Prophylactic Oophorectomy in Surgery for Large-bowel Cancer*

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From 1968 to 1975, 201 women had prophylactic oophorectomy at the time of definitive large-bowel resection, while in 134 patients oophorectomy was not performed. Oophorectomy was performed more commonly in women with cancer of the rectum and rectosigmoid. More patients undergoing oophorectomy had Dukes' C primary carcinoma. Four patients undergoing synchronous oophorectomy (2.0 per cent) had ovarian involvement or metastases from large-bowel cancer. Three patients (2.2 per cent) developed subsequent ovarian disease: two cases of ovarian carcinoma and one case of ovarian metastases from primary breast cancer. No late ovarian recurrences of large-bowel cancer were seen during this study. No patient with ovarian involvement or metastases from large-bowel cancer survived five years nor was the overall survival of the group of women undergoing oophorectomy materially affected. While stage and site significantly influenced survival, oophorectomy, menopausal status, preoperative irradiation, tumor size, and degree of differentiation had no influence. The prevention of primary ovarian cancer in postmenopausal women is considered to be the main benefit of bilateral prophylactic oophorectomy. Selective recommendations for oophorectomy under other circumstances are discussed. [Key words: Oophorectomy, prophylactic; Cancer, large-bowel; Women, postmenopausal; Metastases, ovarian]

FOR THE PAST three decades, prophylactic oophorectomy has been a recommended adjunct at the time of definitive operation for large-bowel cancer. The rationale for oophorectomy has been based upon the hypothesis that occult metastases to the ovary might be removed, preventing the advent of late ovarian metastases, or fortuitiously curing some patients of their cancer. The ovary has been considered a "privileged site" where metastatic disease might still be amenable to cure. An additional factor in favor of oophorectomy has been the elimination of a subsequent risk for the development of ovarian cancer in this largely postmenopausal population.

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The reported incidence of ovarian metastases from cancer of the large bowel has varied from 2.0 to 8.0 per cent. Chlyvitch[1] found ovarian involvement in 2 per cent of 581 patients with cancer of the rectum. Burt[2] described a 3.4 per cent incidence of concomitant or late ovarian metastases in 493 cases of colorectal neoplasia. Rendelman and Gilchrist found 7 per cent of their large-bowel cancer patients with regional spread to serosa, nodes, or adjacent structures to also have ovarian metastases.[3] Sherman *et al.*[4] reported metastatic carcinoma to the ovary in 5 per cent of 162 cases. The same incidence was observed by Antoniades *et al.*[5] in a group of 158 patients. Stearns and Deddish[6] found ovarian metastases in five of 63 patients (8 per cent) with cancer of the rectum who underwent abdominopelvic lymphadenectomy. In a follow-up study, Quan and Sehdev[7] diagnosed metastases to the ovary in six of 100 patients who had oophorectomy for large-bowel cancer. Recently, MacKeigan and Ferguson[8] reported four patients with microscopic ovarian metastases from large-bowel cancer, two patients with gross ovarian metastases, and two patients with late ovarian metastases, for a total of eight, or 6 per cent from a group of 133 patients.

Although the ovaries, on rare occasions, may harbor isolated metastases, such lesions generally represent wider occult spread. Thus, the prognosis for patients having either gross or microscopic ovarian metastases is poor. In a review of the medical literature, MacKeigan and Ferguson[8] could identify only eight patients, including their own, with long-term survival.

Various authors have attempted to define those circumstances in which patients with cancer of the large bowel would benefit from prophylactic oophorec-

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tomy. Some have suggested restriction of oophorectomy to postmenopausal women, to those with direct pelvic extension of their primary tumor, or to women[9] with serosal involvement or metastases to regional lymph nodes.[10] Others have recommended routine oophorectomy for all female patients.[8,11] The ideal clinical population in which to advocate prophylactic oophorectomy has defied simple definition.

This study was conducted to assess the value of prophylactic oophorectomy during our more recent experience at Memorial Sloan-Kettering Cancer Center at the time of curative surgery for large-bowel cancer.

