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Should mucosal bowel invasion in ovarian cancer be assigned to FIGO stage IV disease?

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HIGHLIGHTS

- Depth of recto-sigmoid colon wall invasion does not correlate with prognosis in EOC.
- EOC patients with superficial bowel invasion tended to have more upper abdominal or miliary disease.
- Mucosal recto-sigmoid invasion should not be assigned to stage IV disease.

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ABSTRACT

Objectives. The FIGO staging consensus agreement from 2012 indicates that bowel mucosal invasion for epithelial ovarian cancer (EOC) should be assigned to stage IV disease. Finding no evidence justifying this recommendation, we examined the impact of recto-sigmoid colonic invasion on survival based on depth of invasion.

Methods. Patients having recto-sigmoid resection to achieve complete gross resection for stage IIIC/IV EOC between 2003 and 2011 were included. For this study, mucosal invasion alone was not considered as stage IV. Degree of bowel invasion was defined as: serosal/subserosal vs. muscularis/submucosa/mucosa. Patients with only mesenteric invasion were excluded. Intraperitoneal disease (IP) dissemination patterns were defined as pelvic, lower abdomen, upper abdomen, and miliary disease. Comparisons between groups were evaluated using the log-rank test for progression-free and overall survival (PFS, OS) and the chi-square test for IP dissemination pattern.

Results. Eighty-five patients were included with a mean age of 64.5 years. Most cases were serous (87.1%) and stage IIIC (83.5%). There were 53 (62.4%) patients with serosal/subserosal and 32 (37.6%) with muscularis/submucosa/mucosa invasion. Although not statistically significant, PFS and OS both favored cases with deeper invasion (muscularis/submucosa/mucosa vs. serosal/subserosal invasion: median PFS, 33.5 vs. 18.2 months, $p = 0.34$; median OS, 82.3 vs. 51.5 months, $p = 0.46$). When comparing patterns of disease dissemination, we observed that patients with serosal/subserosal invasion (vs. those with deeper invasion) tended to have more upper abdominal or miliary disease (67.9% vs. 48.4%, $p = 0.08$).

Conclusions. Depth of recto-sigmoid colon wall invasion does not have prognostic significance. Our observations do not support assignment to a higher FIGO stage (IV) based solely on this factor.

1. Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecologic cancer in the USA, but has the highest mortality rate [1]. Although EOC patients with early stage have an excellent prognosis, most patients are diagnosed in advanced stage and have a poor outcome [2]. In spite of achieving a good initial response to treatment with surgery and chemotherapy, most patients will recur. In addition to residual disease, the International Federation of Gynecology and Obstetrics (FIGO) stage is an important prognostic factor [3,4] and is often useful in counseling and assigning treatment. In order to provide better treatment options, there has been tremendous effort in the last decade to understand the

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biology and tumor characteristics of EOC anticipating that this would translate into more effective treatment modalities. Currently, however, these are not included in the current staging system.

The ideal staging system allows a standardized communication between the providers, delivers prognostic information, and enables a well-balanced clinical trial design between the arms. Cancer staging advances as scientific developments occur. EOC staging was updated in 2012 by the FIGO committee; in this latest version, transmural bowel infiltration with mucosal invasion is classified as stage IVB [5]. However, the data regarding the prognostic implication of bowel invasion in EOC is limited. There have been a few studies that showed poorer prognosis with deep bowel invasion however, those studies had significant limitations including heterogeneous study cohort and amounts of residual disease and limited sample size [6,7]. In the present study, we sought to analyze whether deeper bowel invasion has prognostic value. We restricted the analysis to cases who underwent debulking surgery including recto-sigmoid resection for a complete gross resection to eliminate the bias of residual disease. Given the importance of molecular subtype in disease spread, we further investigated the correlation between depth of bowel invasion and disease dissemination patterns in the peritoneal cavity.

2. Methods

This is a single institution, retrospective cohort study that included EOC patients with FIGO stage IIIC and IV. The study was approved by Mayo Clinic institutional review board. Patients who had no residual disease at the end of surgery and who underwent recto-sigmoid resection as part of debulking surgery for EOC, primary peritoneal cancer or fallopian tube cancer between 1/2/2003 and 12/30/2011 were included. Patients were identified from a prospectively maintained surgical ovarian cancer database. Patients who underwent neoadjuvant chemotherapy, who had any macroscopic disease at the end of surgery, patients with mesenteric involvement without any bowel wall invasion, or patients who denied access to medical charts were excluded. Appendectomy alone was not considered as large bowel resection.

