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Survival impact of bowel resection at the time of interval cytoreductive surgery for advanced ovarian cancer

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ABSTRACT

Objectives: To evaluate the impact of bowel resection at the time of interval cytoreductive surgery on survival. *Methods*: We identified patients with advanced ovarian cancer who underwent neoadjuvant chemotherapy and interval cytoreductive surgery between 2008 and 2018 from a single-institution tumor registry. Kaplan-Meier survival analysis and Cox proportional hazards models were performed comparing patients who underwent bowel resection to those who did not.

Results: Of 158 patients, 43 (27%) underwent bowel resection. Rates of optimal (95%) and sub-optimal (5%) resection did not differ with bowel resection. Patients that required bowel resection had worse three-year survival (43% vs. 63%), even after adjusting for confounding variables of age, stage, number of neoadjuvant cycles, R0 resection, and ASA score (HR 2.27, p < 0.01). Adjusted progression-free survival did not differ between groups (HR 0.92, p = 0.72). Patients who underwent bowel resection were more likely to require blood transfusion (p < 0.01), and have a longer hospital stay (5 days vs 7.5 days, p < 0.01).

Conclusions: Bowel resection at the time of interval cytoreduction confers a greater than 2-fold increased risk of mortality and does not impact progression-free survival. Long-term sequelae of the *peri*-operative morbidity of bowel resection may contribute to increased mortality, and bowel resection may be a surrogate for disease biology with poor prognosis.

1. Introduction

Advanced ovarian cancer is the leading cause of death from gynecologic malignancy in the United States and other developed countries (Howlader et al., 2017). More than 75% of women with epithelial ovarian carcinoma present with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or stage IV disease, and the five-year survival rate remains low for advanced disease (Torre et al., 2018).

Historically, the standard of care for ovarian cancer involved aggressive primary debulking surgery followed by adjuvant chemotherapy. However, since 2010, three large randomized control trials have demonstrated the non-inferiority of neoadjuvant chemotherapy prior to cytoreductive surgery for advanced disease (Kehoe et al., 2015; Fagotti et al., 2016; Vergote et al., 2010), and the utilization of preoperative chemotherapy followed by interval cytoreductive surgery has subsequently increased (Meyer et al., 2016; Meyer et al., 2018). The

use of neoadjuvant chemotherapy has allowed for improved rates of optimal cytoreduction as well as decreased post-operative complications and morbidity (Fotopoulu et al., 2017).

Residual disease after cytoreductive surgery is the strongest independent prognostic factor for recurrence and survival (Vergote et al., 2010). To achieve minimal residual disease; bowel resection during cytoreductive surgery is often necessary. Rates of bowel resection at the time of primary cytoreduction are as high as 40–80% (Gockley et al., 2019; Peiretti et al., 2012). In contrast, bowel resection rates are reported to range from 8 to 49% in patients undergoing interval cytoreduction (Kehoe et al., 2015; Vergote et al., 2010; Tozzi et al., 2018; Philip et al., 2016). The morbidity of a bowel resection can be significant—the risk of an anastomotic leak is 0.8–10% per anastomosis (Peiretti et al., 2012; Kalogera et al., 2013) and bowel resections are associated with higher blood loss; longer hospital stays; increased readmission within 30 days, dehydration, and delays to adjuvant

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chemotherapy (Tozzi et al., 2018; Richardson et al., 2006; Fournier et al., 2018; Mourton et al., 2005). Existing studies demonstrate that with increases in the number of required bowel resections for patients undergoing primary surgery, survival worsens (Kalogera et al., 2013; Grimm et al., 2017). Despite the risks of bowel resection associated with cytoreductive surgery in ovarian cancer, there is minimal outcome data on the impact that bowel resection at the time of interval cytoreduction has on survival for patients with advanced ovarian cancer (Philip et al., 2016). We conducted a single institution retrospective cohort study to evaluate the impact of bowel resection on disease progression and survival in this population.