Methods

From January 1, 1968 through December 31, 1975, 350 women with adenocarcinoma of the large bowel had curative resections at Memorial Hospital. Of these, 201 patients were subjected to either unilateral or bilateral oophorectomy at the time of intestinal surgery, while 149 did not have their ovaries removed. Thirty-one patients were excluded from the study for one or more of the following reasons: 1. previous bilateral oophorectomy; 2. previous ovarian cancer; 3. polyposis coli; or 4. death within the immediate postoperative period. Patient selection for oophorectomy was not based upon a protocol. Instead, oophorectomy was based upon the individual surgeon's preference and judgment. Both groups were compared for age, race, menopausal status, use of preoperative irradiation, site of tumor, stage of disease, size of primary tumor, degree of differentiation, and number of involved lymph nodes.

Patients were staged according to the 1932 Dukes' classification:[12] A—lesions confined to the bowel wall; B—lesions penetrating the serosa or the perirectal fat; and C—lesions with positive lymph nodes.

A five-year follow-up was achieved in 32 patients (93 per cent). Disease-free survival, overall survival, and pattern of recurrence were evaluated. The endpoint in the survival analysis was death due to cancer, provided there was pathologic confirmation. In the group of patients not subjected to oophorectomy, the incidence of late ovarian metastases or of primary ovarian cancer was also evaluated.

Statistical analyses of survival and recurrence distributions were carried out by the log rank test.[13] Survival and time-to-recurrence curves were estimated by the Kaplan-Meier method.[14] The cross-classified data in Tables 1 and 2 were analyzed by the chi-square test for contingency tables. Results were deemed significant if $P < 0.05$.

Results

Comparison of the oophorectomy with the nonoophorectomy groups showed the two groups to be comparable for most variables. There were two significant differences between the two groups: more patients with primary tumors located in the rectosigmoid and rectum and more patients with Dukes' C disease were subjected to oophorectomy ($P < 0.05$) (Tables 1 and 2).

No difference was found in survival and recurrence distributions between patients who had oophorectomy and those who did not (Fig. 1). In both groups, survival and recurrence rates were affected by the stage of disease: Dukes' C patients fared substantially worse than Dukes' A and B patients ($P < 0.001$) (Fig. 2). When oophorectomy and nonoophorectomy

TABLE 1. *A Comparison of Patients in the Oophorectomy and Nonoophorectomy Groups by Clinical Findings*

	Oophorectomy		Nonoophorectomy	
	Number	Per Cent	Number	Per Cent
Age				
≤ 60	80	40	45	30
> 60	121	60	104	70
Race				
Caucasian	186	93	142	95
Black	10	5	6	4
Other	5	2	1	
Menopausal Status				
Pre	14	7	6	4
Post	174	87	141	95
Preoperative Irradiation				
Yes	25	13	11	8
No	174	87	136	92

TABLE 2. *A Comparison of Patients in the Oophorectomized and Nonoophorectomized Groups by Pathologic Findings*

Tumor	Status	Oophorectomy		Nonoophorectomy	
		Number	Per Cent	Number	Per Cent
Site*	Right or transverse	14	7	34	23
	Left colon	58	29	42	28
	Rectosigmoid or rectum	129	64	72	49
Size (cm)	< 2	13	7	7	5
	2–4.9	100	50	83	56
	⩾ 5	78	39	52	35
	Not stated	10	4	7	4
Grade	(I) Well differentiated	1	1‡	2	2‡
	(II) Moderate	117	89	82	89
	(III) Poor	13	10	8	9
Number positive nodes	⩽ 3	19	45	34	41
	⩾ 4	23	55	48	59
Dukes' stage†	–A	23	12	15	10
	–B	93	47	91	61
	–C	82	41	42	28

* $P < 0.001$ (Chi square).
† $P < 0.03$ (Chi square).
‡ Seventy patients in the oophorectomy group and 57 patients in the nonoophorectomy group had unknown tumor grade and were excluded from the calculation of percentages.

groups were compared stage by stage, no significant effects of oophorectomy were found among Dukes' B and C patients (Fig. 3). Dukes' A patients were excluded due to small sample size.

