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Surgical Implications of Mesenteric Lymph Node Metastasis From Advanced Ovarian Cancer After Bowel Resection

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Background: Studies addressing mesenteric and mesocolic lymph node metastasis in patients with advanced ovarian cancer that have undergone bowel resection are lacking.
Methods: A retrospective analysis was performed in a series of 50 individuals who underwent surgical cytoreduction for epithelial ovarian cancer that included bowel resection from April 2004 to September 2010.
Results: Forty-one patients had bowel resection with mesenteric lymph nodes that were suitable for analysis. Twenty-four (58.5%) patients underwent retosigmoidectomies, 14 (34.1%) received other types of colectomies, and three (7.3%) underwent small bowel resection. There was serosal involvement in 14 cases (34.1%), muscularis propria invasion in 13 cases (31.7%), submucosa invasion in six cases (14.6%), and mucosa in eight cases (19.5%). Lymphatic invasion was observed in 24 patients (58.5%). A median of 14 mesenteric lymph nodes were analyzed. Metastatic lymph nodes were observed in 29 (70.7%) cases. Invasion into the muscularis propria ($P = 0.036$), lymphatic invasion ($P = 0.045$), and retroperitoneal lymph node metastasis ($P = 0.002$) correlated significantly with mesenteric lymph node involvement.
Conclusions: Resection of regional lymph nodes of affected organs that is similar to surgical procedures that are performed for colorectal carcinoma is an appropriate, optimal debulking surgery for patients with ovarian carcinoma.
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KEY WORDS: ovarian cancer; bowel resection; lymph node metastasis

INTRODUCTION

Ovarian cancer is the leading cause of death from gynecological malignancies in the western world [1]. Retrospective and prospective studies of patients with epithelial ovarian cancer (EOC) with advanced disease have shown that better survival rates correlate with residual tumors that are <1 cm [2–6], even in a neoadjuvant chemotherapy setting [7]. Recent reports have suggested that complete macroscopic disease resection should be the desirable surgical outcome [8–12]. Because the majority of the patients is diagnosed with advanced disease due to peritoneal carcinomatosis and because the gastrointestinal tract is frequently involved, more extensive procedures that include bowel resections might be required [13–21] to achieve optimal cytoreduction.

The standard surgical treatment for colorectal and small bowel cancer is resection of regional lymph nodes in the mesocolon or mesentery. This procedure, which adds a 5-cm normal bowel-free margin, increases overall survival and has a negative impact on locoregional recurrences [22,23]. Lymph node metastasis in colorectal cancer has high prognostic significance and dictates the adjuvant treatment [24].

Patients with advanced ovarian cancer and bowel involvement might experience an alternative pathway of dissemination that resembles the lymphatic spread of primary bowel tumors. For such patients, however, the most appropriate technique for bowel mesentery management is unknown. The aim of our study was to retrospectively analyze the incidence of mesenteric and mesocolic lymph node metastasis in patients with ovarian cancer who have undergone bowel resection and correlate with clinicopathological features.

MATERIALS AND METHODS

This retrospective analysis included a series of 50 individuals with both primary and recurrent ovarian epithelial cancer who were admitted to the Department of Gynecologic Oncology, A.C. Camargo Cancer Hospital, from April 2004 to September 2010. All patients underwent surgical cytoreduction that included bowel resection, only 41 patients had mesenteric or mesocolic lymph nodes that were suitable for analysis.

All pathology slides were reviewed. The clinical features that were analyzed were: age, FIGO stage, segment of bowel that was resected, pelvic and retroperitoneal lymph node dissection, type of cytoreduction that was performed, and amount of residual disease (Table I). The pathology data included: histological type, grade, extent of bowel invasion, presence of necrosis in the implant, presence of lymphatic invasion in the implant, mesenteric lymph node involvement, and pelvic or retroperitoneal involvement (Table II). Follow-up time was considered to span the date of surgery to the last date on which information was available.