2. Methods

A tumor registry at a single academic institution was accessed for all cases of ovarian cancer that received chemotherapy prior to cytoreductive surgery. All patients diagnosed with stage IIIC or IV ovarian, tubal, or peritoneal cancer between 2008 and 2018 who underwent interval cytoreductive surgery were initially included. Patients who underwent minimally invasive interval cytoreduction were excluded from our analysis as none of these patients had a bowel resection. Medical records, including operative reports, hospital, and clinic notes were reviewed. Data on neoadjuvant chemotherapy course, operative and post-operative factors, and adjuvant chemotherapy course were abstracted. Surgeon description of residual disease at the start of a cytoreductive procedure was used to qualify disease as significant, moderate, or minimal. Pathology reports were abstracted to collect the largest size of extra pelvic disease post-chemotherapy. Follow-up data was available through March 2020.

The primary outcome was overall survival between patients who did and did not undergo bowel resection at the time of interval cytoreduction, with a secondary outcome of progression free survival. Three years was chosen as an end point as approximately 60% of our cohort did not have follow-up beyond 3 years. Overall survival was defined as the time from initiation of pre-operative chemotherapy to death or last contact. Progression-free survival was defined as the time from starting pre-operative chemotherapy and subsequent progression or recurrence of disease. Additional secondary outcomes were rates of optimal cytoreduction and *peri*-operative complications.

Patients who underwent bowel resection were compared to those who did not using Wilcoxon rank-sum and Pearson's chi-squared tests; the Kaplan Meier method was used to analyze overall and progressionfree survival. The American Society of Anesthesiologist (ASA) score was used as a proxy for pre-operative performance status, which has been validated for use with oncology patients (Young et al., 2015). Cox proportional hazard ratios were modeled controlling for clinical elements that could independently influence survival (age, stage, ASA score, number of cycles of pre-operative chemotherapy, and R0 resection). Continuous variables were grouped as follows: cycles of preoperative chemotherapy as 3 or fewer, 4-6, and 7 or more; age was grouped as <60, 60-70, and >70; stage was dichotomized between IIIC and IV. All analyses were performed using statistical software STATA 13.0 and 95% confidence intervals were used for presentation of all variables. A two-sided 5% type I error rate was used for all of our statistical analyses.

This study was approved by our institution's Human Research Protection Program Institutional Review Board protocol ID#19-29072. The requirement for individual Research HIPAA Authorization was waived for all subjects. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

3. Results

The tumor registry identified 219 patients diagnosed between January 2008 and December 2018, of which 195 met the broad

inclusion criteria, and 158 underwent open interval cytoreduction.

A total of 44 out of 195 (23%) patients were scheduled for a minimally invasive interval cytoreduction, and 37 (84%) of these were completed laparoscopically, resulting in a 16% conversion rate. Table 1 describes patient characteristics by interval cytoreductive technique. Patients who underwent laparoscopic cytoreduction were more likely to have stage IV disease (p = 0.017) and were more likely to be overweight (p = 0.02). No laparoscopic cases had suboptimal resections or bowel resections. Median duration of laparoscopic cases was shorter by 63 min compared to open (p < 0.01). Due to these inherent differences in patient populations, and that no laparoscopic cases involved bowel resections, the 37 patients who underwent laparoscopic interval cytoreduction were not included in the remainder of the analysis presented here.

Patient and tumor characteristics by bowel resection are shown in Table 2. The groups were similar, without any major differences in age, stage, histology, pre-operative albumin levels, or ASA status. Patients who underwent bowel resection had lower BMI (p=0.02).

Forty-three (27%) patients underwent at least one bowel resection. All bowel resections were performed due to disease burden. A majority (n = 27, 62.8%) of patients who underwent bowel resection required rectosigmoid resections; 11 (25.6%) required other large bowel resections (transverse or descending colon), and few (n = 5, 11.6%) required small bowel resections. Of patients who underwent bowel resection, 6 (14%) required 2 or more resections and only two (4.6%) required diverting loop ileostomies. The number of cycles of preoperative chemotherapy did not impact the risk of requiring bowel resection. In a logistic regression model controlling for stage, odds ratio for bowel resection was 0.71 (p = 0.37) for patients receiving 4–6 cycles compared to 3 or fewer, and 2.1 (p = 0.39) for those who received 7 or more cycles.

