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# Ovarian Carcinoma Metastases to Gastrointestinal Tract Appear to Spread like Colon Carcinoma: Implications for Surgical Resection[1]

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**Objective: To profile the incidence of mesenteric lymph node metastases in patients with ovarian carcinoma and metastases to the gastrointestinal tract in order to determine the optimal technique for surgical debulking. Methods: The slides and charts of all patients with ovarian carcinoma who had undergone bowel resection were retrospectively reviewed and follow-up information was obtained. Results: Of 100 separate bowel resections 44% had penetration of metastases to the muscularis, 18% had invasion through the submucosa, 4% had mucosal perforation, and two patients had clinical perforation. Fifty-five percent of all resections demonstrated lymph–vascular space invasion (LVSI). In the 33 specimens which included pathologic analysis of mesenteric lymph nodes, 79% had positive LVSI, which correlated with the presence of mesenteric lymph node metastases ($P = 0.05$) but not histologic grade ($P = 0.20$). When surgery was performed for secondary debulking, the frequency of mesenteric node metastasis was higher ($P = 0.15$). There was a trend for patients with positive mesenteric nodes to fail sooner (median survival, 20 months vs 32 months). Conclusions: Because ovarian carcinoma metastases to the gastrointestinal tract are frequently associated with metastases to mesenteric lymph nodes, gynecologic oncology surgeons may wish to consider resection of the mesentery in a wedge fashion similar to current standards of resection for primary bowel carcinoma in cases in which a bowel resection is being performed with the intent to debulk to zero visible residual disease.** 

## INTRODUCTION

The prognosis of ovarian carcinoma is a function of stage, grade, histologic type, and volume of residual disease [1]. For patients with advanced-stage surface epithelial ovarian carcinoma, primary cytoreductive surgery leaving no measurable residual disease has been reported to provide the highest likelihood of cure [2–7]. In order to effectively debulk to zero visible residual, procedures such as bowel resection [8–15], splenectomy [16–18], and peritoneal stripping [19–22] have been recommended in addition to the standard staging procedures (i.e., hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, and lymph node dissection). The resection of bowel in a sleeve fashion, removing the segment of involved intestine without the mesentery, followed by primary reanastomosis has been shown to be a safe and effective method of cytoreduction [7, 13–15, 23–26]. However, in recent years, we have seen a number of patients who have undergone bowel resection as part of their cytoreductive surgery and have had gross or microscopic evidence of spread of ovarian carcinoma metastases longitudinally along bowel wall lymphatic channels as well as into mesenteric nodes, analogous to the spread pattern of primary colon carcinoma. In light of this finding, it would be important to consider whether the standard sleeve resection technique provides adequate resection for the subset of patients who are candidates for thorough cytoreductive surgery. We thus undertook a formal retrospective review of patients treated at Stanford University Hospital for ovarian carcinoma who underwent bowel resection for intestinal metastases.

## MATERIALS AND METHODS

The Department of Pathology files and the Department of Obstetrics and Gynecology Faculty Practice Plan files from January 1981 to the present were each searched for patients who had a diagnosis of ovarian carcinoma and who underwent bowel resection. All microscopic slides were reviewed. Features evaluated included the histological type and grade of the carcinoma, the extent of bowel wall invasion, the segments of bowel involved by carcinoma, the presence of lymph–vascular space involvement, and mes-

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**TABLE 1**
**Types of Surgical Specimens by Types of Surgeries ($n$ = 71)**

| | No. of patients (%) | | |
|---|---|---|---|
| | Primary | Secondary | Total |
| One colon resection[a] | 23 (32) | 11 (15) | 34 (48) |
| One small bowel resection | 7 (10) | 8 (11) | 15 (21) |
| Two colon resections | 6 (8) | 1 (1) | 7 (10) |
| Two small bowel resections | 0 (0) | 1 (1) | 1 (1) |
| One colon/one small bowel | 5 (7) | 3 (4) | 8 (11) |
| One colon/two small bowel | 1 (1) | 1[b] (1) | 2 (3) |
| Two colon/one small bowel | 2 (3) | 1 (1) | 3 (4) |
| Two colon/two small bowel | 1 (1) | 1 (1) | 1[c] (1) |
| Total | 45 (63) | 26 (37) | 71 (100) |