The database was generated in SPSS, version 16.0 (SPSS,

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TABLE I. Clinical Characteristics

Variable	No. of patients	%
Median age	59 years (range: 25–80 years)	
FIGO stage		
IIIA	1	2.4
IIIB	3	7.3
IIIC	33	80.5
IV	4	9.8
Time of surgery		
Primary cytoreduction	11	26.8
Secondary cytoreduction	30	73.2
Size of residual disease		
No residual disease	27	65.9
Disease $\leq$1 cm	11	26.8
Disease >1 cm	2	4.9
Bowel resected		
Small bowel	3	7.3
Colon	14	34.1
Rectosigmoid	24	58.5
Pelvic lymphadenectomy		
No	25	61
Yes	16	39
Retroperitoneal lymphadenectomy		
No	23	56.1
Yes	18	43.9

Inc., Chicago, IL) for Mac. The association between lymph node metastasis and other variables was assessed by chi-square test. For all tests, an alpha error up to 5% ($P < 0.05$) was considered significant.

TABLE II. Pathological Characteristics of the 41 Patients With Bowel Resections Suitable for Lymph Node Analysis

Variable	No. of patients	%
Tumor histology		
Serous	37	90.2
Mucinous	2	4.9
Endometrioid	2	4.9
Depth of invasion		
Serosal involvement	14	34.1
Muscularis propria	13	31.7
Submucosa	6	14.6
Mucosa	8	19.5
Lymphovascular invasion		
Absent	17	41.5
Present	24	58.5
Histological grade		
Grade 1	2	4.9
Grade 2	13	31.7
Grade 3	26	63.4
Implant with necrosis		
No	14	34.1
Yes	27	65.9
Mesenteric metastasis		
No	12	29.3
Yes	29	70.7
Pelvic node metastasis		
No	8	50
Yes	8	50
Retroperitoneal node metastasis		
No	9	50
Yes	9	50

RESULTS

Forty-one patients had at least one bowel resection with mesenteric lymph nodes that were suitable for analysis. The median age was 59 years (range: 25–80 years). All patients had epithelial cancer, and 37 patients (90.2%) patients had serous histology. One subject (2.4%) had FIGO stage IIIA disease, three (7.3%) had stage IIIB, 33 (80.5%) had stage IIIC, and four (9.8%) had stage IV. After a median follow-up of 10.8 months, 21 (51.2%) patients relapsed, and 10 (24.4%) died from the disease.

Primary cytoreduction was performed in 11 patients (26.8%), and secondary cytoreduction was performed in 30 (73.2%). Thirty-eight (95%) patients achieved optimal cytoreduction, and no visible disease remained in 27 subjects (67.5%). Regarding bowel resections, 24 patients (58.5%) underwent retosigmoidectomies, 14 (34.1%) received other colectomies, and three (7.3%) underwent small bowel resection.

Of the bowel specimens, 14 cases (34.1%) had serosal-only involvement, 13 cases (31.7%) had invasion of the muscularis propria, six cases (14.6%) had submucosal invasion, and eight cases (19.5%) had mucosa (Fig. 1). Of all subjects, lymphatic invasion was demonstrated in 24 patients (58.5%, Fig. 2). Implant necrosis was present in 27 patients (65.9%). High-grade histology was observed in 25 patients (61%).

Eighteen patients (43.9%) also underwent retroperitoneal lymph node dissection, wherein a median of 26 nodes were resected (range: 2–57), nine (50%) of whom had metastatic retroperitoneal involvement. Sixteen (39%) underwent pelvic lymph node dissection, for a median of 19.6 nodes (range: 1–44), and eight patients (50%) had metastatic lymph nodes.

A median of 14 mesenteric or mesocolic lymph nodes were analyzed (range: 1–123). Metastatic mesenteric or mesocolic lymph nodes were present in 29 (70.7%) cases (Fig. 3), which had a median of three positive lymph nodes (range: 1–117).

