or progression-free survival (11.9 months (pre-robotic era) vs 16.5 (robotic era) months, $p=0.4$; [Figure 1B](#)). After controlling for stage and age, robotic surgery was not a significant predictor of overall survival ($HR=0.9\pm 0.3$, $p=0.6$) or progression-free survival ($HR=0.8\pm 0.2$, $p=0.4$); neither of the covariates was significant.

Patients who underwent robotic-assisted interval cytoreductive surgery were then analyzed independently. Patient and tumor characteristics are presented in online supplementary appendix III. The majority of patients had high-grade (97%), serous (90%), and stage III (75%) disease. Surgical outcomes following robotic cytoreductive surgery are summarized in [Table 3](#). Complete cytoreduction was achieved in 82% of cases and the remaining 18% of patients had <1 cm residual disease.

There were six conversions to laparotomy (10.5%) in the robotic cohort including three (5%) mini-laparotomies in order to achieve

optimal cytoreduction and necessitating a rectosigmoid resection, a hemicolectomy, and dissection of a densely adherent omentum. The three left upper quadrant mini-laparotomies were performed to remove omental disease in the left upper quadrant, where it was densely adherent to the splenic flexure and the spleen.

The median blood loss for the robotic cohort was 100 mL (mean 135 mL, range 10–1250 mL) and 5% of patients required blood transfusions intra-operatively. Post-operatively, 14 (25%) patients were transfused. Note that because some patients may have been transfused for low pre-operative hemoglobin due to neoadjuvant chemotherapy, the number of patients transfused was analyzed among those with a pre-operative hemoglobin level of at least 100 g/L, yielding transfusion rates of 4% intra-operatively and 12% post-operatively. Patients in the robotic cohort also had a median hospital stay of 1 day (range 1–17 days) with 84% of patients discharged within the first 2 days post-operatively. Adjuvant chemotherapy was given after a median of 13 days from surgery (range 6–75 days) in the robotic cohort.

After a median follow-up of 41 months (range 6–86 months) among patients who underwent robotic surgery, there was a global mortality rate of 44% (median overall survival 47.2 ± 9.8 months), including two patients in the robotic cohort who died due to reasons unrelated to ovarian cancer, and a global rate of recurrence of 75% (median progression-free survival 20.6 ± 2.4 months). There were no incidences of isolated port-site metastasis, although three patients had port-site implants in the context of abdominal carcinomatosis at the time of recurrence with diffuse peritoneal disease.

To control for the time bias and to ensure that the lack of significant difference between the two periods was not due to an outperforming laparotomy group in the robotic surgery era, the survival analysis was repeated and compared between patients who underwent robotic cytoreduction and those who were operated on by laparotomy in the pre-robotic era and in the robotic era. The robotic group tended to have superior overall survival ([Figure 2A](#); median 37.9 months for the laparotomy group in the pre-robotic era, 37.8 months for the laparotomy group in the robotic era, and 47.2 months for the robotic group; $p=0.04$) and progression-free survival ([Figure 2B](#); 11.9, 13.9, and 20.6 months, respectively; $p=0.005$), given that patients were selected prior to being offered robotic-assisted surgical debulking. Cox proportional hazard models were employed to control for stage and age, and patients who underwent robotic surgery were associated with better overall survival ($HR=0.5\pm 0.1$, $p=0.02$) and progression-free survival ($HR=0.5\pm 0.1$, $p=0.002$).

The progression-free survival analyses were repeated using a clinical date of recurrence when patients began a second line of treatment; if patients refused or were incapable of receiving a second-line intervention, the date the treatment was offered was used instead. Similar results were obtained as in the primary analysis and there were no significant differences between the pre-robotic and robotic surgery eras.