Table 3 describes immediate surgical outcomes and complications for patients with and without bowel resection. Patients who required bowel resection were more likely to have significant residual disease after neoadjuvant chemotherapy (p < 0.001) as described in surgeon operative reports. Rates of upper abdominal procedures including diaphragmatic stripping, liver resection, and splenectomy did not differ between cohorts (p = 0.64). Rates of optimal and R0 cytoreduction did not differ between groups. Median surgical time was 120 min longer for cases that involved bowel resection (p < 0.01). Patients who underwent bowel resection had higher rates of some *peri*-operative surgical complications (Table 4). Estimated blood loss was higher among patients who underwent bowel resection (p < 0.001), they were more likely to

Table 1Patient characteristics by interval cytoreductive technique.

| | <u> </u> | | |
|-------------------------------------|--------------------------------|---------------------------------------|--------|
| | Open cytoreduction $(n = 158)$ | Laparoscopic cytoreduction $(n = 37)$ | P |
| Median age (years) | 63.5 (56–71) | 65 (59–69) | 0.75 |
| Median BMI | 25 (21-27) | 28 (23-32) | 0.02 |
| Median ASA score | 3 (2–3) | 3 (2–3) | 0.48 |
| Clinical FIGO stage | | | |
| IIIC | 90 (57%) | 13 (35%) | 0.02 |
| IV | 68 (43%) | 24 (65%) | |
| Residual disease at time of IDS | | | |
| No residual (R0) | 94 (60%) | 26 (70%) | 0.26 |
| Residual < 1 cm | 56 (35%) | 11 (30%) | |
| Residual > 1 cm | 8 (5%) | 0 (0%) | |
| Median procedure time* (minutes) | 404 (302–505) | 341 (271–383) | < 0.01 |
| Median # NAC cycles | 3 (3–4) | 4 (3–6) | 0.08 |
| | | | |

Data are median (IQR) or n(%).

^{*}Procedure time measured from skin incision to closure.

Table 2Description of pre-operative population characteristics by bowel resection requirement.

| requirement. | | | | |
|----------------------------|-----------------|---------------------------------|--------------------------------------|-------------|
| | Total $N = 158$ | Non-bowel resection $(n = 115)$ | 1 or more bowel resection $(n = 43)$ | P value* |
| Median age (years) | 64 (56–71) | 63 (56–71) | 64 (56–70) | 0.96 |
| Age group | | | | |
| <60 | 56 (36%) | 40 (35%) | 16 (37%) | 0.93 |
| 60–70 | 62 (39%) | 45 (39%) | 17 (40%) | |
| >70 | 40 (25%) | 30 (26%) | 10 (23%) | |
| Median BMI | 25 (22–27) | 25 (22–28) | 22 (21–26) | 0.02 |
| Median pre-op | 3.8 | 3.8 (3.4-4) | 3.65 (3.2-4.1) | 0.44 |
| albumin | (3.3-4) | | | |
| Median ASA score | 3 (2–3) | 3 (2–3) | 3 (2–3) | 0.58 |
| Clinical FIGO stage | | | | |
| IIIC | 90 (57%) | 61 (53%) | 29 (67%) | 0.10 |
| IV | 68 (43%) | 54 (47%) | 14 (33%) | |
| Histology | | | | |
| High-grade | 128 | 93 (85%) | 35 (85%) | 0.99 |
| serous | (85%) | 93 (8370) | 33 (6370) | 0.55 |
| Others† | 22 (15%) | 16 (15%) | 6 (15%) | |
| ' | (,-) | () | - () | |
| Primary disease site | 100 | TO ((00)) | 00 (700/) | 0.05 |
| Ovary | 109 (70%) | 79 (69%) | 30 (73%) | 0.85 |
| Fallopian Tube | 23 (15%) | 17 (15%) | 6 (15%) | |
| Peritoneal | 23 (15%) | 18 (16%) | 5 (12%) | |
| Median # NAC cycles | 3 (3–4) | 4 (3–4) | 3 (3–4) | 0.60 |
| Grouped NAC cycles | | | | |
| 3 or fewer | 79 (59%) | 56 (49%) | 23 (53%) | 0.34 |
| 4–6 | 72 (46%) | 55 (48%) | 17 (40%) | |
| 7 or more | 6 (4%) | 3 (2%) | 3 (7%) | |
| NAC chemotherapy | | | | |
| Regimen | 1.40 | 104 (010/) | 00 (000/) | 0.01 |
| Carboplatin/ Paclitaxel | 142 | 104 (91%) | 38 (88%) | 0.91 |
| | (90%) | E (404) | 2 (E0/) | |
| Carboplatin/ Docetaxel | 7 (4%) | 5 (4%) | 2 (5%) | |
| Other | 9 (6%) | 6 (5%) | 3 (7%) | |
| Onici | 2 (070) | 0 (0/0) | 5 (7 /0) | |

