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# Multiple large bowel resections: Potential risk factor for anastomotic leak ☆,☆☆

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## HIGHLIGHTS

- Multiple large bowel resections increased the risk of anastomotic leak (AL) and protective diverting stomas decreased the risk.
- AL patients had longer length of stay and were less likely to start chemotherapy.
- AL patients tended to have higher 90-day mortality and were more likely to have poorer overall survival.

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## ABSTRACT

*Objectives.* Identify risk factors of anastomotic leak (AL) after large bowel resection (LBR) for ovarian cancer (OC) and compare outcomes between AL and no AL.

*Methods.* All cases of AL after LBR for OC between 01/01/1994 and 05/20/2011 were identified and matched 1:2 with controls for age (±5 years), sub-stage (IIIA/IIIB; IIIC; IV), and date of surgery (±4 years). Patient-specific and intraoperative risk factors, use of protective stomas, and outcomes were abstracted. A stratified conditional logistic regression model was fit to determine the association between each factor and AL.

*Results.* 42 AL cases were evaluable and matched with 84 controls. Two-thirds of the AL had stage IIIC disease and >90% of both cases and controls were cytoreduced to <1 cm residual disease. No patient-specific risk factors were associated with AL (pre-operative albumin was not available for most patients). Rectosigmoid resection coupled with additional LBR was associated with AL (OR = 2.73, 95% CI 1.13–6.59, $P = 0.025$), and protective stomas were associated with decreased risk of AL (0% vs. 10.7%, $P = 0.024$). AL patients had longer length of stay ($P < 0.001$), were less likely to start chemotherapy ($P = 0.020$), and had longer time to chemotherapy ($P = 0.007$). Cases tended to have higher 90-day mortality ($P = 0.061$) and were more likely to have poorer overall survival (HR = 2.05, 95% CI 1.18–3.57, $P = 0.011$).

*Conclusions.* Multiple LBRs appear to be associated with increased risk of AL and protective stomas with decreased risk. Since AL after OC cytoreduction significantly delays chemotherapy and negatively impacts survival, surgeons should strongly consider temporary diversion in selected patients (poor nutritional status, multiple LBRs, previous pelvic radiation, very low anterior resection, steroid use).



## Introduction

Ovarian cancer (OC) is widely recognized as a systemic disease given its propensity to disseminate along peritoneal surfaces, frequently involving the bowel and extending to the upper abdomen. Most patients (up to 70%) will present with advanced stage disease [1,2]. Primary cytoreductive surgery followed by platinum- and taxane-based chemotherapy constitutes current standard treatment [3]. Despite advances in surgical techniques and systemic chemotherapy over the past 3 decades, ovarian cancer remains the leading cause of cancer death among women with gynecologic malignancies [4] with 5-year disease-free survival rates not exceeding 30% [5].

*Abbreviations:* OC, ovarian cancer; LBR, large bowel resection; AL, anastomotic leak; BMI, body mass index; LOS, hospital length of stay; TTC, time to chemotherapy; OS, overall survival; RD, residual disease; RSR, rectosigmoid resection.

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An increasing number of studies report a significant survival improvement with cytoreduction to microscopic residual disease (RD) compared to the current definition of "optimal" cytoreductive surgery (RD ≤1 cm) [6–10]. In order to achieve maximal cytoreduction, extensive surgery, including large bowel resection (LBR), may be required.

A well-recognized complication of LBR is anastomotic leak (AL) which, although infrequent, can be a catastrophic event associated with significant morbidity, mortality and increased hospital costs. Rates of AL range from 0.8% to 6.8% in the gynecologic oncology literature [11–15]. In colorectal literature, published mortality rates associated with AL range from 6% to 22% [16–21]. Historically, AL was thought to only impact 30-day mortality and not long-term colon cancer survival [22,23], however, more contemporary studies indicate that an AL portends a significant reduction in long-term survival as well [24–28]. Although the impact of AL in the long-term survival of OC patients has not been previously studied, the consequences of AL and the resultant delay in chemotherapy in a cancer where approximately 95% of patients will require adjuvant chemotherapy may be substantially more detrimental than in colorectal cancer patients.

Patient-specific and intraoperative factors have been shown to independently predict AL after LBR in colon cancer patients and include poor nutritional status (preoperative albumin <3.0 g/dL), compromised physical status (ASA score 3 or 4), alcohol and steroid use, smoking, obesity, prior bevacizumab receipt, previous pelvic irradiation, operative time more than 2 h, intra-operative septic conditions, peri-operative blood transfusion, and most importantly, distance of anastomosis from the anal verge [17,29–38]. The limited number of studies in the OC patient population have shown that previous pelvic irradiation, poor nutritional status and distance of anastomosis from the anal verge are all important factors, with a very low anastomosis being the most reproducible and significant risk factor [14,15,39–42].

In comparison to colorectal literature, there is a relative paucity of data examining risk factors and short- and long-term outcomes of AL in OC. Given the profound impact that AL carries in OC patients additional information to guide peri-operative decision making on diverting stomas is needed. We thus sought to identify factors contributing to AL after LBR during cytoreductive surgery. Secondarily we aimed to compare short- and long-term outcomes between OC patients who suffered a post-cytoreduction AL and matched control patients without AL.