Depth of bowel invasion was defined in two ways. In the first method, patients were separated into two groups based on depth of invasion. The first group included patients with serosal invasion up to the subserosa. The second group consisted of patients with deeper invasion to the muscularis, submucosa or mucosal layer of recto-sigmoid colon. In the second method, patients were divided into three groups; serosa/subserosal vs. muscularis vs. mucosal/submucosa. Depth of bowel invasion was extracted from pathology reports. For patients who did not have specific depth of invasion information in the report, pathology slides were pulled and re-reviewed by an experienced gynecologic pathologist (YH).

Definition of intraperitoneal (IP) dissemination patterns were described previously [8]. Briefly, patients with stage III disease and operative stage IV disease were divided into four categories; pelvic, lower abdomen, upper abdomen, and military disease. Criteria for assignment to each category were presented in Supplementary Table 1. A gynecologic oncology physician (DT) reviewed the operative reports and assigned each patient into one category. Inter-observer variability was tested and validated previously [8]. The following variables were abstracted from the medical records: date of birth, date of primary debulking surgery, body mass index, American Society of Anesthesiologists (ASA) score, preoperative albumin, FIGO grade and stage, histology, concomitant surgical procedures, data and location of recurrence, vital status, and date of last follow-up or death. Surgical complexity was assigned using previously published methods and classified as low, intermediate, or high complexity surgery [9].

The Kaplan-Meier method was used to estimate progression-free and overall survival (PFS, OS) following primary debulking surgery. Comparisons between depth of invasion groups were evaluated using the log-rank test for PFS, OS and the Fisher's exact test or chi-square test for IP dissemination pattern and surgical complexity. All calculated p values were two-sided and p values <0.05 were considered statistically significant. SAS version 9.4 package (SAS Institute, Inc.; Cary, NC) was used for the analysis.

3. Results

Between 2003 and 2011, 617 patients underwent primary debulking surgery for stage IIIC and IV EOC. Among 617 patients, 107 patients had a large and/or small bowel resection without any residual disease at the end of surgery. Eighty-five patients met inclusion criteria and had recto-sigmoid resections and were included. Mean age of the study cohort was 64.5 and the majority of patients had serous EOC (87.1%). The remainder of the demographic and clinical characteristics of the 85 patients in the study cohort population is presented in Table 1. Regarding depth of invasion, 53 patients (62.4%) had serosal/subserosal invasion and 32 (37.6%) patients had deep (muscularis/submucosa/mucosa) invasion. For patients who had a separate large bowel segment resection in addition to recto-sigmoid colon, none of these patients had deeper invasion than the recto-sigmoid invasion ($n = 8$).

Among the 85 patients, 47 deaths have been documented at the time of medical record review and the median time to last follow-up for the remaining 38 patients was 4.9 years (interquartile range, 3.1–6.5 years). The long-term outcomes were not significantly different between the two depth of invasion groups (Fig. 1; PFS, $p = 0.34$; OS, $p = 0.46$). However, the median PFS and OS were longer among women with deeper invasion (muscularis/submucosa/mucosa) compared to those with serosal/subserosal invasion (median PFS, 33.5 vs. 18.2 months; median OS, 82.3 vs. 51.5 months). When we further divided patients into three categories based on depth of invasion, there were 53 patients in serosa/subserosal, 15 patients in muscularis, and 17 patients in mucosal/submucosa group. There were no statistical differences in PFS ($p = 0.62$) or OS ($p = 0.15$, Supplementary Fig. 1) between the groups but we again observed the longest median PFS and OS in cases with deepest invasion.

Eighty-four patients had IP dissemination pattern data available for analysis. Among patients serosal/subserosal invasion, the majority of

Table 1
Demographic and clinical characteristics.

