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Research Report

When we open and close: Postoperative outcomes after aborted primary cytoreduction for ovarian cancer

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ABSTRACT

Objective: Little data exists to adequately counsel patients on the postsurgical morbidity and outcomes of an aborted primary debulking (AD) for advance stage epithelial ovarian cancer. Our objectives were to examine the 30-day morbidity of AD, percentage of patients who subsequently undergo neoadjuvant chemotherapy (NACT) and interval cytoreductive surgery (ICS), residual disease at ICS, and predictors for complications after AD.

Methods: This was a single-institution retrospective analysis of patients who underwent AD for ovarian cancer from 01/2008 to 12/2020 using ICD-10 diagnoses and procedure codes. Patient demographics, perioperative metrics, and residual disease at ICS were collected. Thirty-day postoperative complications were graded by the Common Terminology Criteria for Adverse Events. Fisher's exact tests compared categorical and Wilcoxon rank-sum tests compared continuous variables. Logistic regression provided unadjusted odds ratios to identify predictors for post-AD complications.

Results: Forty-eight patients underwent AD, and 43 were included for analysis. All had at least stage IIIC high grade serous ovarian cancer. All patients subsequently underwent ICS, with 21 (48.8%) achieving no residual macroscopic disease and 21 (48.8%) to $\leq$ 1 cm of macroscopic disease. After AD, 16 (37.2%) experienced at least one G $\geq$ 3 event within the first 30 days. The most common complication was gastrointestinal complications. Preoperative albumin was the only significant predictor for G $\geq$ 3 complication after AD.

Conclusions: Approximately one-third of patients will experience at least one G $\geq$ 3 complications after AD. Complications may be anticipated by low preoperative albumin. Patients can be counseled that, after AD, proceeding to subsequent NACT and ICS and achieving optimal debulking is common.

1. Introduction

The standard treatment for advanced epithelial ovarian cancer (EOC) includes cytoreductive surgery (CRS) and platinum-based adjuvant chemotherapy. (Straubhar et al., 2020; Aletti et al., 2006; Peiretti et al., 2010; Wright, 2017; Wright et al., 2011) The volume of residual disease after CRS is a significant independent prognostic factor for overall survival. The goal of cytoreductive surgery has evolved in recent years to no visible remaining disease (complete CRS, or R0), as it affords patients the highest survival benefit. (Straubhar et al., 2020; Aletti et al., 2006; Peiretti et al., 2010; Wright, 2017; Wright et al., 2011; Rutten et al., 2015; Narasimhulu et al., 2015) Residual disease > 10–20 mm (suboptimal CRS, R2) confers minimal, if any, survival benefit (Rutten et al., 2015; Narasimhulu et al., 2015). Several prediction models utilizing clinical, biochemical, or radiologic findings alone or in combination have been proposed to diagnose disease extent and to properly refer patients to primary CRS or to neoadjuvant chemotherapy (NACT) with subsequent interval cytoreductive surgery (ICS). (Straubhar et al., 2020; Engbersen et al., 2021; Zeff, 2018; van de Vrie et al., 2019; Rutten et al., 2017; Fagotti et al., 2013) Alternatively, to assess the extent of disease prior to attempted primary CRS for ovarian cancer and to prevent suboptimal surgical resections, some investigators have evaluated the performance of diagnostic laparoscopy with associated scoring systems, such as the Fagotti score, (Zeff, 2018; van de Vrie et al., 2019; Rutten et al., 2017; Fagotti et al., 2013) and the application of the peritoneal carcinomatosis index, which has been well-studied in cancers such as

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colorectal cancers, gastric cancers, and peritoneal mesotheliomas. (Elzarkaa et al., 2018; Jónsdóttir et al., 2021; Ahmed et al., 2019) There continues to be evolving discussions regarding the optimal selection model in ovarian cancer. Although none of the models have been widely implemented or validated for triaging patients with ovarian cancer, older age, poor performance status, extensive disease burden, and low preoperative albumin are generally predictors of worse postoperative morbidity after primary CRS. (Straubhar et al., 2020; Aletti et al., 2006)