[a] Five of these colon resections (primary) also included an appendectomy.
[b] Colon resection was a secondary surgery.
[c] One patient underwent a primary as well as a secondary partial colectomy with small bowel resection.

enteric lymph node involvement. The extent of bowel wall invasion was scored as extension into serosal and subserosal tissues only, extension into muscularis propria, but not submucosa, extension into submucosa, and extension into mucosa with perforation (either gross or microscopic). Chart review with exhaustive attempts to obtain follow-up data was undertaken. The data were analyzed using Excel Spreadsheet and StatView 4.0 contingency tables, and $\chi^2$ and Kaplan–Meier survival analysis were performed using JMP 3.0 for the Macintosh.

## RESULTS

There were 100 separate bowel resections. A single bowel resection was performed in 49 (69%) patients, while 16 (23%) patients had two resections, and 6 (8%) had three or more (Table 1). For the purposes of analyzing tumor virulence, each bowel resection was considered separately; however when evaluating impact on survival, each patient was included only once in the analysis. Primary and secondary surgeries were analyzed separately.

Invasion of the bowel wall was identified in 62 (62%) specimens, or 68% of small bowel and 59% of large bowel segments (Table 2). Since there was no significant difference in rates of colon invasion versus small bowel invasion, all lesions were analyzed together. Of all specimens demonstrating more than serosal involvement, 44% invaded into the muscularis propria (Fig. 1), 14% invaded into the submucosa, and 4% invaded through the entire thickness of bowel wall. Perforation was clinically occult in two cases. All four cases of perforation occurred in the secondary surgical subset (Table 2).

Although it was difficult to determine in a retrospective fashion the lateral or longitudinal extent of intestinal wall involvement, in three cases a subserosal nodule was clinically evident separated from the visible serosal tumor by as much as 4 cm. In many cases small (often microscopic) foci of metastatic carcinoma were identified within the submucosa or the muscular layers of the bowel wall without gross or microscopic evidence of contiguous spread from the primary metastatic nodule (Figs. 1B and 2). In most of these cases, there was prominent associated lymph–vascular space involvement (Fig. 2).

Histologic grade did not correlate with extent of mural invasion or the presence of lymph–vascular space invasion. Vascular space invasion was observed in 55% of all surgical specimens (Table 3).

In 33% of the resection specimens, mesenteric lymph nodes had been dissected; of those, 70% were positive (Fig. 3). Vascular space invasion was observed in 81% of this subset of surgical specimens and was significantly correlated with the presence of mesenteric nodal metastasis ($P$ = 0.05) but not with histologic grade ($P$ = 0.20). The type of surgery was not associated with a higher likelihood of nodal metastasis (Table 4).

Survival distributions by Kaplan–Meier survival analysis

**TABLE 2**
**Correlation of Maximum Extent of Intestinal Wall Invasion with Type of Surgery ($n$ = 100 Segments of Bowel)**

| | $n$ (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Primary surgery | | | Secondary surgery | | | Total specimens | | |
| Depth of invasion | Small | Large | Total primary: | Small | Large | Total secondary: | Small | Large | All |
| Serosa and subserosa | 6 (31) | 21 (46) | 27 (41) | 5 (33) | 6 (30) | 11 (31) | 11 (32) | 27 (41) | 38 (38) |
| Muscularis propria | 10 (52) | 19 (41) | 29 (45) | 6 (40) | 9 (45) | 15 (42) | 16 (47) | 28 (42) | 44 (44) |
| Submucosa | 3 (17) | 6 (13) | 9 (14) | 2 (13) | 3 (15) | 5 (14) | 5 (14) | 9 (14) | 14 (14) |
| Mucosal perforation | 0 | 0 | 0 | 2 (13) | 2 (10) | 4 (11) | 2 (6) | 2 (3.0) | 4 (4) |
| Total | 19 | 46 | 65 (100) | 15 | 20 | 35 (100) | 34 | 66 | 100 (100) |