DISCUSSION

Our study showed that, in very select patients, the use of robotic interval cytoreduction is feasible. In contrast to the wide incorporation of minimally invasive surgery in the treatment of uterine

Table 2 Surgical outcomes before and after the use of robotic surgery for ovarian cancer

	Pre-robotic era: laparotomy only (n=22)	Robotic era: laparotomy + robotics (n=91)	P value
Cytoreduction			0.005
Complete cytoreduction, n (%)	9 (40.9%)	69 (75.8%)	
≤1 cm residual disease, n (%)	11 (50.0%)	18 (19.8%)	
>1 cm residual disease, n (%)	2 (9.1%)	4 (4.4%)	
Estimated blood loss (mL), mean (SD)	505 (599)	271 (307)	0.001
Hgb differential*, mean (SD)	-15.1 (13.0)	-11.9 (15.5)	0.49
Blood transfusion†, n (%)			
Intra-operative blood transfusion	5 (25.0%)	17 (18.7%)	0.54
Intra-operative transfusion with pre-operative Hgb ≥100‡	4 (20.0%)	5 (5.5%)	0.054
Post-operative blood transfusion	12 (60.0%)	35 (38.5%)	0.087
Post-operative transfusion with pre-operative Hgb ≥100‡	8 (40.0%)	21 (23.1%)	0.16
Procedure time§, mean (SD)	213 (74)	282 (95)	0.0001
Length of stay (days)			0.0001
Mean (SD)	8.6 (6.3)	4.6 (5.7)	
Median (range)	6 (4–27)	2 (1–35)	

*Post-operative minus pre-operative hemoglobin (Hgb).

†Transfusion of blood products documented in 20 out of 22 subjects in the pre-robotic era. Data represent number of patients transfused with blood products including packed red blood cells, fresh frozen plasma, platelets, and/or albumin.

‡Transfusion of blood products among patients with a pre-operative hemoglobin (Hgb) of 100g/L or more in order to control for low Hgb due to reasons other than surgery (eg, neoadjuvant chemotherapy).

§Procedure time taken from skin incision to closure.

cancers, the standard approach for ovarian cancer has remained cytoreductive surgery via laparotomy. Concerns for intra-operative spillage, port-site metastases, sub-optimal cytoreduction, and adequacy of lymphadenectomy have been among the obstacles in the adoption of any minimally invasive surgical technique.^{23–25}

In 1990, Reich et al published a single case report on the management of a stage I ovarian cancer by laparoscopy.²⁶ In 1994, Querleu and LeBlanc reported a case series on the first full pelvic and infra-renal para-aortic lymphadenectomy via laparoscopy for restaging and second-look procedures.²⁷ In the following years, reports emerged demonstrating the feasibility of the laparoscopic management of ovarian cancer, but its use has been largely limited to surgeries for diagnosis as well as the assessment of resectability and second-look procedures,^{25 27–29} and in the staging of select cases of early-stage disease.^{24 28 30–34} Some studies have also reported on laparoscopic cytoreduction in highly selected patients with advanced ovarian cancer.^{14–17}

To date, only a few studies have been published on the feasibility of robotic cytoreductive surgery in ovarian cancer,^{20 35–37} as well as secondary cytoreductive surgery for recurrent disease.^{38 39} In 2011, Magrina et al published a case–control study with 25 patients who underwent robotic surgery, 15 of whom had advanced-stage ovarian cancer and 6 of whom received neoadjuvant chemotherapy. While they reported greater progression-free survival in their robotic and laparoscopy groups compared with laparotomy, this is likely due to a selection process, similar to our data, wherein patients who underwent a laparotomy were more likely to have advanced-stage disease, undergo more extensive debulking procedures, and less

likely to be completely debulked.³⁵ Feuer et al compared 63 selected patients (37 with advanced-stage disease, 33 received neoadjuvant chemotherapy) who underwent robotic cytoreduction to 26 patients (19 with advanced-stage disease, 4 received neoadjuvant chemotherapy) who underwent the same surgery by laparotomy for ovarian cancer.³⁷ This study also reported on the decreased blood loss and the shorter hospital stay, with adequate survival at 1 year.³⁷ The MISSION trial evaluated the feasibility of minimally invasive interval surgery (n=26 laparoscopically, n=4 robotically) in a selected cohort of patients who had a clinical complete response to neoadjuvant chemotherapy.¹⁹ While median follow-up was limited (10.5 months), peri-operative and psycho-oncological outcomes were promising as complete cytoreduction was achieved in 97% of patients, there were no early post-operative complications, and most patients reported moderate discomfort on psychometric assessment.¹⁹ More recently, the retrospective multicenter INTERNATIONAL MISSION study reported on 127 patients who were highly selected to undergo minimally invasive interval surgery by either laparoscopy or robotic surgery.¹⁸ Although a comparison with laparotomy was not performed, oncologic outcomes revealed the feasibility of complete cytoreduction (100% optimal cytoreduction, 96% of whom had no residual disease) and a recurrence rate of 58% after a median follow-up of 37 months,¹⁸ prompting calls for prospective randomized trials in this area.⁴⁰