Even in patients for whom primary CRS appears feasible, gynecologic oncologists may still encounter surgical findings prompting the intraoperative decision to abort the surgery due to an inability to perform an optimal resection. These procedures are commonly referred to as aborted primary cytoreductive surgery or aborted primary debulking (AD), futile laparotomy, and "open and close" laparotomy. (Straubhar et al., 2020; Zeff, 2018) Commonly reported reasons for AD include significant bowel involvement requiring multiple resections, extensive mesenteric retraction, need for major hepatic or vascular resection, or surgeon comfort with radical surgery. (Wright et al., 2011; Zeff, 2018; Heitz et al., 2016) The rates of AD and R2 resection at primary CRS range from 5% (Straubhar et al., 2020; Straubhar et al., 2020) to 39%. (Rutten et al., 2017)

Although there are many studies on patients undergoing primary CRS for ovarian cancer, there is surprisingly little data on the specific clinical course for patients who undergo an AD. It is postulated that patients with ovarian cancer who undergo AD have poor surgical outcomes, presumably due to the large cancer burden, morbidity of an open and close surgery, and the delay in initiating subsequent therapy. However, because so little objective data exists to describe the postoperative outcomes after AD for EOC, gynecologic oncologists may find it difficult to counsel these patients about their risk of immediate postoperative complications or their chances of subsequently undergoing successful ICS.

The primary objectives of this study were to describe the 30-day postoperative morbidity of AD, the percentage of patients who subsequently undergo NACT and ICS, and the residual disease (RD) at ICS. Secondary analyses were performed to evaluate for predictors of complications after AD.

2. Methods

2.1. Ethics statement

This study was approved by the Institutional Review Board (IRB#00071620) at the University of Wisconsin School of Medicine and Public Health.

2.2. Data collection

This study was a retrospective observational cohort study. Using International Classification of Disease (ICD)-10 codes for diagnosis of ovarian cancer (C56 and C57.1–57.4) and various procedure codes for procedures used in cytoreductive surgeries during the same admission, the University of Wisconsin Clinical Research Data Service captured our institution's surgical data on patients with ovarian cancer who underwent an attempted CRS from January 2008 through December 2020. Patients who underwent AD were identified after review of their surgical history, and the number of patients were additionally confirmed by utilizing our institution's prospectively collected database (GOLD CUP – Gynecologic Oncology Longitudinal Data Collection and Utilization Program). Inclusion criteria were patients who underwent a laparotomy for aborted primary debulking during the study period. Patients were excluded if they had incomplete medical records. The study end date reflected the most up to date data for patients who had at least 6 months of follow-up after their AD.

The medical records of patients who underwent an AD were abstracted for preoperative and clinical characteristics. These included age (years), body mass index (BMI, kg/m^2), Eastern Cooperative Oncology Group (ECOG) performance status (PS), American Society of Anesthesiologist (ASA) score, preoperative CA 125 (U/dL), albumin (g/dL), and preoperative computed tomography (CT) findings including pleural effusion, ascites, carcinomatosis. Cancer staging and grading were consistent with The International Federation of Gynecology and Obstetrics guidelines. (Prat and Committee, 2014) Additional measures collected included operating room (OR) time in minutes, estimated blood loss (EBL, mL), presence of ascites at surgery (yes/no), duration of hospital stay (days), postoperative blood transfusion (yes/no), postoperative unplanned intensive care unit (ICU) stay (yes/no), 30-day unplanned readmission, surgical complication within 30 days after AD, and RD at ICS.

To retrospectively and objectively stratify our patients who eventually underwent AD into those who would have been preoperatively categorized as high-risk for post-CRS complications (and thus may have been more suitable for NACT) versus not high-risk (and thus safe to undergo primary CRS), we applied the Mayo triage algorithm (Narasimhulu et al., 2019; Jiang and Li, 2021) to each patient in our analytic cohort. This is a validated model for identifying patients with ovarian cancer at high risk for surgical morbidity and mortality (M/M) after primary CRS. (Jiang and Li, 2021) This algorithm was not utilized by our surgeons to initially triage patients to primary CRS or NACT, as the decision was made at the discretion of individual surgeons. Patients were categorized as high-risk if one of the following three criteria was met: albumin < 3.5 g/dL; age ≥ 80 years; or age 75 to 79 years with one of three additional risk factors (ECOG PS > 1 or ASA score 3–4; stage IV disease; or if the procedure will require more than hysterectomy, bilateral salpingo-oophorectomy, and omentectomy). (Narasimhulu et al., 2019)

Surgical complications within 30 days after AD were abstracted and graded according to by the Common Terminology Criteria for Adverse Events version 5.0. (Criteria, 2018) We collected complications related to: venous thromboembolism (VTE) diagnosed by imaging, abdominal infections, wound complications, gastrointestinal (GI) disturbances, and major cardiopulmonary events. Complications experienced directly due to NACT use, such as chemotherapy-induced gastrointestinal symptoms or common chemotherapy- related laboratory abnormalities, were not included to limit confounding of surgical complications with chemotherapy complications.