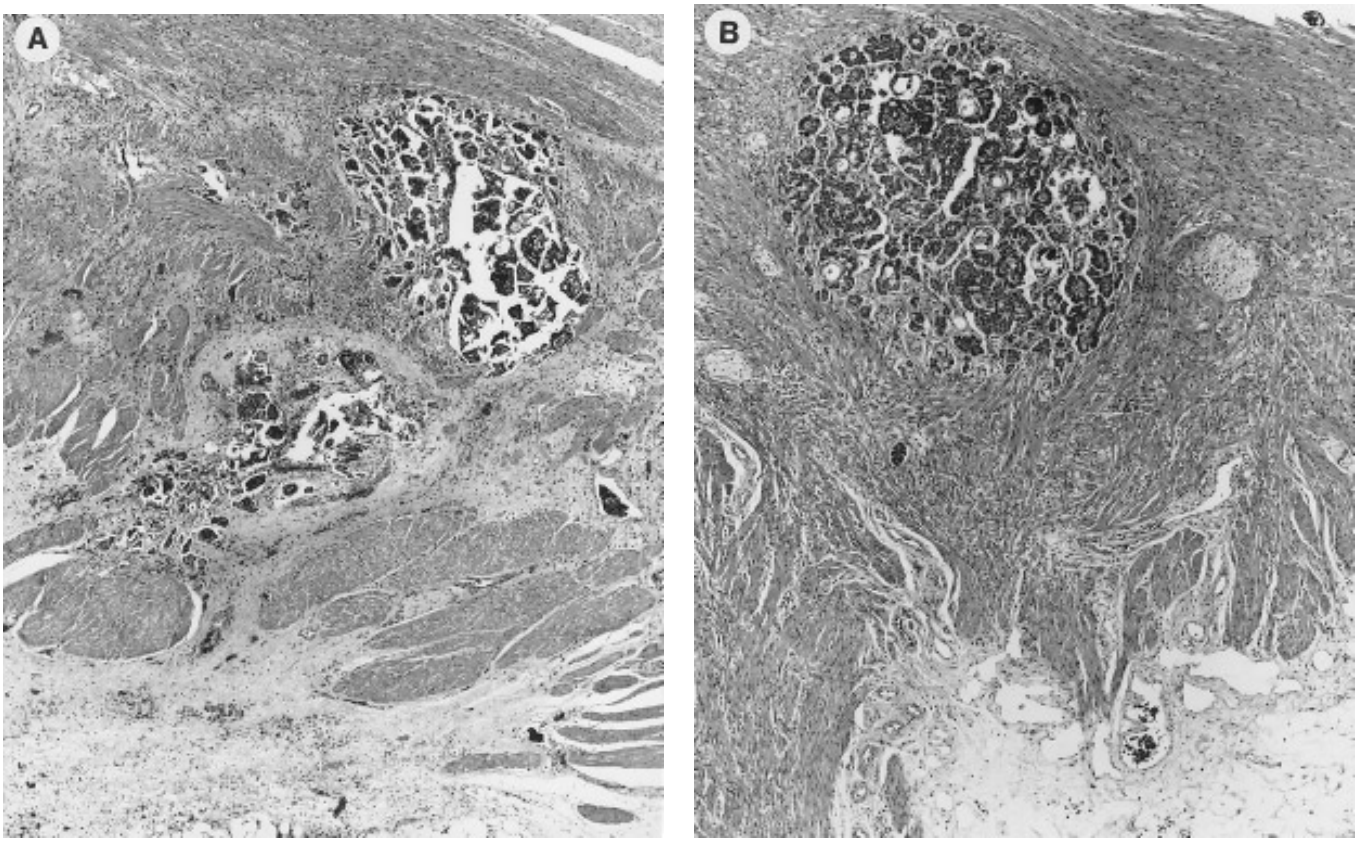


**FIG. 1.** These photomicrographs depict deposits of metastatic surface epithelial ovarian carcinoma within the muscularis propria of the bowel wall. Note that both metastatic deposits are associated with lymph–vascular space invasion. (A) Although the bulk of metastatic carcinoma in this photomicrograph lies within the muscular layer of the bowel wall, small aggregates of carcinoma are present within the subserosal tissues, consistent with direct invasion. (B) In contrast, the intramural deposit of metastatic tumor within this photomicrograph demonstrates no evidence of direct, contiguous spread from a subserosal tumor nodule. This pattern suggests longitudinal spread along the intestinal wall, possibly along lymphatic spaces.

reveal that survival times tended to be shorter in cases with mesenteric nodal metastasis (20 month vs 32 month median survival).

