

Observational Study

Minimally invasive cytoreductive surgery in advanced ovarian cancer: A nonselected consecutive series of robotic-assisted cases

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Abstract

The gold standard for advanced-stage ovarian cancer surgery entails exploration via a midline vertical laparotomy. Studies have shown that minimally invasive surgery (MIS) can be a safe and effective method for the surgical management of early ovarian cancer. In some cases, MIS can also be selectively used for cytoreductive surgery in cases with advanced-stage ovarian cancer. The robotic platform has the potential to provide similar outcomes to the laparotomy-based standard of care in advanced complex surgery while accelerating recovery, minimizing morbidity, and reducing perioperative complications. The primary objective of this study was to evaluate surgical and perioperative outcomes in patients with advanced ovarian carcinoma who underwent robotic-assisted cytoreduction. A chart review of a nonselected consecutive series of all patients undergoing surgical management of advanced ovarian cancer between 7/1/2017 and 12/31/2021 was conducted. All patients that were diagnosed with Stage III to IV ovarian cancer between the timeframe underwent robotic-assisted cytoreductive surgery at two urban community teaching hospitals in Los Angeles. Twenty-five patients were identified and included in this study. All surgeries were performed by a single surgeon. Optimal or complete CRS was achieved in 96% of the patients (24 of 25 cases). Seven (28%) underwent primary cytoreduction (PCRS) and 18 (72%) underwent interval cytoreduction (ICRS). The estimated median blood loss was 100 mL (25-500 mL), the median operative time was 5.9 hours (3.1-10.5 hours), and the conversion rate to open laparotomy was 0%. There were no intraoperative complications and the readmission rate within 30 days was 4% (1 patient) for ileus, which was managed conservatively. Currently, 64% of the patients in the case series remain alive. The median survival has not been reached. The median follow-up is 4.08 years. Results presented from this nonselected, consecutive case series illustrate how a minimally invasive robotic approach can be safely used in place of the standard exploratory laparotomy for ovarian cytoreduction.

Introduction

Among gynecological malignancies, ovarian cancer remains the leading cause of death, partly due to diagnosis most often occurring at an advanced stage [1-5]. Minimally invasive surgery has been already incorporated into diagnosing, staging early disease, and determining eligibility for primary cytoreductive surgery (PCRS) versus neoadjuvant therapy (NACT), followed by interval cytoreductive surgery (ICRS) for advanced disease [6]. Diagnostic laparoscopy along

with scoring algorithms such as the Fagotti score, is used to determine the feasibility of PCRS [7-10]. However, studies focusing on minimally invasive cytoreduction in advanced stages are more limited, and patient cohorts are highly selected [11-15].

Data strongly suggests that post-surgical residual tumor size is inversely related to survival [8,16-20]. It is thought that the efficacy of CRS is at least somewhat related to tumor biology. The efficacy of PCRS in advanced disease is theorized

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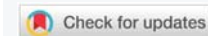
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to stem from the removal of a large proportion of tumor cells, some of which may harbor a propensity for chemoresistance, or from possible increased turnover of tumor cells in response to local injury, rendering them more susceptible to chemotherapy [21,22]. However, multiple clinical studies now support survival noninferiority of ICRS after NACT [8,9,23]. Hence, current standards endorse both PCRS and ICRS in the treatment of advanced ovarian cancer, with the goal of eliminating or minimizing residual disease at some point in the treatment course in order to gain the most survival benefit [28]. The question is whether this can be safely achieved with minimally invasive surgery.

Minimally invasive cytoreductive surgery from non-randomized and mostly highly selected patient cohort data sets has shown similar or more favorable outcomes compared to an open surgical approach [8,11,24-27]. Robot-assisted (RA) surgical staging showed significantly shorter operative times than the laparoscopic approach in early-stage ovarian cancer patients [10]. There have been a number of robotic and laparoscopic series published addressing ICRS but the patients were highly selected [28,29]. To further explore its potential as a surgical option in patients with advanced ovarian carcinoma, we evaluated the surgical and perioperative outcomes of robotically assisted minimally invasive PCRS and ICRS in a consecutive nonselected series and compared them to the literature concerning cytoreduction perioperative outcomes after laparotomy.

Materials and methods

Institutional Review Board (IRB) exemption was obtained from the two participating healthcare centers. A retrospective chart review was performed of a nonselected consecutive series of advanced-stage ovarian cancer patients undergoing PCRS and ICRS at two urban community teaching hospitals in Los Angeles between 7/1/2017 and 12/31/2021 (n=25). Since this was a consecutive series, preoperative or intraoperative scoring systems to determine whether or not to proceed with PCRS were not utilized. Patients that underwent cytoreductive surgery during that period were logged at the time of surgery, and outcomes were followed by a medical chart review to confirm the pathological diagnosis and collect data focused on the stage, median operative time, and complication rate. Other data points collected include age, race, body mass index (BMI), median blood loss, antibiotic redoses, and readmission rate. The number of surgical procedures performed during cytoreduction was collected from each operative report (Table 1). This helps illustrate the effort required to achieve optimal cytoreduction. All statistical analyses were conducted using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA).