To mitigate our selection bias, we sought to evaluate whether there were any changes in the outcomes of our entire patient population undergoing interval cytoreduction as a result of the availability and selected utilization of robotics. We demonstrate that the robotic

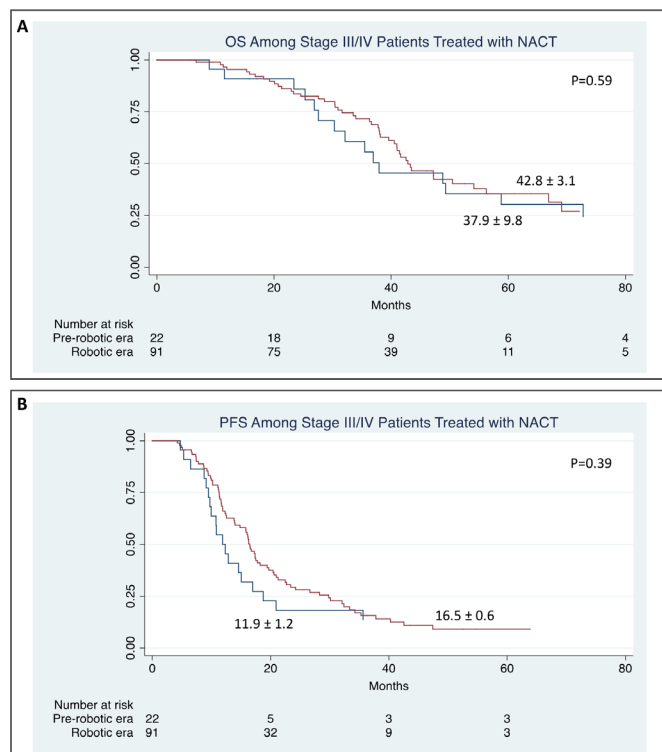


Figure 1 Overall survival (OS) and progression-free survival (PFS) before and after the use of robotic surgery for ovarian cancer. Overall survival (Figure 1A) and progression-free survival (Figure 1B) were compared between patients in the pre-robotic era (laparotomy only) and the robotic era (combination of laparotomy and robotics in selected cases). NACT, neoadjuvant chemotherapy.

approach allowed for satisfactory rates of complete cytoreduction (82%), with adequate surgical outcomes. Indeed, the careful selection of some patients for robotic interval cytoreduction at our center has seemingly not compromised the overall or progression-free survival of our patient population. However, one should note that our study was not designed, powered, or with sufficient follow-up to determine oncologic outcomes.

The rate of conversion to laparotomy was 10.5% (six patients), half of which were mini-laparotomies. Our management of conversion for advanced disease necessitating complex bowel or additional procedures coincides with the suggestion by Magrina et al that such patients might be better served by an open approach.³⁵ Of note is that all conversions were done to safely remove extensive disease and there were no conversions for intra-operative complications.

There are several limitations to our study. This was a retrospective study, which carries some inherent biases, although all consecutive patients were included. The sample size was also limited, and even within the robotic surgery era, a fraction (63%) underwent robotic surgery, further lowering the power to detect any potentially deleterious effects of the surgery. Additionally, operations were performed by a group of surgeons experienced in robotics within a single institution, which may restrict the generalizability of the findings. Patients with extensive disease who were deemed unlikely to

Table 3 Surgical outcomes following robotic surgery

	Robotic surgery cohort (n=57)
Cytoreduction	
Complete cytoreduction, n	47 (82.5%)
≤1 cm residual disease, n	10 (17.5%)
>1 cm residual disease, n	0 (0%)
Estimated blood loss (mL), mean (SD)	135 (210)
Hgb differential*, mean (SD)	-12.3 (12.8)
Blood transfusion†, n (%)	
Intra-operative blood transfusion	3 (5.3%)
Intra-operative transfusion with pre-operative Hgb ≥100‡	2 (3.5%)
Post-operative blood transfusion	14 (24.6%)
Post-operative transfusion with pre-operative Hgb ≥100‡	7 (12.3%)
Procedure time§, mean (SD)	312 (84)
Length of stay (days)	
Mean (SD)	2.1 (2.6)
Median (range)	1 (1–17)