Data are median (IQR) or n(%). ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index (kg/m^2) ; FIGO, International Federation of Gynecology and Obstetrics.

require blood transfusion (p < 0.01), and had longer post-operative hospital stays (p < 0.01). Rates of ICU admission post-operatively, organ space infections, and rates of post-operative ileus trended higher the bowel resection cohort, but the difference was not significant. The hazard ratio (HR) for composite post-operative complications (ICU stay, ileus, surgical injury, and post-operative infection) with bowel resection was 2.83, [p < 0.01, 95% confidence interval (CI) 1.4–4.9]. Sixty-day and ninety-day mortality was low overall, with only one patient dying within 60 and 90 days of surgery; this patient did not undergo bowel resection. A large majority of patients went on to receive adjuvant chemotherapy (n = 144, 97%); time to starting post-operative chemotherapy and the regimens used did not differ between cohorts.

Over a median follow-up of 34 months (range 6–140 months), 132 (85%) patients experienced disease recurrence, and 95 (60%) died. Overall survival was worse among patients that required bowel resection (Fig. 1): their 3-year survival rate was 43%, compared to 63% for patients who did not undergo bowel resection. While median survival was 32 months for the bowel resection group, it has not been met at 3 years for the non-bowel resection group. The uncontrolled hazard ratio

Table 3 Peri-operative details and outcomes.

| | Total N = 158 | Non-bowel resection | 1 or more bowel resection | P |
|--|--------------------|------------------------|---------------------------------|---------|
| | | (n = 115) | (n = 43) | |
| Extent of disease after NACT | | | | |
| Minimal residual disease | 24 (16.6%) | 24 (22.6%) | 0 (0.0%) | < 0.001 |
| Moderate residual disease | 58 (40.0%) | 48 (45.3%) | 10 (25.6%) | |
| Significant residual disease | 63 (43.4%) | 34 (32.1%) | 29 (74.4%) | |
| Size of largest extra- pelvic implant | 3 (0.6–5.25) | 2.1 (0.5–5) | 3.95 (2.8–6.85) | 0.009 |
| Upper abdominal surgery required | | | | |
| Diaphragm ablation/ stripping | 26 (76%) | 13 (72%) | 13 (81%) | 0.64 |
| Liver resection Splenectomy | 4 (12%) 4 (12%) | 2 (11%) 3 (17%) | 2 (12%) 1 (6%) | |
| Residual disease at | | | | |
| time of IDS | | | | |
| No residual (R0) | 94 (60%) | 66 (58%) | 28 (65%) | 0.43 |
| Residual < 1 cm | 56 (35%) | 44 (38%) | 12 (28%) | |
| Residual > 1 cm | 8 (5%) | 5 (4%) | 3 (7%) | |
| Median procedure | 404 | 379 | 498 | < 0.01 |
| time* (minutes) | (302–505) | (293–445) | (422–587) | |
| Median hospital stay (days) | 5 (4–7) | 5 (4–6) | 7.5 (6–9) | < 0.01 |
| Adjuvant | | | | |
| chemotherapy (AC) | 4 (00/) | 0 (00/) | 1 (00/) | 0.00 |
| No adjuvant | 4 (3%) | 3 (3%) | 1 (2%) | 0.88 |
| therapy Adjuvant | 144 (91%) | 103 (89%) | 41 (95%) | |
| chemotherapy | 177 (9170) | 103 (0970) | 71 (2370) | |
| Missing data | 10 (6%) | 9 (8%) | 1 (2%) | |
| Median time to AC | 42 (29–59) | 42 (29–55) | 42 (29–65) | 0.49 |
| (days) | .2 (2) (3)) | (_, 00) | .2 (25 00) | 0 |
| Median # AC cycles | 3 (3–4) | 3 (3–4) | 3 (3–4) | 0.84 |
| AC regimen | | | | |
| Carboplatin/ Paclitaxel | 112 (79%) | 78 (76%) | 34 (83%) | 0.19 |
| Carboplatin/ Docetaxel | 5 (3%) | 5 (5%) | 0 (0%) | |
| Cisplatin/ Paclitaxel | 5 (3%) | 5 (5%) | 0 (0%) | |
| Carboplatin/ Gemcitabine | 11 (8%) | 6 (6%) | 5 (12%) | |
| Other | 10 (7%) | 8 (8%) | 2 (5%) | |