Of 201 patients submitted to oophorectomy at the time of curative surgery for colorectal cancer, four (2 per cent) were found to have ovarian metastases. Of these, two (1 per cent) had only microscopic tumor. In the group of 134 patients with a five-year follow-up who were not subjected to oophorectomy at the time of surgery, three (2 per cent) developed a late ovarian tumor. The cases of these seven patients are summarized below.

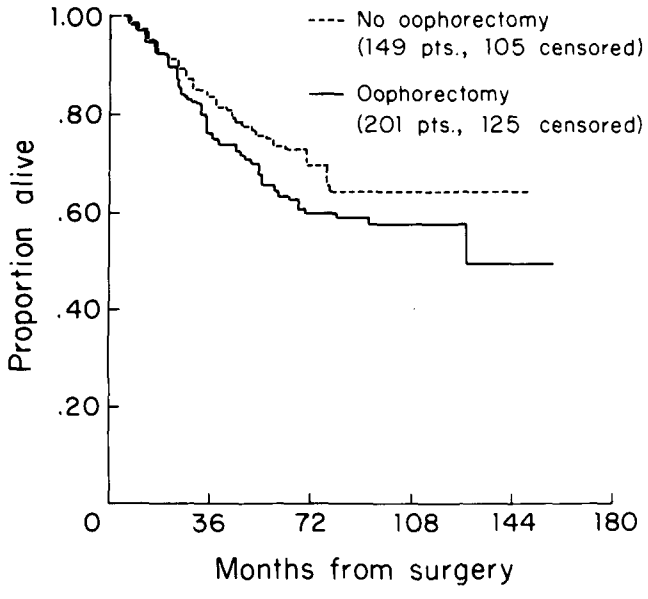

FIG. 1. Prophylactic oophorectomy in surgery for large-bowel cancer. There is no statistically significant difference in survival between women who have or who have not undergone bilateral oophorectomy at the time of their resection for colorectal cancer.

Concomitant Cancer in Ovaries: 1. A 65-year-old postmenopausal woman had a carcinoma of the cecum with direct involvement of the right ovary. Right hemicolectomy and *en bloc* right salpingo-oophorectomy were performed. A normal appearing left ovary was also removed. Histologic evaluation showed a Dukes' B adenocarcinoma of the cecum, moderately well differentiated, invading and replacing the right ovary. The left ovary was normal histologically. No other evidence of metastases was detected. Distant metastases developed six months later and the patient died of large-bowel cancer 20 months after operation.

2. A 49-year-old perimenopausal woman had rectal cancer treated by low anterior resection. Prophylactic bilateral salpingo-oophorectomy was performed. A Dukes' B moderately well-differentiated mucinous adenocarcinoma was described. Bilateral micrometastases were found located superficially in both ovaries. This patient had a local recurrence 23 months later and died of large-bowel cancer 25 months after her initial operation.

3. A 54-year-old postmenopausal woman had a sigmoid carcinoma and bilateral ovarian cystic disease treated by sigmoid resection and bilateral salpingo-oophorectomy. Pathology revealed a moderately well-differentiated adenocarcinoma, extending through the pericolonic fat with adjacent lymph-node metastases (Dukes' C). Both ovaries demonstrated benign cysts but metastatic adenocarcinoma replaced the ovarian parenchyma bilaterally. Thirty months later, lung and bone metastases developed and the patient died of cancer 41 months after her initial operation.

4. A 42-year-old premenopausal woman had sigmoid carcinoma and grossly cystic ovaries removed by radical sigmoid resection and bilateral salpingo-oophorectomy. Histologic examination showed a moderately well-differentiated adenocarcinoma of the sigmoid extending through the pericolonic fat with involved lymph nodes (Dukes' C). Metastases were detected in both ovaries. Carcinomatosis became evident six months later and the patient died of large-bowel cancer 38 months after her initial operation.