Results

All patients in this case series were diagnosed with stage III-IV ovarian carcinomas. Those that underwent PCRS were

staged surgically and those that underwent ICRS were staged clinically, primarily using CT scan findings. Those undergoing PCRS presented with pelvic masses, suspicious for cancer, and/or with elevated markers, but no obvious bulky disease on imaging. Of these patients, those that were found to have carcinomatosis intraoperatively were included in this series.

Substages were as follows: two (8%) stage IIIA, one (4%) stage IIIB, fifteen (60%) stage IIIC, two (8%) stage IVA, five (20%) stage IVB. None of the Stage IIIC cases were based solely on adenopathy. Optimal or complete cytoreduction was achieved in 96% of the patients (24 of 25 cases). Seven (28%) underwent PCRS and 18 (72%) underwent ICRS. All but one patient in the case series received a robotic-assisted simple or modified radical hysterectomy and bilateral salpingo-oophorectomy. One patient previously had a simple hysterectomy at an outside facility for a benign etiology. Other procedures performed were collected from operative reports and included: modified radical hysterectomy, pelvic and para-aortic lymphadenectomy, ureterolysis, total omentectomy, diaphragmatic and peritoneal stripping, resection of the falciform ligament, appendectomy, resection of the upper abdominal mass and repair of umbilical hernia. No patients required bowel resections or low anterior resections. Among patients that underwent ICRS, the median number of cycles administered preoperatively was three (3-8 cycles). All patients received Carboplatin and Paclitaxel for neoadjuvant chemotherapy. The median age was 65 years old (50-89 years old). The median BMI was 25.1 kg/m² (19.9-33.7 kg/m²). The estimated median blood loss was 100 mL (25-500 mL). The median operative time was 5.9 hours (3.1-10.5 hours). The conversion rate to open laparotomy was 0% and no primary laparotomies were performed. Antibiotics were redosed in 42% of patients intraoperatively. The median length of stay was one day (1-5 days). There were no intraoperative complications and the readmission rate within 30 days was 4% (1 patient) for ileus and emesis, which was managed conservatively. One patient required a transfusion of one unit packed red blood cells intraoperatively secondary to low starting hemoglobin. There were no intraoperative organ injuries or hemorrhages. The perioperative mortality was 0%. At this time, 64% of the patients in the case series remain alive, the median follow-up is 4.08 years, and the median survival has not been reached.

Discussion

Optimally (< 1 cm) cytoreduced disease is a consistent predictor of survival rate, with even better results if complete (no gross residual) cytoreduction can be achieved. Optimal or complete CRS can be achieved in more than 90 percent of patients with epithelial ovarian cancer and/or intraperitoneal disease [30,31]. Cytoreduction via laparotomy remains the gold standard today; however, it is associated with substantial morbidity. This includes up to 900 mL of mean estimated blood loss, 4.6 days of mean hospital stay, and 19.5% readmission

**Table 1:** The number of surgical procedures performed during cytoreduction was collected from each operative report.

Primary (P) vs. Interval (I) Debulk	Age (years)	Body Mass Index	Number of Procedures	Operative Time (mins)	Estimated Blood Loss (mL)	Length of Stay (days)
I	50	22	6	385	50	2
I	52	25	6	381	100	1
I	55	20	7	359	50	2
I	57	25	7	408	100	1
I	59	28	7	330	25	1
I	60	20	6	376	100	1
I	63	23	6	363	150	1
I	65	25	5	350	20	1
I	65	26	7	374	100	2
I	66	31	9	396	200	2
I	68	31	5	229	100	1
I	73	21	5	274	50	2
I	74	25	6	399	250	2
I	74	33	7	627	500	4
I	77	26	4	308	200	1
I	77	26	10	465	50	4
I	79	23	4	371	75	2
I	79	30	6	185	50	1
P	51	27	7	275	50	1
P	52	21	5	328	100	1
P	57	21	10	187	30	1
P	65	23	4	228	100	3
P	69	26	8	378	200	5
P	74	25	8	286	50	1
P	89	23	4	250	150	3

rate within 30 days compared to 108 mL, 1.8 days, and 4% in our study, respectively—all factors correlated with increased patient morbidity and mortality, independent of oncologic factors [12,32].

Minimally invasive robotic surgery (MIS) is being used more frequently in the treatment of gynecologic malignancies. The robotic platform has enhanced complex minimally invasive surgery with a 3-D camera, articulating instruments, integrated table motion, and a rotating boom which facilitates four-quadrant abdominal surgery and advanced pelvic surgery. Recent studies suggest that robotic surgery may be a safe and effective alternative to open laparotomy in ovarian cancer debulking in selected patients [11,29,33]. However, even with increasing evidence of its technical non-inferiority, and potential superiority, to the standard open laparotomy, adoption rates and attitudes towards its use remain mixed. A survey of Society of Gynecologic Oncology physician members was recently published, evaluating the frequency of MIS utilization for the surgical treatment of ovarian cancer, aiming to identify how MIS was being utilized and any barriers to its adoption [13]. They found that approximately 70% of physicians in this cohort (15% of the 1551 physicians who responded) used MIS for primary staging of early ovarian cancer and interval cytoreduction in selected patients. The main cited procedures performed were hysterectomy, adnexectomy, node dissection, and omentectomy [13]. Up to 40% reported that they would like to perform more advanced minimally invasive cytoreductive procedures, such as bowel resection, low anterior resection, splenectomy and

diaphragmatic stripping [13]. The main barrier (84%) to the implementation of MIS was concern about leaving residual disease. Of note, 8-9% cited a lack of training in MIS, both laparoscopic and robotic [13].