Primary cytoreduction, serous histology, presence of implant necrosis, and grade 3 tumors were statistically unrelated to mesenteric lymph node metastasis. Histological grade did not correlate with depth of invasion or presence of lymphatic invasion.

Of patients with invasion into the muscularis propria, 75.9% had positive mesenteric lymph node metastasis versus 24.1% of patients with tumors that were limited to the serosa ($P = 0.036$). Lymphatic invasion was present in 69% of patients with mesenteric lymph node metastasis ($P = 0.045$). Concomitant retroperitoneal lymph node metastasis was present in 81.8% of patients with mesenteric lymph node metastasis who underwent retroperitoneal dissection and in

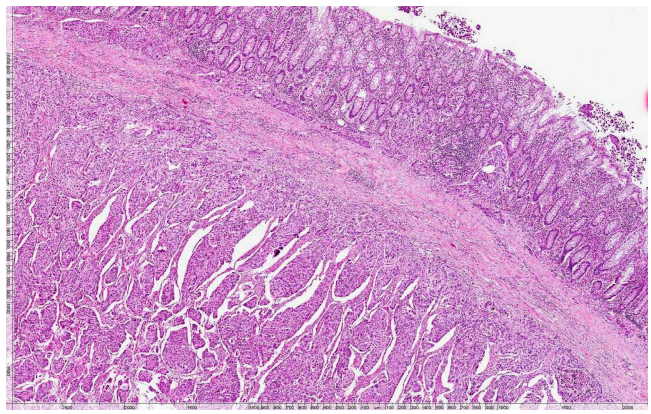

Fig. 1. Low-power microphotograph aspect of ovarian cancer showing bowel invasion into mucosa (4×).

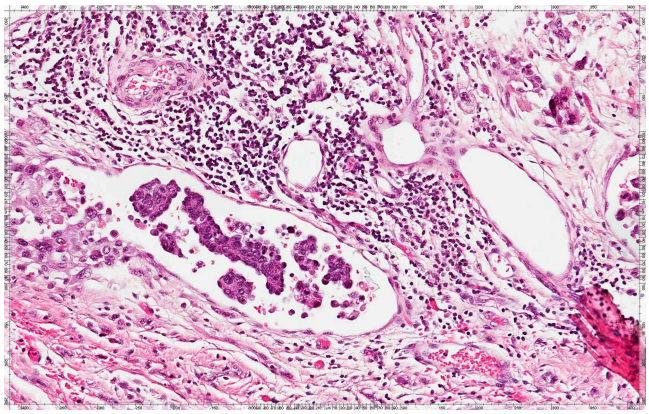

Fig. 2. Microphotograph aspect of lymphovascular space invasion (20×).

18.2% of patients with no retroperitoneal involvement ($P = 0.002$, Table III).

Presence of lymphatic invasion correlated with depth of invasion; a 70.4% lymphatic invasion rate was observed when the tumor invaded the muscularis propria versus 35.7% when the tumor was confined to the serosa ($P = 0.033$).

TABLE III. Mesenteric Lymph Node Status and Correlation With Clinicopathological Features

	Mesenteric lymph node metastasis—n (%)		
Variable	Absent 12 (29.3%)	Present 29 (70.7%)	*P* value
Depth of invasion			
Serosal involvement	7 (50)	7 (50)	0.036
Muscularis propria	3 (23.1)	10 (76.9)	
Submucosa	1 (16.7)	5 (83.3)	
Mucosa	1 (12.5)	7 (87.5)	
Type of cytoreduction			
Primary	4 (33.3)	7 (24.1)	0.70
Secondary	8 (66.7)	22 (75.9)	
Histology			
Serous	9 (75)	28 (96.6)	0.068
Nonserous	3 (25)	1 (3.4)	
Lymphatic invasion			
Presence	4 (33.3)	20 (69)	0.045
Absence	8 (66.7)	9 (31)	
Tumor with necrosis			
Presence	8 (66.7)	19 (65.5)	1.0
Absence	4 (33.3)	10 (34.5)	
Histological grade			
Grade 3	8 (66.7)	17 (58.6)	0.73
Grades 1 and 2	4 (33.3)	12 (41.4)	
Pelvic lymph node metastasis			
Presence	1 (16.7)	7 (70)	0.11
Absence	5 (83.3)	3 (30)	
Retroperitoneal lymph node metastasis			
Presence	0 (0)	9 (81.8)	0.002
Absence	7 (100)	2 (18.2)	