RD after ICS was classified as complete CRS or R0 if there was no macroscopic residual disease, optimal CRS or R1 if the macroscopic disease was ≤ 10 mm, and suboptimal CRS or R2 if the macroscopic disease was > 10 mm.

2.3. Primary and secondary analyses

The primary objective was to describe the 30-day postoperative morbidity of AD, the percentage of patients who subsequently undergo NACT and ICS, and residual disease at ICS. Secondary analyses assessed preoperative contributors to experiencing at least one grade ≥ 3 ($G \geq 3$) complication within 30 days after AD.

2.4. Statistics

Patient characteristics and postoperative outcomes were described with frequencies, medians, and interquartile ranges where appropriate. Wilcoxon rank-sum test was used for group comparisons for distributions of continuous variables and Fisher's exact test for comparisons of categorical variables. Logistic regression was used to obtain unadjusted odds ratios. Multivariate logistic models were not feasible due to the small sample size and corresponding small number of events observed. P-values < 0.05 were considered statistically significant. All statistical analyses were performed with STATA version 17.0 (College Station, TX).

3. Results

3.1. Cohort characteristics

From January 2008 to December 2020, 844 patients with ovarian cancer had cytoreductive surgeries at our institution. Of those, 48 patients (5.7%) had aborted primary debulking and a total of 43 patients met criteria for analysis after excluding five patients for incomplete medical records. Preoperative and tumor characteristics of patients included in the study were described in Table 1. All patients had at least stage IIIC high-grade serous epithelial ovarian cancers. Patients included in the study had a median age of 66 years (interquartile range [IQR] 58–73). Median preoperative CA-125 level was 760.8 U/mL (IQR 373–1,463) and albumin was 3.45 g/dL (IQR 3.3–3.8). Most patients were classified with an ECOG PS of 0 (76.7%) and an ASA score of ≤ 2 (62.8%). One (2.3%) underwent a diverting loop ileostomy at time of AD due to impending large bowel obstruction from significant tumor burden.

3.2. Primary objective

Postoperative morbidity and subsequent NACT and ICS events were described in Table 2. Over one-third (37.2%) of patients experienced a CTCAE-grade 3 and/or grade 4 surgical complication within 30 days after AD. There were no perioperative deaths. Grade 3 complications were experienced by 32.6% of patients, the most common being gastrointestinal disturbances (paralytic ileus, small bowel obstruction, and anorexia) requiring parenteral nutrition or nasogastric tubes (n = 7); one patient had upper gastrointestinal bleeding requiring transfusion. Other grade 3 complications included wound infections (n = 4), pulmonary emboli (n = 3), abdominal infections such as *Clostridioides difficile* colitis and pyelonephritis (n = 4), and cardiopulmonary events such as pneumonitis and significant pleural effusions (n = 5). Grade 4 events were seen in two patients (4.7%): one patient who developed postoperative pneumonia and required mechanical ventilation and another patient who had a fascial dehiscence that needed reoperation. All patients went on to receive NACT and ICS. After completion of neoadjuvant chemotherapy, 41 (95.3%) demonstrated radiological partial response to chemotherapy and two (4.7%) had complete response. All patients had cancer on specimens collected at time of ICS. At the time of ICS, in addition to common debulking procedures performed, such as hysterectomies, bilateral salpingo-oophorectomies, or omentectomies, there were seven (16.3%) bowel resections, seven (16.3%) splenectomies, six (14.0%) upper abdomen or diaphragm peritonectomies, and two (4.7%) cardiophrenic lymph node debulking. After ICS, 97.6% achieved R0 (48.8%) or R1 (48.8%), and one (2.3%) patient experienced a R2 resection.

Table 1
Preoperative and tumor characteristics of patients included in the study.