A recent systematic meta-analysis did not identify significant differences in overall survival in patients treated with MIS versus laparotomy [14]. The authors discussed that the heterogeneity in study design, follow-up, and technique amongst surgeons makes it difficult to draw definitive conclusions due to potential biases [14]. The rates of complete disease cytoreduction were not statistically different between the two groups, and the length of hospital stay was significantly shorter in the MIS group [14]. According to the meta-analysis, the majority of studies examining the use of MIS in ovarian cancer surgery acknowledge that the feasibility of a minimally invasive approach increases in patients that have received NACT [14]. A phase III randomized trial, the Laparoscopic Cytoreduction after Neoadjuvant Chemotherapy (LANCE) trial is underway and attempts to compare outcomes of laparotomy versus minimally laparoscopic invasive surgery in patients with advanced-stage high-grade epithelial ovarian cancer [15]. Patients with imaging evidence of tumor deemed not amenable to minimally invasive resection are excluded. This imaging evidence includes diaphragmatic disease, splenic or hepatic surface disease, colon or rectal involvement, and mesenteric involvement. As such it may be difficult to compare outcomes given high selection bias and specific inclusion and exclusion criteria of patients in this study. It could be argued that in many cases the resection exclusion criteria in



the LANCE trial represent findings that would not present a barrier to robotic excision. This, of course, depends on the robotic surgery skill set available.

Neoadjuvant chemotherapy (NACT) was initially recommended by the National Comprehensive Cancer Network (NCCN) in 2012 for patients that were poor surgical candidates for PCRS. The rates of NACT with ICRS have increased due to data from randomized trials demonstrating non-inferiority with unchanged progression-free and overall survival compared to PCRS [23,34]. NACT decreases tumor burden allowing optimal cytoreduction in patients deemed to be initially inoperable. Studies demonstrated that patients who underwent NACT followed by ICRS had significantly shorter lengths of stay, lower rates of post-operative complication-related deaths, improved quality of life, shorter time to ambulation and return of intestinal function, and significantly fewer intestinal diversions compared to PCRS [1,3,5].

The majority (72%) of patients in this series received NACT, after percutaneous biopsy, prior to interval surgery. This is by the choice of the primary surgeon in the face of these patients presenting with bulky upper abdominal disease and/or significant ascites. Fagotti imaging criteria were not explicitly used in the upfront setting to determine which patients should receive NACT [35]. However, upon data review, the selection of patients that did subsequently receive NACT aligned with the Fagotti imaging criteria for NACT and ICRS in most cases [35]. It was also due to the primary surgeon's practice pattern prior to this series to approach most advanced ovarian cancer patients with NACT due to the published noninferiority data. None of the patients required bowel resections or low anterior resections which is consistent with the fact that most patients received NACT. The data presented further supports the NACT ICRS approach which may lead to the optimization of the overall quality of life in advanced ovarian cancer patients throughout their medical-surgical treatment course.

A strength of this study is that it is a consecutive, nonselected case series. Limitations of this study include the relatively small number of patients and the fact that only one surgeon performed the cytoreductive surgeries. Therefore, the results may not be readily generalizable.

Conclusion

This nonselected, consecutive case series supports the feasibility of performing robotically assisted cytoreductive surgery in patients undergoing both primary and interval cytoreductive surgery. Given the high percentage of patients that achieved complete or optimal cytoreduction in this nonselected case series, we believe that robotic cytoreduction can be considered in many, if not most, patients if surgeons with an advanced robotic skill set are available. Additional patient selection criteria are best determined locally based on this factor. Although complete or optimal cytoreduction was achieved in patients that underwent PCRS in this case

series, the majority of the patients received neoadjuvant chemotherapy. Therefore, this data mainly supports the feasibility of using robotic surgery in patients that have received NACT.

The results presented in this case series also highlight how a robotic minimally invasive approach could be equivalent—if not less—morbidity than laparotomy, allowing for faster recovery. More definitive conclusions cannot be drawn without an open laparotomy case-matched control group. Further, this study was intended to demonstrate the feasibility to achieve robotic optimal or complete cytoreduction in a nonselected series, which may serve as a partial proxy for oncologic safety. In order to fully address this question additional studies are required.

Author contributions

Conception & Design of Study: SV, ELSS, RA, NS; Data collection: RA, LS, SV, ELSS; Data Analysis & Interpretation: NS, RA, CK, SV; Responsible Surgeon or Imager: SV, ELSS; Statistical Analysis: NS, RA, SV; Manuscript Preparation: NS, SV, ELSS, CK.

Disclosure statement: Dr. Vasilev is a proctor for Intuitive Surgical and a speaker for Aspira Labs.

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