## DISCUSSION

Ovarian carcinoma commonly involves the intestines and this involvement plays an important role in disease progression [27, 28]. Several investigators have suggested that bowel resection for intestinal metastases of ovarian surface epithelial carcinoma may not improve survival [4, 5, 19, 26, 29–32]. Our results suggest that tumor residual may be left in the lymphatics of the adjacent palpably negative mesenteric tissue or in the adjacent 5 cm of bowel wall.

Although the spread of ovarian surface epithelial carcinoma characteristically involves peritoneal and serosal surfaces, the capacity for this tumor to invade visceral organs, including the intestinal wall, and metastasize to lymph nodes is well known ]6, 33]. Wu *et al.* described frank invasion by ovarian carcinoma metastases into the intestinal wall in 38% of surgical specimens examined, with invasion through the bowel wall into the mucosa in 21% of cases [9]. In a series of autopsy cases, Dvoretsky *et al.* observed intestinal wall invasion in 71% of large bowel and 74% of small bowel ovarian carcinoma metastases [34]. These investigators described two microscopic patterns of intestinal wall invasion: a ''buckshot'' distribution usually associated with lymphatic invasion and direct invasion with bulky replacement of the muscularis propria, both patterns that were also recognized in our series [28]. In the autopsy series, metastases to retroperitoneal lymph nodes were often the most common site of nodal dissemination and most of these were metastases from mesenteric lymph nodes [34]. This pattern of spread primarily reflects drainage from the small and large intestines and suggests that the optimal surgical management of these patients must in some cases include resection procedures commonly performed for primary intestinal carcinoma.

Colonic carcinomas typically first access the rich lymphatic network of the muscularis mucosa (Fig. 4) and submucosa by invading through the lamina propria and into the