Characteristic	$N = 85$
Age (years), mean (SD)	64.5 (12.2)
BMI (kg/m^2), mean (SD)	27.9 (6.1)
BMI (kg/m^2)	
<25.0	30 (35.3)
25.0–29.9	26 (30.6)
30.0–34.9	16 (18.8)
≥35.0	13 (15.3)
ASA score ≥ 3	29 (34.1)
Preoperative albumin (g/dL)	
≥3.5	48 (56.5)
<3.5	10 (11.8)
Not available	27 (31.8)
FIGO grade	
2	4 (4.7)
3	80 (94.1)
Not recorded	1 (1.2)
FIGO stage	
IIIC	71 (83.5)
IV	14 (16.5)
Histology	
Non-serous	11 (12.9)
Serous	74 (87.1)
Surgical complexity	
Intermediate	29 (34.1)
High	56 (65.9)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.
Results are reported as N (%) unless otherwise noted.

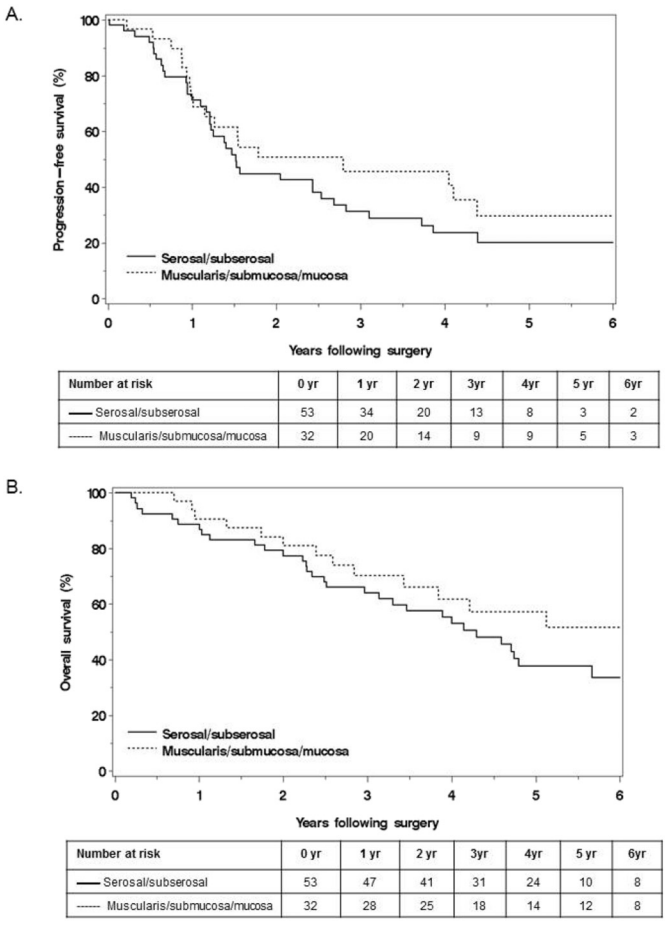

Fig. 1. Progression-free (A) and overall (B) survival by depth of bowel invasion.

the patients had upper abdominal disease (54.7%, Table 2). Miliary pattern of disease was more common in women with serosal/subserosal disease (13.2%) compared to those with deeper invasion (3.2%), although not significant given the size of the groups ($p = 0.25$). Overall, patients with serosal/subserosal invasion were more likely to have upper abdominal or miliary disease compared to patients with muscularis/submucosa/mucosa invasion, though this did not reach statistical significance (67.9% vs. 48.4%, odds ratio 2.26 [95% CI 0.91–5.61], $p = 0.08$). Upon comparing surgical complexity between the two groups, we observed that high surgical complexity was more common among patients with serosal/subserosal invasion vs. muscularis/submucosa/mucosa invasion (71.7% vs. 56.3%); however this difference did not reach statistical significance ($p = 0.15$).

4. Discussion

Our data show that deeper recto-sigmoid colon wall invasion is not associated with a worse surgical outcome when all disease is resected.

Table 2
Disease distribution pattern of patients by depth of bowel invasion.

Intraperitoneal dissemination pattern	Depth of bowel invasion	
	Serosal/subserosal $N = 53$	Muscularis/ = submucosa/mucosa $N = 32$
Pelvic	6 (11.3)	3 (9.7)
Lower abdominal	11 (20.8)	13 (41.9)
Upper abdominal	29 (54.7)	14 (45.2)
Miliary	7 (13.2)	1 (3.2)

Results are reported as N (% of non-missing); intraperitoneal dissemination pattern was missing for 1 patients in the muscularis/submucosa/mucosa group.