## Methods

After obtaining approval by the Institutional Review Board of Mayo Foundation, all patients who underwent LBR with primary anastomosis during cytoreductive surgery for primary or recurrent OC (including fallopian tube and primary peritoneal cancer, collectively referred to as OC for this study) between January 1, 1994 and May 20, 2011 at the Mayo Clinic were identified. Medical records including operative reports were reviewed by the authors and all cases of AL were identified. We defined AL as follows: 1) feculent fluid from drains, wound, or vagina, 2) definitive radiographic evidence of extravasation at the anastomotic site, or 3) AL found at reoperation. Cases of isolated pelvic abscesses near the anastomotic site with no proven communication with the bowel lumen were not included. AL cases were matched 1:2 with cases of LBR for OC without AL (controls) on date of birth (±5 years), stage (IIIA/IIIB; IIIC; IV), and date of surgery (±4 years).

Patient-specific risk factors (including age, body mass index (BMI), ASA score, diabetes mellitus, use of tobacco, preoperative albumin, preoperative hemoglobin, history of abdominal and/or pelvic surgery), intraoperative risk factors (including type of LBR (rectosigmoid resection (RSR) alone, RSR coupled with an additional LBR, isolated non-pelvic LBR), perioperative RBC transfusion, end-operative body temperature, operative time), creation of diverting protective stomas at initial surgery, and outcomes (including hospital length of stay (LOS), ability to start chemotherapy, time to chemotherapy (TTC), 30- and 90-day mortality, overall survival (OS)) were abstracted. Patients were followed until death or last follow-up. Patients were considered positive for tobacco use if they were smokers at time of surgery or if they had quit less than 10 years prior to surgery. Continuous variables were dichotomized as follows: BMI ≥ 35 kg/m$^2$ (WHO classes II and III obesity), ASA ≥ 3, preoperative albumin <3.0 g/dL, preoperative hemoglobin <10 g/dL and end-operative body temperature ≤36 °C.

The distribution of each factor was summarized using standard descriptive statistics, separately for the cases and controls. For each factor of interest, a separate stratified conditional logistic regression model was fit to evaluate the association between the factor and case/control status, thereby taking into account the matching between the cases and controls. The functional form of BMI, end-operative body temperature, and operative time were first evaluated using smoothing splines. Each was identified as having a linear relationship with the probability of being a case and was therefore analyzed as a continuous measure. A stratified Cox proportional hazards regression model was fit to compare OS between AL cases and controls. Statistical analysis to compare OC patients with LBR with protective stoma vs. patients with LBR with no stoma included Chi-square test for categorical variables and Wilcoxon rank sum test for continuous variable. OS between stoma and no stoma patients was compared using the Wilcoxon test. All calculated *P*-values were two-sided and *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc., Cary, NC).

## Results

There were 43 cases of AL among the 725 cases of LBR with primary anastomosis performed during the study period. Among the 43 AL cases, 42 were included in our study cohort and matched 1:2 with controls. The single case of excluded AL had no matched controls due to unique factors (age, stage, era of surgery). Distribution of stage and RD in cases vs. controls is summarized in Table 1A. Over 90% of the AL cases had stage IIIC or IV disease. More than 90% of both cases and controls were debulked to ≤1 cm RD, with 33.3% of the cases and 34.2% of the controls having no gross RD. Specific data on RD were not available in 2 controls. Among those who had an AL, 54.8% underwent RSR alone (vs. 70.2% of controls), 38.1% underwent RSR coupled with an additional LBR (vs. 19.1% of

**Table 1**
Distribution of stage and residual diseases; A. AL cases vs. controls; B. Stoma vs. no stoma patients.

| A. | Cases (n = 42) | Controls (n = 84) | *P*-value[a] |
|---|---|---|---|
| Stage | | | – |
| III, IIIA, IIIB | 4 (9.5%) | 8 (9.5%) | |
| IIIC | 27 (64.3%) | 54 (64.3%) | |
| IV | 11 (26.2%) | 22 (26.2%) | |
| Residual disease[b] | | | 0.81 |
| 0 cm | 14 (33.3%) | 28 (34.2%) | |
| 0–1 cm | 24 (57.2%) | 47 (57.3%) | |
| >1 cm | 4 (9.5%) | 7 (8.5%) | |
| **B.** | **Stoma (n = 9)** | **No stoma (n = 75)** | ***P*-value[c]** |
| Stage | | | 0.56 |
| III, IIIA, IIIB | 0 (0%) | 8 (10.7%) | |
| IIIC | 6 (66.7%) | 48 (64%) | |
| IV | 3 (33.3%) | 19 (25.3%) | |
| Residual disease | | | 0.48 |
| 0 cm | 3 (33.3%) | 25 (39.1%) | |
| 0–1 cm | 6 (66.7%) | 32 (50%) | |

[a] *P*-value from a univariate conditional logistic regression model.
[b] Missing data on residual disease in 2 controls.
[c] Categorical variables: Chi-square test.