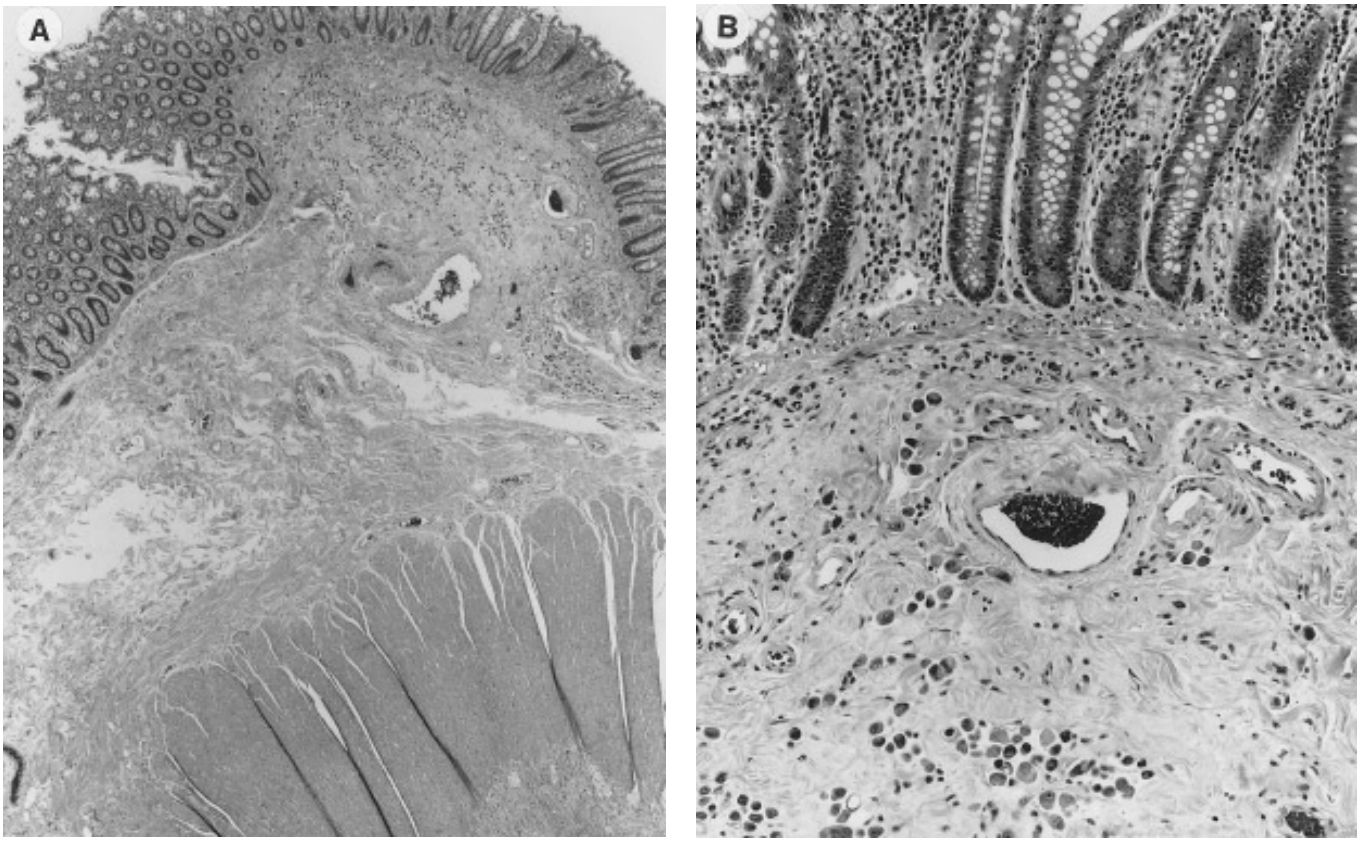


**FIG. 2.** This set of photomicrographs depicts bowel wall metastases of ovarian carcinoma involving submucosa, but not muscularis propria or serosa. This pattern of involvement presumably reflects longitudinal lymphatic spread along the intestinal wall. Note the prominent lymph–vascular space involvement in (B).

muscularis mucosa. With deeper invasion, the subserosal lymph channels are accessed. These lymph channels drain into the paracolic nodes in the mesentery and then into the intermediate nodes which subsequently empty into the proximal mesenteric and aortic nodes [35]. Occasionally, large tumor deposits are identified either in the subserosa or, more rarely, in the muscularis propria with no gross or microscopic evidence of direct spread from the primary tumor. It has been hypothesized that, in some of these cases, tumor emboli may lodge within lymphatic aggregates within the bowel wall and ultimately result in a clinically observable subserosal or intramural nodule at sites removed from the primary

**TABLE 3**
**Correlation of Tumor Grade with Maximum Extent of Intestinal Wall Invasion, the Presence of Lymph–Vascular Space Invasion, and the Presence of Mesenteric Lymph Node Metastases ($n$ = 100)**

| | Number of specimens (%) | | | | | |
|---|---|---|---|---|---|---|
| | Depth of invasion ($P$ = 0.18) | | | | LVSI ($P$ = 0.20) | |
| Grade | Ser | Mus | Smuc | Perf | Absent | Present |
| 1 | 2 (5) | 2 (5) | 2 (14) | 2 (50) | 1 (4) | 5 (9) |
| 2 | 8 (21) | 15 (34) | 3 (21) | 1 (25) | 6 (24) | 18 (33) |
| 3 | 28 (74) | 27 (61) | 9 (64) | 1 (25) | 18 (72) | 32 (58) |
| Total | 38 | 44 | 14 | 4 | 25 | 55 |