Characteristic	Total (n = 43)
Age (years), median (IQR)	66 (58–73)
BMI (kg/m2), median (IQR)	27.1 (21.6–33.6)
ECOG PS (#), n (%)	
0	33 (76.7)
1–2	10 (23.3)
ASA score (#), n (%)	
1–2	27 (62.8)
3	15 (34.9)
N/A	1 (2.3%)
Preoperative CA125 (U/mL), median (IQR)	760.8 (373–1,463)
Preoperative Albumin (g/dL), median (IQR)	3.5 (3.3–3.8)
CT evidence of pleural effusion, n (%)	12 (27.9)
CT evidence of ascites, n (%)	42 (97.7)
CT evidence of carcinomatosis, n (%)	40 (93.2)
High risk by Mayo criteria preoperatively, n (%)	24 (55.8)
High grade serous histology, n (%)	43 (100.0)
Stage $\geq$ IIIC, n (%)	43 (100.0)

Legend: IQR = interquartile range, BMI = body mas index, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ASA = American Society of Anesthesiologists, CT = computed tomography, N/A = not available

Table 2
Surgical outcomes after aborted debulking.

	Total (n = 43)
30-day post AD complications, n (%)	
Non-infectious gastrointestinal complication	8 (18.6)
Wound complication	4 (9.3)
Abdominal infection	4 (9.3)
Pulmonary embolism	3 (7.0)
Cardiopulmonary complication	5 (11.6)
30-day unplanned readmission	11 (25.6)
30-day unplanned reoperation	1 (2.3)
Highest CTCAE-graded complication per patient, n (%)	
Combined grade 3 and 4	16 (37.2)
Grade 3	14 (32.6)
Grade 4	2 (4.7)
Post-AD unplanned ICU stay	1 (2.33)
Subsequent NACT and ICS	43 (100)
Residual disease at interval cytoreduction	
R0	21 (48.8)
R1	21 (48.8)
R2	1 (2.3)

Legend: AD = aborted debulk, CTCAE = Common Terminology for Adverse Events, ICU = intensive care unit, NACT = neoadjuvant chemotherapy, ICS = interval cytoreductive surgery, R0 = no macroscopic residual disease, R1 = $\leq$10 mm of residual disease, R2 = >10 mm residual disease

3.3. Secondary objective

Patients with a G $\geq$ 3 complication had significantly lower preoperative albumin level (3.3 vs 3.7 g/dL, p = 0.008) when compared with those without any G $\geq$ 3 events (Table 3). There were no other significant differences between the two groups for the characteristics examined. In univariate logistic regression models, the odds ratio for preoperative albumin level was 0.13 [95% C.I. 0.2–0.67, p = 0.014] and was the only characteristic significantly associated with G $\geq$ 3 events (Table 3). Being classified as high-risk by the Mayo triage algorithm (Narasimhulu et al., 2019) was not significantly associated with complications after AD, but 75% of patients who experienced a G $\geq$ 3 complication were high-risk compared to 44% of patients who did not experience a G $\geq$ 3 complication.

4. Discussion

Following AD, over one-third of patients in our study experienced at least one CTCAE-graded G $\geq$ 3 complication within 30 days. Nonetheless, all patients subsequently underwent NACT and ICS with all but one patient achieving R0 or R1 after ICS. Low preoperative albumin appeared to be associated with experiencing at least one G $\geq$ 3 complication after AD. Being categorized as high-risk by the Mayo triage algorithm (Narasimhulu et al., 2019) was not significantly associated with post-AD complications but is clinically meaningful, as approximately 44% of patients who were retrospectively deemed appropriate for primary CRS by the Mayo algorithm did not experience a G $\geq$ 3 complication while 75% who would have been recommended for NACT did. These findings highlight that, while patients undergoing AD experience high rate of morbidity related to their procedure, they can still achieve high rate of optimal cytoreduction at ICS that is comparable to percentages of optimal CRS at ICS in published literature. (Straubhar et al., 2020; Chi et al., 2012; Vergote et al., 2010; Coleridge et al., 2021; Fagotti et al., 2020; Onda et al., 2020)

To our knowledge, this was the first study to directly examine the perioperative and subsequent outcomes of aborted primary CRS for EOC. These findings should inform gynecologic oncologists when counseling these patients about what to expect in the immediate

Table 3
Preoperative and intraoperative predictors at time of aborted debulk for patients with at least one grade 3 or higher complication after aborted debulk.