Data are median (IQR) or n(%).

for death with bowel resection was 1.80 (p $=0.03,\,95\%$ CI 1.05 – 3.05). After controlling for confounding variables such as age, stage, number of neoadjuvant cycles, R0 resection, and ASA score, the hazard ratio for death in the bowel resection group over three years was 2.27 (p $<0.01,\,95\%$ CI 1.2–4.2).

Progression-free survival, however, did not significantly differ between groups (Fig. 2). The median progression-free survival was 15 months in the bowel resection group and 16 months among the non-bowel resection group. The uncontrolled hazard ratio for recurrence or progression over the first three years after treatment initiation was $1.00\ (p=0.98,95\%\ CI\ 0.67–1.48)$. The hazard ratio after controlling for confounders was $0.92\ (p=0.72,95\%\ CI\ 0.58–1.45)$.

4. Discussion

Our study demonstrates that bowel resection at the time of interval

^{*}P values are calculated using Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables.

 $[\]dagger Of$ the 22 women with other histologies, 2 had clear cell carcinoma, 2 had endometrioid, 1 had carcinosarcoma, and 17 had non-specified Mullerian carcinoma

^{*}Procedure time measured from skin incision to closure.

Data are median (IQR) or n(%).

Table 4 Peri-operative complications.

| | Total | Non-bowel resection | 1 or more bowel resection | P |
|--|------------------|------------------------|---------------------------|---------|
| | N = 158 | (n = 115) | (n = 43) | |
| Estimated blood loss | 500 (300–850) | 400 (200–700) | 800 (500–1350) | < 0.001 |
| Units of blood transfused | | | | |
| 0 | 52 (35%) | 44 (40%) | 8 (20%) | 0.04 |
| 1-2 | 58 (39%) | 42 (39%) | 16 (40%) | |
| 3-4 | 25 (17%) | 16 (15%) | 9 (23%) | |
| 5 or more | 14 (9%) | 7 (6%) | 7 (18%) | |
| Post op ICU admission | | | | |
| No | 130 (82.3%) | 98 (85.2%) | 32 (74.4%) | 0.11 |
| Yes | 28 (17.7%) | 17 (14.8%) | 11 (25.6%) | |
| Organ-space SSI | | | | |
| No | 155 (98.1%) | 114 (99.1%) | 41 (95.3%) | 0.12 |
| Yes | 3 (1.9%) | 1 (0.9%) | 2 (4.7%) | |
| Ileus | | | | |
| No | 152 (96.2%) | 111 (96.5%) | 41 (95.3%) | 0.73 |
| Yes | 6 (3.8%) | 4 (3.5%) | 2 (4.7%) | |
| 60-day post- operative mortality | 1 (0.5%) | 1 (0.5%) | 0 (0%) | 0.54 |
| 90-day post- operative mortality | 1 (0.5%) | 1 (0.5%) | 0 (0%) | 0.54 |

cytoreduction is associated with significantly worse three-year survival and increased surgical morbidity among women with stage IIIC or IV ovarian cancer. Bowel resection is not associated with a difference in progression-free survival over the same time period. We observed a greater than two-fold increased hazard ratio for death over three years among patients who underwent bowel resection during interval cytoreductive surgery (HR 2.27), with an equivalent risk of recurrence (HR 0.92). We also observed that patients who undergo bowel resection are 2.83 times more likely to have a post-operative complication than those that do not. Rates of additional upper abdominal procedures were not

different between cohorts (p=0.64), so do not explain this difference. These findings suggest that post-operative complications related to bowel resection and their sequelae, and not disease recurrence and progression, may contribute to the observed increased risk of death among the bowel resection group.