*Note*. $P$ values given as likelihood ratio test/Pearson test. LVSI, lymph–vascular space invasion; Ser, serosal and subserosal tissue involvement only; Mus, invasion into muscularis propria; Smuc, invasion into submucosa; Perf, mucosal perforation.

tumor site. Additionally, it has been hypothesized that tumor accessing the transverse, circumferential intestinal lymph channels may enter and completely replace the lymph nodes in the mesentery giving rise to a large deposit of carcinoma [36]. Most of the current colon cancer staging protocols reflect these patterns of direct and nodal spread [37]. Typically, at least 2 cm (optimally 5 cm) of palpably uninvolved longitudinal bowel length is resected beyond the palpable primary site. Also, a wedge of mesentery is resected to include the paracolic and intermediate nodes if the mesentery is palpably uninvolved by tumor. When mesenteric nodes are suspicious, the proximal nodes are resected in a much larger wedge of mesentery and a longer segment of bowel is removed consistent with the lymphatic drainage of that portion of colon. The lymphatic drainage of the small bowel requires similar considerations of resection margins and mesenteric wedging [38].

Given the high concentration of lymphatic channels in the subserosal region of the large and small intestines, it is not surprising that tumor implants invading from the serosal surface (in contrast to the mucosal surface) would easily enter the lymphatic channels and embolize to the regional lymph nodes. Our results confirm this tendency and indicate that even when extension into the bowel wall is minimal, invasion into the lymphatics may have occurred. This spread pattern suggests that the sleeve resection of the intestine without an underlying wedge of mesentery or adequate longitudinal margin may leave residual tumor in the mesenteric nodes or in the wall. Therefore, surgeons may wish to consider removing a longitudinal negative margin of at least 2 cm (preferably 5 cm) with a wedge of mesentery including the paracolic and intermediate level nodes when intestinal resection is indicated, if it appears that the patient can otherwise be debulked 100%. If the mesenteric nodes are palpably involved, consideration should be given to resecting even the proximal segment of the mesentery, as long as the surgeon anticipates debulking the patient to zero visible residual.

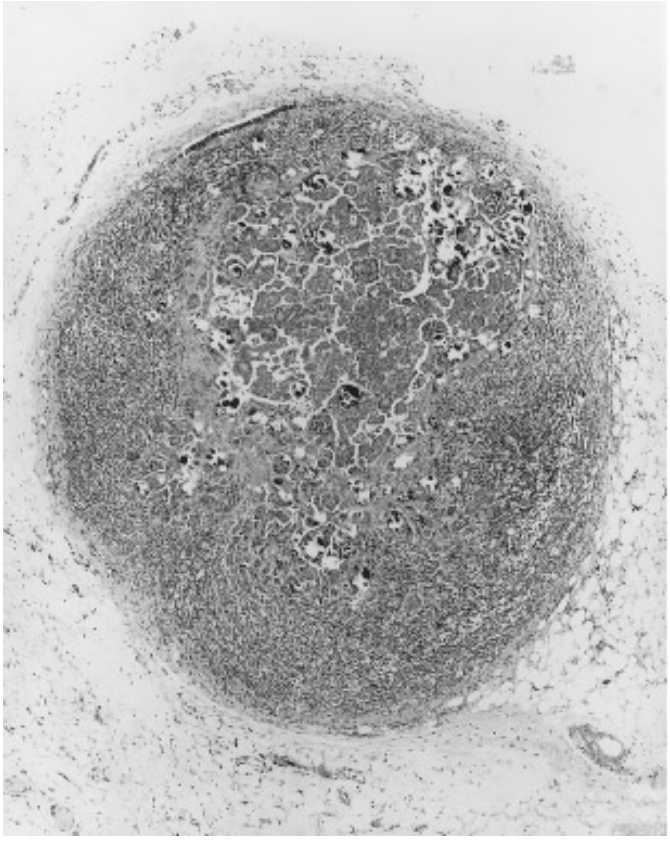

**FIG. 3.** Metastatic ovarian serous carcinoma in a mesenteric lymph node.

**TABLE 4**

**Correlation of Mesenteric Nodal Metastasis with the Maximum Extent of Intestinal Wall Invasion, the Presence of Lymph–Vascular Space Invasion, Histologic Grade, and Type of Surgery in the Subset of Specimens Which Included Dissection of Mesenteric Nodes ($n$ = 33)**