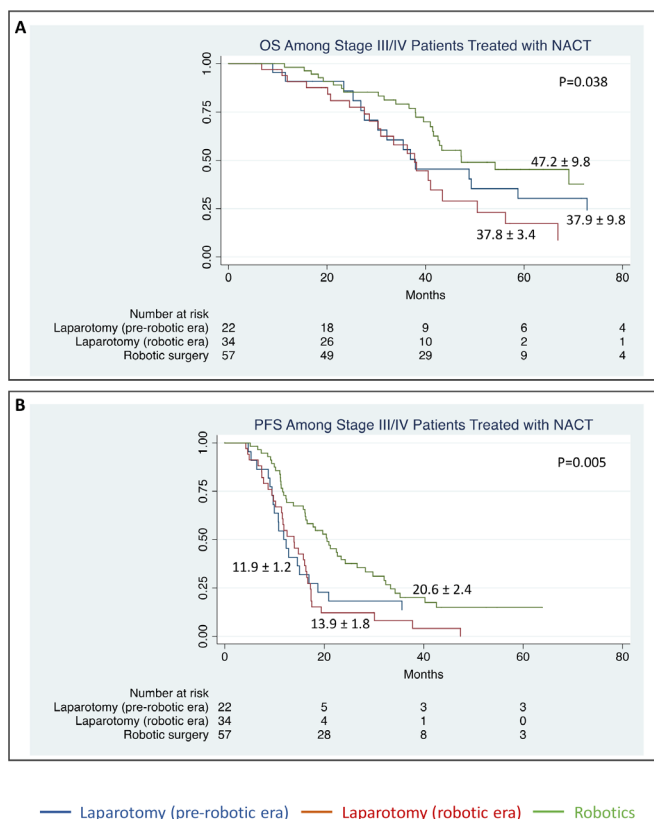


Figure 2 Overall survival (OS) and progression-free survival (PFS) before and after the use of robotic surgery for ovarian cancer, by surgical approach. Overall survival (Figure 2A) and progression-free survival (Figure 2B) were compared between patients who underwent laparotomy during the pre-robotic era, laparotomy during the robotic era, and robotic surgery during the robotic era. NACT, neoadjuvant chemotherapy.

be optimally debulked by robotic surgery underwent laparotomy, thus an appropriate control group is lacking and there is a clear selection bias that would favor the robotic group. This selection bias was addressed by including all the patients in the robotic period in a pre-post analysis. As in all such analyses, there is the possibility of confounders such as other changes in the management of epithelial ovarian cancers, including changes in chemotherapy regimens, variations in the performance of imaging studies, and developments in peri-operative care. While the degree of aggressiveness of debulking surgeries continues to be debated in the literature,⁴¹ we showed comparable outcomes between the pre-robotic and the robotic eras. This could be the result of appropriate selection of patients to undergo radical procedures by laparotomy, as well as the use of neoadjuvant chemotherapy, which permitted us to achieve optimal cytoreductive surgeries in the patients selected to undergo robotically. The study's focus on patients who underwent neoadjuvant chemotherapy helps homogenize the patient population, but, at the same time, presents a second selection bias as the utilization of neoadjuvant chemotherapy in the initial phase of its use (ie, within the pre-robotic era) would have been offered primarily to patients with the most inoperable cancers. To address this bias, the analysis was expanded to include all patients who underwent cytoreductive surgery for advanced ovarian cancer, either upfront primary cytoreductive or interval cytoreductive surgery. Similar findings were obtained and there were no significant differences between the robotic surgery era (combining 61 laparotomy and 75 robotic cases) and the laparotomy only era (n=62) as it pertained to overall survival (online supplementary appendix IV–A; median survival 40.0 vs 47.2 months before and after the initial use of robotics, p=0.6) and progression-free survival (online supplementary appendix IV–B; 12.7 vs 16.1 months, respectively, p=0.4). One should also note that the design of this study does not allow for definitive conclusions regarding oncologic outcomes.

Robotic surgery for the management of selected patients with ovarian, tubal, and peritoneal cancers in the interval debulking setting seems to be feasible and warrants further investigation as a surgical option. Further follow-up and randomized controlled trials are necessary to validate survival outcomes following robotic surgery compared with standard surgical treatment via laparotomy. Future studies should elucidate the specific population that may benefit most from the incorporation of robotic surgery into their surgical management.

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