Our findings are comparable to previously published studies about mortality (Kalogera et al., 2013; Grimm et al., 2017) and peri-operative morbidity (Tozzi et al., 2018; Richardson et al., 2006; Fournier et al., 2018; Mourton et al., 2005) after bowel resection during primary cytoreductive surgery. Our findings contribute to the small body of literature on the impact of bowel resection at the time of interval cytoreduction. One observational study by Philip et al. in 2016 evaluated 97 patients at a single institution who underwent pre-operative chemotherapy followed by interval cytoreduction (Philip et al., 2016). In their sample, nearly half of patients required bowel resection at time of interval surgery. They demonstrated that there was a negative impact of bowel resection on overall survival; however, this difference persisted but lost significance when considering only patients who underwent optimal cytoreduction. This study had a small sample size and a high rate of suboptimal cytoreduction (34%). It is possible that our results are similar but with higher significance due to our larger sample size and higher rate of optimal cytoreduction.

Our study has a few important limitations to consider. These data are observational and the sample size is relatively small; a priori analysis indicated that we would need a sample of 704 patients to find a statistically significant result for overall survival over the entire study period. Despite this, our primary outcome of difference in overall survival was significant with a p value of <0.01. As we included patients in our analysis with diagnoses as recent as December 2018, we have only 2 years of follow-up data for a minority of our patients. By limiting our analysis to 3 years after starting treatment for all subjects, we minimized any time-window bias that may have otherwise impacted our findings (Suissa et al., 2011). However, with our small sample size, it is possible that a difference in progression-free survival between groups was masked.

Some authors argue for universal laparoscopic evaluation at the time of diagnosis with a disease burden scoring system to triage patients who would most benefit from pre-operative chemotherapy; (Fagotti et al., 2016) however, this approach is not our current practice due to the financial and logistic implications of scheduling surgeries for the appropriate duration and maximizing operating room use. Our general

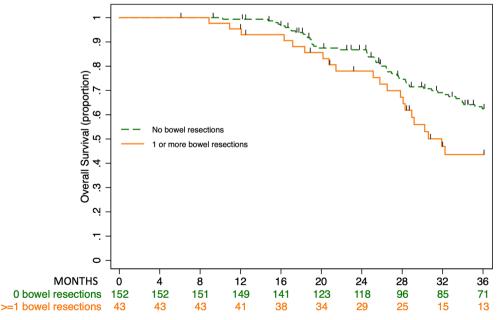


Fig. 1. Overall Survival by Bowel Resection.

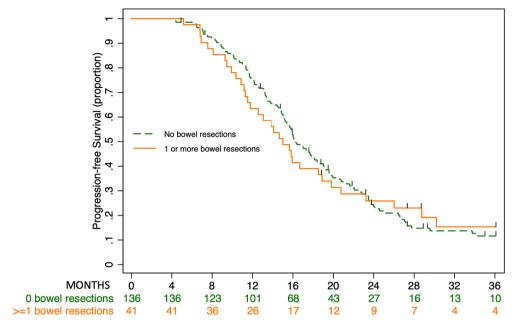


Fig. 2. Progression Free Survival by Bowel Resection.

approach is to offer primary cytoreductive surgery for healthy patients who have radiographic evidence of disease amenable to optimal cytoreduction. Our group's approach, which is the practice of many hospital systems, should be taken into consideration when considering the results presented here.

Other recent data has suggested that inferior response to neoadjuvant chemotherapy corresponds to decreased progression-free survival (Cohen et al., 2019). While we did find that patients who required bowel resection were more likely to have worse disease burden after neoadjuvant chemotherapy (p < 0.001), the equivalency of progression-free survival among our bowel resection and non-bowel resection cohorts is notable and may be related to our high rates of optimal cytor-eduction. As overall survival is relatively long in ovarian cancer, the impact of time to first recurrence may not reflect the overall health impact of surgery during the entire trajectory of the disease course. Additionally, although existing research suggests that surgical complications delay the start of adjuvant chemotherapy (Castro et al., 2018), our study demonstrated no difference in time to post-operative chemotherapy for patients who underwent bowel resection.