DISCUSSION

Since the seminal report by Griffiths et al. [25], several studies have demonstrated that the amount of residual tumor after cytoreductive surgery correlates well with progression-free and overall survival rates [2–12]. When adequate cytoreduction is achieved, median survival nearly doubles [26], and for each 10% increase in maximal cytoreduction, median survival time increases by approximately 6.0% [27].

Although there is a consensus regarding the importance of maximal surgical effort, the value of pelvic and retroperitoneal lymphadenectomy for advanced ovarian cancer is debated. In advanced ovarian cancer, the rate of node involvement ranges from 55% to 75% [28]. Serous histology and high-grade tumors have the highest incidence of node metastasis [28]. Although retrospective studies have demonstrated a therapeutic effect of systematic lymphadenectomy [29–34], Panici et al. [35], the only prospective randomized trial for advanced ovarian cancer, noted that patients who underwent systematic lymphadenectomy rather than lymph node debulking had improved progression-free survival rates but unchanged overall survival.

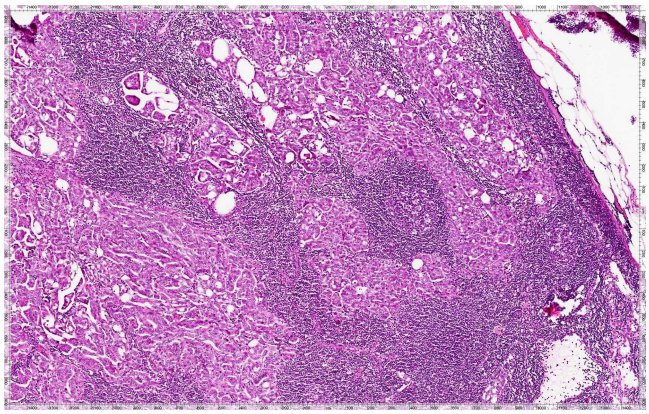

Fig. 3. Microphotograph aspect of mesenteric lymph node metastasis due to high-grade serous ovarian cancer (10×).

Because advanced-stage ovarian cancer usually involves the pelvic and abdominal organs, more extended surgical procedures might commonly be required, such as posterior pelvic exenteration, pelvic and diaphragmatic peritoniectomy, splenectomy, and bowel resection [36]. Retosigmoidectomy is the most common surgical procedure that is performed when an intestinal resection is required to achieve optimal cytoreduction [20] and effects acceptable morbidity rates [20,37,15,38,39]. Aggressive surgical resections do not indicate the worst prognosis when the outcomes are adjusted for residual disease [36], and the amount of residual disease that is associated with radical procedures is an independent predictor of survival [38].

As ovarian cancer spreads onto the peritoneal surface, the tumor implants usually involve serosal visceral organs [40] and subsequently invade the intestinal wall. Wu et al. [41] observed invasion into the mucosa in 21% of cases. Dvoretsky et al. [42] analyzed 100 autopsies and noted wall invasion in 74% of small bowels and 71% of large bowels. They documented a 47% rate of mesenteric lymph node metastasis and observed that the retroperitoneal lymph node was a common site of metastasis. The group suggested that the retroperitoneal lymph node metastasis was due directly to mesenteric lymph node involvement.