| | Mesenteric nodal metastasis: $n$ (%) | |
|---|---|---|
| | Absent ($n$ = 9) | Present ($n$ = 24) |
| Depth of invasion | | |
| Serosal involvement only | 5 (50) | 5 (50) |
| Muscularis propria | 3 (25) | 9 (75) |
| Submucosa | 0 | 7 (100) |
| Mucosal perforation | 1 (25) | 3 (75) |
| $P$ = 0.08/0.15 | | |
| Lymph–vascular space | | |
| Negative | 4 (57) | 3 (43) |
| Positive | 5 (19) | 21 (81) |
| $P$ = 0.06/0.05 | | |
| Grade | | |
| 1 | 1 (11) | 4 (17) |
| 2 | 2 (22) | 13 (54) |
| 3 | 6 (67) | 7 (29) |
| $P$ = 0.14/0.14 | | |
| Primary surgery | 6 (67) | 12 (50) |
| Secondary surgery | 3 (33) | 12 (50) |
| $P$ = 0.39/0.39 | | |

*Note.* $P$ values are given as likelihood ratio test/Pearson test.

## CONCLUSIONS

We have confirmed that invasion of the bowel wall by metastatic ovarian surface epithelial carcinoma is a frequent event. Once ovarian carcinoma involves the bowel wall, the probability of longitudinal nodal spread or circumferential metastasis to the mesenteric nodes appears to be increased.

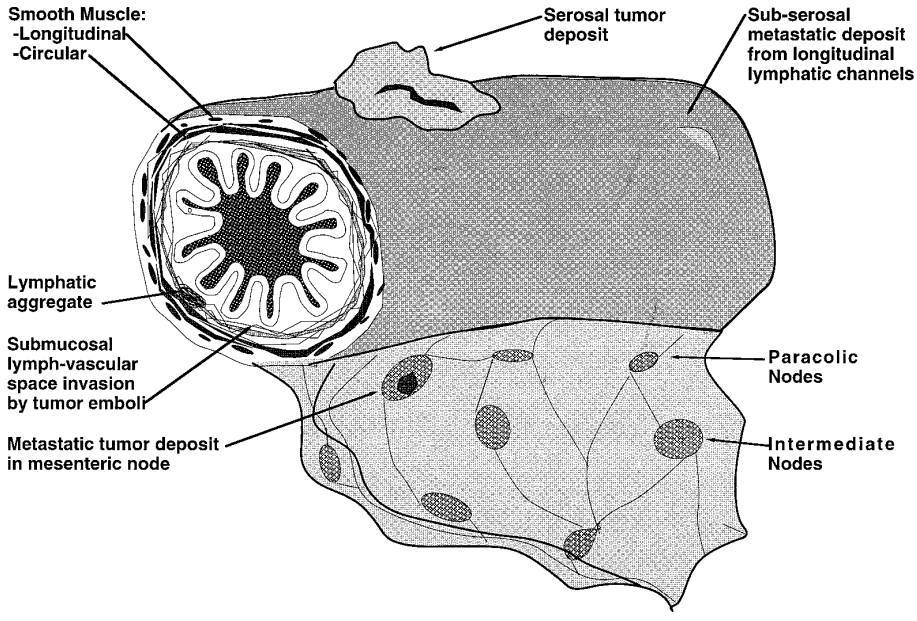


**FIG. 4.** Schema of pathobiology of ovarian carcinoma within the bowel wall. Both mesenteric and longitudinal subserosal metastases can be resected by adequate margins in the patient with no other visible residual carcinoma.

Therefore, when surgeons are preparing to debulk all measurable disease in patients with intestinal metastases, they should consider resection of involved segments of the intestine to include a 2 to 5-cm longitudinal margin of palpably negative intestine, and a wedge of mesentery to include the paracolic and intermediate nodes, especially in the presence of clinically suspicious palpable mesenteric disease.

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