Late cancer in ovaries: 5. Primary ovarian cancer developed in a 57-year-old postmenopausal woman four years after sigmoid resection for a moderately well-differentiated Dukes' B sigmoid carcinoma. One year later, lung metastases were diagnosed radiologically. She died 33 months later (eight years after her colonic operation) from ovarian cancer.

6. A 63-year-old postmenopausal woman underwent curative resection of a Dukes' B, moderately well-differentiated adenocarcinoma of the transverse colon. Twelve months later she had an intestinal obstruction. At laparotomy both ovaries had gross tumor which extended to the sigmoid colon. Microscopic examination showed bilateral primary ovarian carcinoma. The patient died six months later of ovarian cancer.

7. A 56-year-old postmenopausal woman had a curative low anterior resection for a moderately differentiated adenocarcinoma located in the rectum which invaded the muscularis propria with regional lymph-node involvement (Dukes' C). One year later primary breast cancer developed. Five years after radical mastectomy metastases from breast cancer to the ovaries and peritoneum developed. This was confirmed by laparotomy and the patient died one year later of metastatic breast cancer.

Discussion

Among the 201 patients who had concomitant oophorectomy at the time of colonic resection, only four (2 per cent) were found to have ovarian involvement by colonic carcinoma. Among the 134 patients who did not have adjunctive oophorectomy, three patients (an additional 2.2 per cent) subsequently had either primary or secondary carcinoma in their ovaries, but not from the colon.

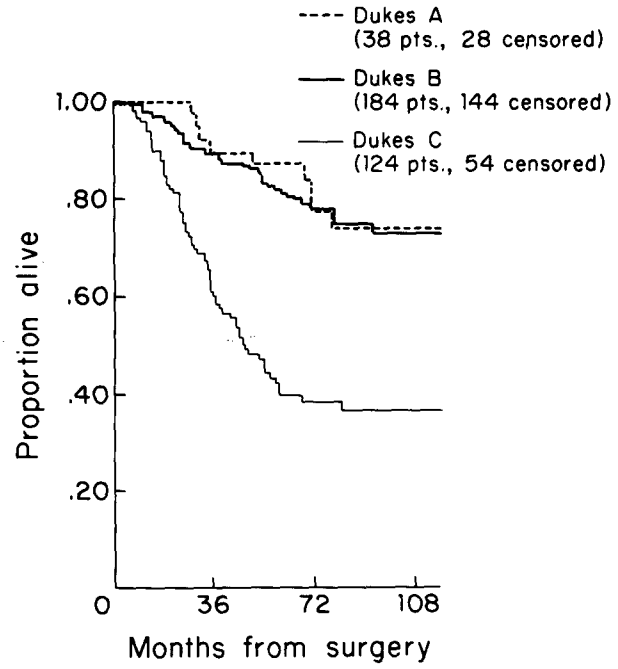

FIG. 2. Survival of patients after surgery for large-bowel cancer by Dukes' stage. Dukes' C patients fared substantially worse than either A or B patients for both survival and recurrence rates ($P = < 0.001$).