There are little data on the frequency of mesenteric or mesocolic lymph node metastasis. O'Hanlan et al. [43] evaluated 33 large and small bowel specimens and observed lymph node metastasis in 72.7% of cases, in which there was a correlation with lymph-vascular space invasion but not with grade or depth of invasion.

Scarabelli et al. [18] reported a series of 66 patients who underwent retosigmoid colon resection for advanced ovarian cancer. All

patients experienced invasion of the muscularis propria, resulting in a 37.9% rate of mesocolic lymph node metastasis. Notably, 63.6% of patients with bowel wall infiltration and positive mesocolic lymph nodes developed hepatic recurrence.

Salani et al. [44] also reported 39 patients with rectosigmoid colon involvement with mesocolic lymph nodes that were suitable for analysis. They observed a 79.5% rate of mesocolic involvement, which correlated with retroperitoneal metastasis and with any degree of bowel invasion. However, the risk of metastasis was not associated with an increasing of depth of invasion. They did not evaluate lymphatic invasion.

Our series had a 70.7% rate of mesenteric or mesocolic lymph node metastasis, which correlated statistically with invasion into the muscularis propria and lymphatic invasion. We propose a pathway of dissemination, in which the tumor invades the intestinal wall, accesses the lymphatic channels, and embolizes to the mesenteric lymph nodes. We also observed a link between mesenteric lymph node involvement and retroperitoneal involvement. Although not all patients underwent retroperitoneal and pelvic lymphadenectomy, a route of dissemination from the mesentery directly to the retroperitoneal node without involvement of the pelvic nodes might exist. Nevertheless, lymphatic drainage of the ovaries via the infundibulopelvic ligament is still regarded as the chief pathway [45].

Colorectal carcinomas invade deep into the bowel wall and typically access the rich lymphatic network of the muscularis mucosa and subserosal channels. The frequency of lymph node metastasis is significantly associated with the depth of tumor invasion [46]. These lymphatic channels drain into the epicolic and paracolic lymph nodes, which subsequently empty into the retroperitoneal nodes [47]. Seventy-two percent of patients with serosal involvement from colorectal carcinoma develop mesocolic lymph node metastases [46], similar to our rates of mesenteric lymph node metastasis.

The current colorectal cancer staging protocol monitors the patterns of direct and nodal spread [48]. Optimally, 5 cm of palpably uninvolved longitudinal bowel length needs to be resected beyond the primary site. A wedge of mesentery is also resected to include the paracolic and intermediate nodes, even if there is a clinically uninvolved mesentery. The lymphatic drainage of the small bowel requires similar considerations with regard to resection margins and mesenteric wedging [49].

Because the subserosal region has a high density of lymphatic channels, tumors that invade from the serosal surface can easily invade these channels and embolize to regional lymph nodes [43]. In our series, there was a high incidence of mesenteric node metastasis, even in cases with minimal bowel invasion. Yet, when the tumor invaded the muscularis propria, the rate of lymph node metastasis was higher, which might be attributed to increased tumor volume, which is generally observed when deep bowel invasion occurs, giving the tumor easy access to the lymphovascular space.

This alternative metastatic pathway resembles the lymphatic spread of primary intestinal malignancies. Thus, a resection of regional lymph nodes of affected organs that is similar to surgical procedures that are performed for primary malignancies, such as colorectal carcinoma, might be an appropriate optimal debulking surgery for patients with ovarian carcinoma. This pattern of spread suggests that a sleeve resection of the intestine that lacks an underlying wedge of mesentery or an adequate longitudinal margin might leave residual tumor in the mesenteric lymph nodes or in the wall, which can become the source of local tumor recurrence.

Nevertheless, the contribution of bowel mesentery nodal disease to overall survival disease burden and the amount of residual disease remains poorly defined. Pathologists and gynecologic oncologist/surgeons should be aware of this metastatic pathway and examine lymph nodes from resected intraabdominal organs, such as the bowel, in cases of advanced ovarian carcinoma.

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