	G < 3 Complication (n = 27)	G ≥ 3 Complications (n = 16)	p-value	Unadjusted Odds Ratio (95% CI)
Age (years), median (IQR)	66 (57–73)	66 (58–72)	0.985	1.00 (0.94–1.07)
BMI (kg/m2), median (IQR)	20.19 (18.0–33.6)	28.43 (24.2–33.8)	0.165	1.03 (0.96–1.12)
ECOG PS (#), n (%)			0.182	0.34 (0.06–1.85)
0	19 (70.4)	14 (87.5)		
1–2	8 (29.6)	2 (12.5)		
ASA score (#), n (%)			0.746	0.73 (0.19–2.72)
1–2	16 (61.5)	11 (68.8)		
3	10 (38.5)	5 (31.3)		
Preoperative CA125 (U/mL), median (IQR)	797 (300.5–1400.6)	745.9 (424.3–1658.0)	0.813	1.00 (1.00–1.00)
Preoperative Albumin (g/dL), median (IQR)	3.7 (3.3–4)	3.3 (2.9–3.7)	**0.008**	**0.13 (0.2–0.67)**
CT evidence of ascites, n (%)	26 (96.3)	16 (100.0)	1.000	
CT evidence of pleural effusion, n (%)	5 (18.5)	7 (43.8)	0.077	3.42 (0.86–13.67)
CT evidence of carcinomatosis, n (%)	25 (92.6)	15 (93.8)	1.000	1.20 (0.10–14.39)
High risk by Mayo criteria preoperatively, n (%)	12 (44.4)	12 (75.0)	0.064	3.75 (0.96–14.65)
OR time (minutes), median (IQR)	143 (121.0–155.0)	136.5 (122.5–189.5)	0.936	1.09 (0.93–1.28)
Estimated blood loss (mL), median (IQR)	50 (50–100)	50 (50–130)	0.957	1.03 (0.94–1.13)
Presence of ascites at surgery, n (%)	24 (88.9)	16 (100.0)	0.282	–

Legend: bold = statistical significance $p < 0.05$, BMI = body mass index, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ASA = American Society of Anesthesiologists, CT = comuputed tomography, OR = operating room, AD = aborted debulking, R0 = no macroscopic residual disease, R ≥ 1 = any macroscopic residual disease, IQR = interquartile range, CI = confidence interval

postoperative setting after AD. In these unfortunate circumstances, patients and families can now be given information about the chances of postoperative complications and undergoing a successful NACT and ICS.

Prior to this study, the closest available data to inform gynecologic oncologists about outcomes after aborted surgeries for EOC came from patients with colorectal cancers and other non-gynecologic malignancies who underwent aborted Hyperthermic Intraperitoneal Chemotherapy (HIPEC) procedures. (Rodt et al., 2013; Guerrero et al., 2018) In one retrospective observational study, Rodt et al. (Rodt et al., 2013) reported that 9.4% of 35 patients undergoing aborted HIPEC due to disease extent experienced postoperative complications (rectal stump leakage, infected hematoma, and sepsis). Their complications were not graded, which limits comparison and extrapolation to the care of patients with EOC. Further, their patient cohort cannot be compared with our study's patients as palliative surgeries such as bowel resections or diversions were performed when clinically indicated for their patients whereas we excluded similar patients in our cohort undergoing AD. In another retrospective review of 23 patients with peritoneal surface malignancies, which included one patient with ovarian cancer, the investigators reported 13% of patients experiencing G ≥ 3 complications (by Clavien-Dindo classification) (Clavien et al., 2009) after aborted HIPEC, 9% 30-day mortality, 17% readmission, and only 48% underwent further chemotherapy. (Guerrero et al., 2018) Their low percentage of patients undergoing further chemotherapy may be related to the heterogeneity of the cancers in their study and the different treatments for those cancers. As a result, the anticipated postoperative course and outcomes cannot be fully extrapolated to the care of EOC patients.