In addition, there does not appear to be a strong association between depth of bowel wall invasion and disease dissemination patterns. In fact, patients with deeper bowel invasion were less likely to have upper abdominal or miliary disease, and we have previously shown that patients with abdominal or miliary disease have poorer OS compared to those with other patterns of intraperitoneal dissemination [12]. Overall we did not find any evidence to support that deep or mucosal invasion should be used solely as a criterion for stage IV disease. We cannot comment on the prognostic influence when residual disease is left in situ, but this further highlights the benefit of complete resection in cases with bowel invasion.

There are a few studies investigating the prognostic value of depth of bowel invasion in EOC. Di Giorgio et al., analyzed 52 EOC patients who underwent primary ($n = 30$) or secondary cytoreduction ($n = 22$) and all underwent hyperthermic intraperitoneal chemotherapy after surgery [7]. Their group divided the depth of invasion into three groups; serosal, muscular, and mucosal invasion. In addition to complete resection, depth of colorectal invasion was independently associated with prognosis and patients with deeper invasion had worse 5-year survival ($p = 0.004$) [7] and none of the patients with mucosal invasion were alive at 5 years. In another study, Park et al. evaluated 60 patients with EOC (46 primary and 14 recurrent) who underwent low anterior resection divided patients into two groups; invasion up to serosa/subserosal and up to muscle or mucosa layer [6]. Their study demonstrated that patients with serosa/subserosal invasion had longer disease-free survival ($p = 0.01$) but OS was not different between the groups ($p = 0.08$) [6]. Contrary to these two studies, we have shown that deeper recto-sigmoid invasion was not associated with worse survival outcomes. The important differences in these studies include smaller sample size, inclusion of primary and recurrent disease, inclusion of cases with residual disease, and the types of postoperative therapy. We designed our study to minimize confounding factors known to be associated with survival (i.e. excluded patients with gross residual disease and only included patients with primary debulking surgery) to specifically examine the impact of depth of bowel invasion.

There has been a continual evolution of the goal of primary surgery toward complete gross resection as this is associated with better outcomes in multiple studies [3,10–12]. Upper abdominal disease is associated with lower rates of complete resection [8,13]. Furthermore, patients with upper abdominal or miliary disease patterns are more likely to have a mesenchymal molecular subtype of EOC [8,13]. Mesenchymal subtype has been shown to be independently associated with poorer OS [14,15]. In our study, patients with serosal/subserosal invasion actually had worse survival outcomes, although not statistically significant. This might be explained by IP dissemination patterns as patients with superficial invasion of the bowel tended to have more upper abdominal or miliary disease (67.9% vs. 48.4%, $p = 0.08$), and we have previously shown that patients with upper abdominal or miliary disease patterns have poorer OS [12]. Additionally we did not observe any correlation between depth of bowel invasion and complexity of surgery.

There are some limitations of our study. We did not perform a centralized pathology review of all cases; however all cases were initially reviewed by a gynecologic pathologist. Any cases missing a detailed description of the depth of bowel wall invasion were reviewed by an experienced gynecologic pathologist for the present study. We chose to focus on recto-sigmoid resection because of its prevalence and importance in EOC, but this means we did not specifically measure the effect in other colonic or small bowel resections. However, our data demonstrated that recto-sigmoid depth of invasion was deeper than other sites of bowel invasion when multiple segments were resected which supports this analysis. Strengths include relatively homogenous study population lacking significant other confounders such as residual disease and evaluating only primary disease, which is the setting for initial staging that would be assigned. All patients were treated at a single institution with a standard approach to management of advance stage EOC.

In conclusion, our data does not support assignment of deeper bowel invasion to stage IV disease: this may be important in future consensus and staging deliberations. We see no reason to exclude cases with deep invasion on study protocols for patients who would otherwise be considered stage IIIC disease.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.018.

Conflict of interest statement

All authors declare no conflict of interest.

Author contribution

Ismail Mert, William A. Cliby and Amanika Kumar conceived the idea, designed the study, analyzed the data and prepared the manuscript. Diogo Torres categorized the dissemination patterns of the entire study cohort. Yajue Huang reviewed the pathology slides and determined the depth-of-bowel invasion. Amy L. Weaver and Michaela E. McGree performed the statistical analysis, participated in data analysis and writing of the manuscript.

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