These data suggest that post-operative complications of bowel resection may be an important driver of survival. Our study demonstrates increased post-operative complications (HR 2.83, (p < 0.01)) among patients who underwent bowel resection. Additionally, rates of organ-space SSI, which are an imperfect marker and likely underestimate the incidence of anastomotic leak after bowel resection (Rickles et al., 2013), were low overall, but were twice as likely to occur among patients who had bowel resection (1% vs 5%, p = 0.12). Recent studies have examined the impact of allogeneic red blood cell transfusion on recurrence and survival among patients undergoing surgery for ovarian cancer, with overall mixed results (Zhang et al., 2020; Hunsicker et al., 2019; Pergialiotis et al., 2020). Given that our bowel resection cohort was much more likely to receive a blood transfusion (p < 0.01), consideration of this impact is warranted if transfusion of blood products is ultimately determined to be an independent predictor of worse recurrence and survival.

These differences may contribute to the long-term survival differences between bowel resection and non-bowel resection cohorts. Hypoalbuminemia is a known independent predictor of post-operative complication and poor survival prior to both primary and interval cytoreductive surgery (Ataseven et al., 2015; Dai et al., 2020). While pre-operative albumin was not statistically different between our bowel

resection and non-bowel resection cohorts, it trended lower among those patients who ultimately needed a bowel resection. Efforts to optimize albumin prior to cytoreduction may lend themselves to improved survival for patients who undergo bowel resection, and is one area of potential further inquiry. Additionally, as the immune system impacts response to cancer treatments in various ways (Turner et al., 2016), further evaluation of the interaction between the morbidity of surgery and survival may identify opportunities for intervention.

We did not find that more cycles of pre-operative chemotherapy significantly impacted the rates of bowel resection at interval cytoreduction, although this may have been due to insufficient power. Recent studies have demonstrated a survival benefit to giving more than the standard three cycles of chemotherapy if it enables a complete cytoreduction at interval surgery; (Phillips et al., 2018; Plett et al., 2020) however, giving five or more cycles may convey worse prognosis even with maximal cytoreduction (Liu et al., 2020). There may be further benefit to giving additional cycles if patients have a response to initial cycles of neoadjuvant chemotherapy yet are thought to remain at high risk for requiring a bowel resection. With the understanding that some genetic subtypes of ovarian cancer may have a more modest chemotherapy response (Murakami et al., 2016), additional neoadjuvant cycles may not always reduce residual disease at the time of surgery.

Additionally, we recognize that an improved genetic and molecular understanding of epithelial ovarian cancer has identified molecular subtypes (such as mesenchymal) that are associated with more invasive disease, worse response to chemotherapy, and an overall worse prognosis (Konecny et al., 2014). While we do not have molecular subtyping for our cohort, bowel resection may be a surrogate marker for a more aggressive molecular tumor profile and the clinical impacts of molecular subtypes warrants further investigation.

Bowel resection remains a necessary intervention to achieve complete cytoreduction after neoadjuvant chemotherapy in many patients. Although rates of bowel resection have decreased for interval compared to primary cytoreduction, operative morbidity remains significantly higher for patients who require bowel resection compared to those who patients do not. In this cohort, we demonstrated an increased risk of mortality over three years among patients who underwent bowel resection, without an impact on progression-free survival. Further study in a larger cohort with a focus on understanding the risk factors associated with and specific health impacts of bowel resection, as well as contributions of molecular subtype, may improve our understanding of

the associations identified in this project and provide us with the data to mitigate the risks of bowel resection.

CRediT authorship contribution statement

Blair McNamara: Conceptualization, Data Curation, Formal analysis, Methodology, Writing - original draft, Writing- review & editing. Rosa Guerra: Conceptualization, Methodology, Writing- review & editing. Jennifer Qin: Data curation, Writing- review & editing. Amaranta D. Craig: Data curation, Formal analysis, Software, Writing-review & editing. Lee-may Chen: Supervision, Writing- review & editing. Madhulika G. Varma: Methodology, Supervision, Writing- review & editing. Jocelyn S. Chapman: Conceptualization, Formal analysis, Methodology, Supervision, Writing- original, Writing- review & editing.

Synopsis

Bowel resection at the time of interval cytoreductive surgery for advanced ovarian cancer is associated with a 2-fold increased risk of surgical mortality over three years, with no impact on progression-free survival.

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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