Interestingly, in our patient cohort, over one-third experienced a G ≥ 3 complication within 30 days after AD, which is higher than reported rates of 10–26% for G ≥ 3 events after optimal primary CRS in the literature. In particular, Chi et al. (Chi et al., 2012) reported that only 10% of patients experienced G ≥ 3 complications in their retrospective review of patients who underwent primary CRS for advance stage EOC, while Bartels et al. (Bartels et al., 2019) found 21.2% G ≥ 3 complications in their *meta*-analysis of patients undergoing primary CRS for advance stage EOC. Fagotti et al. (Fagotti et al., 2020) saw 25.9% of patients experiencing G ≥ 3 complications within 30 days after primary CRS in the SCORPION trial, a superiority trial of primary CRS versus NACT and ICS for advance stage EOC. Using similar postoperative complication grading scales, these studies all reported lower rates of postoperative complications after primary CRS than our cohort who underwent AD.

There are many theoretical reasons why patients who undergo short "open and close" surgeries might experience higher morbidity. One consideration relates to the risks of performing a laparotomy on patients with active malignancy without decreasing tumor burden, as both are well-known risk factors for VTE. Lim et al. (Lim et al., 2010) reported less postoperative VTEs in patients with clear cell ovarian cancer who are optimally debulked and found fewer VTEs when compared with studies that had higher suboptimal debulking rates. It can be postulated that AD significantly increases risk of VTE, as the procedure involves a laparotomy and leaves behind tumor that have substantial thrombogenic potential. Additionally, Hunsicker et al. (Hunsicker et al., 2015) identified that removal of malignant ascites triggers an increase in fluid demand, alters circulatory blood flow, and leads to postoperative hemodynamic instability in their study of patients with EOC undergoing debulking surgery. These fluid and circulatory shifts are likely worsened after AD, as significant cancer burden is left unresected and ascites is expected to reaccumulate. Lastly, it is also important to consider that these patients are often already under significant distress from a recent ovarian cancer diagnosis and now are coping with the additional psychosocial distress associated with an unsuccessful debulking. (Cloyd and Stevens, 2021) The association between psychosocial stress and worse postoperative outcomes in patients with patients has been well described. (Rosenberger et al., 2006; Wada et al., 2020) Unfortunately, patients after AD experience many of the same postoperative symptoms as other patients do after a successful primary CRS, but, after AD, these patients still need to recover from the surgery with the knowledge that they may continue to have potentially unresectable disease at ICS. Although preexisting psychosocial factors prior to AD and psychosocial outcomes after AD were not collected here and may be an area of future study, our data can potentially provide surgeons with evidence to better counsel patients regarding their chances at successful ICS after AD.

Strengths of our study include using data over 13 years from a high-volume ovarian cancer surgery center with a rate of R0 and R1 at primary CRS comparable to those reported contemporary literature. In our institution, our rate of R0 and R1 resection was 91.6%. Chi et al reported a 71% optimal debulking rate in their cohort of patients who underwent primary CRS. (Chi et al., 2012) In a single institution randomized trial of primary CRS versus NACT for advanced EOC, the investigators reported a 92.8% optimal cytoreduction rate at primary CRS at their institution. (Fagotti et al., 2020) Given our comparable CRS rates at primary debulking, our AD results may also be comparable to cancer centers like our own. Our study is also enhanced by the completeness of follow-up data for our patients due to a prospectively collected database

Limitations include the small sample size and the single-institutional nature of our study. A larger sample size would allow us to examine characteristics together in multivariate models and provide the power to

examine long-term survival outcomes. Our findings are also constrained by the inherent limitations of retrospective and descriptive studies. Our study only included patients with advance stage and high grade serous EOC. As such, the data does not permit generalizability to other types of epithelial ovarian cancers. The 30-day postoperative complications described in the study included those most likely to have occurred as a result of AD, but the chance that these complications were confounded by NACT use cannot be fully excluded as all patients received NACT.

In conclusion, after performing an aborted primary CRS, gynecologic oncologists can counsel patients that there is a high chance they may experience at least one grade 3 or higher postoperative complication, even though the extent of the surgery performed is small. Low preoperative albumin level appears to increase the risk of $G \geq 3$ complications after AD. Despite an anticipated complicated postoperative course after AD, surgeons can now reassure their patients that there is still a high likelihood of proceeding to and undergoing successful subsequent cytoreduction at ICS.

CRediT authorship contribution statement

Connor C. Wang: Conceptualization, Methodology, Data curation, Writing – original draft. **Matthew K. Wagar:** Data curation, Writing – review & editing. **Amy Godecker:** Methodology, Formal analysis, Writing – review & editing. **Ahmed Al-Niaimi:** Data curation, Writing – review & editing. **David M. Kushner:** Conceptualization, Methodology, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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