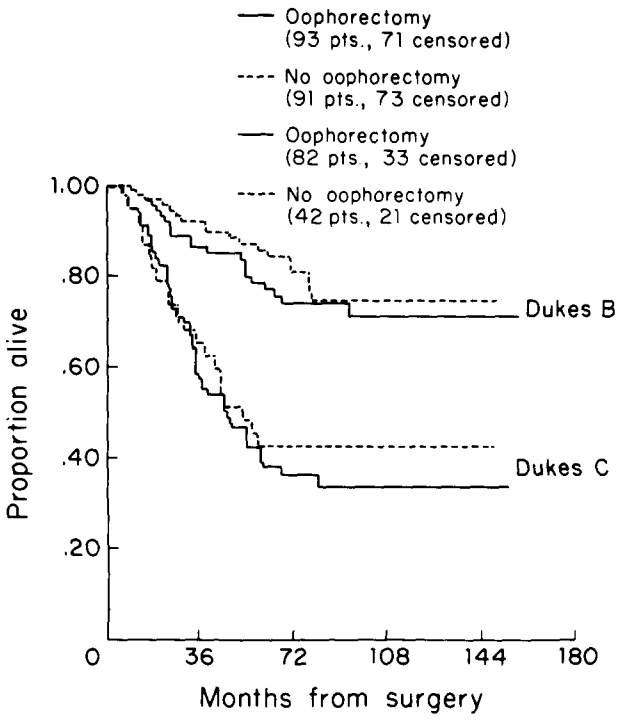

FIG. 3. Prophylactic oophorectomy in surgery for large-bowel cancer by stage of disease. No significant effect of oophorectomy is present within each staging group.

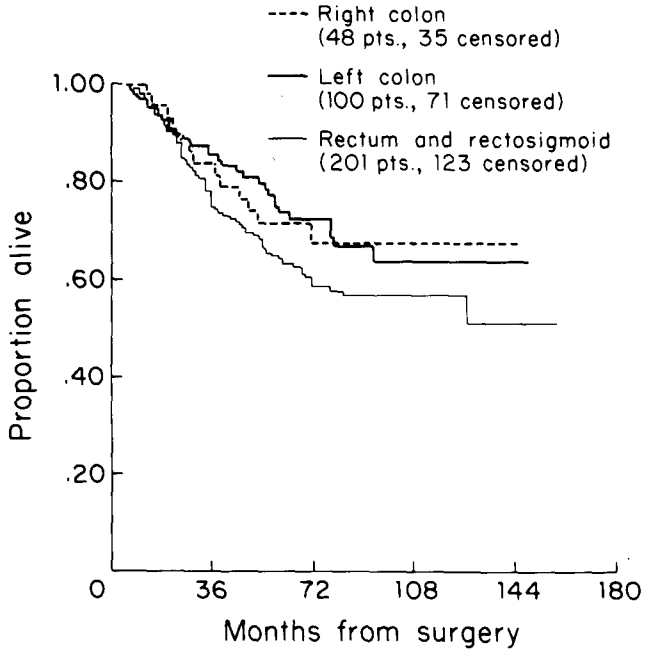

FIG. 4. Prophylactic oophorectomy in surgery for large-bowel cancer. Survival of patients by site of disease.

In examining the effects of oophorectomy, we found that no patient with initial oophorectomy, where either gross or microscopic disease was identified pathologically, became a long-term survivor. This is the rule which, with only the rarest exception,[8] has become the reported experience of other investigators. Nor for that matter was survival materially prolonged by this effort, as most of our patients with ovarian involvement died with rapid progression of their disease. Benefit from oophorectomy was also not apparent when the overall survival of the two groups was compared. If anything, the survival curves of the oophorectomized patients were slightly worse than those of the nonoophorectomized patients (Fig. 1). This difference can be explained by the excess of patients with rectal cancer and with stage C disease in the oophorectomized group with their associated poorer prognosis (Table 2) (Fig. 4).

As in all studies, patients with Dukes' C cancer fared significantly worse than patients with either Dukes' A or B cancers (Fig. 2) but these data were also unaffected by ovariectomy. No effects of oophorectomy became manifest by segregating Dukes' B and C patients (Fig. 3).

No benefit from oophorectomy was observed in relation to menopausal status (Fig. 5), presence or absence or preoperative irradiation (Fig. 6), tumor size, or degree of differentiation.

If anything, the benefit of concomitant oophorectomy, in this study, was limited to the prevention of subsequent ovarian cancer which was observed in two of 134 patients who had their ovaries retained. We surmise that a comparable proportion of patients with initial oophorectomy escaped a subsequent primary ovarian carcinoma. From these data, however, we are unable to comment upon protection against subsequent metastatic bowel cancer to the ovaries as none was seen in the 134 women who were available for long-term follow-up.

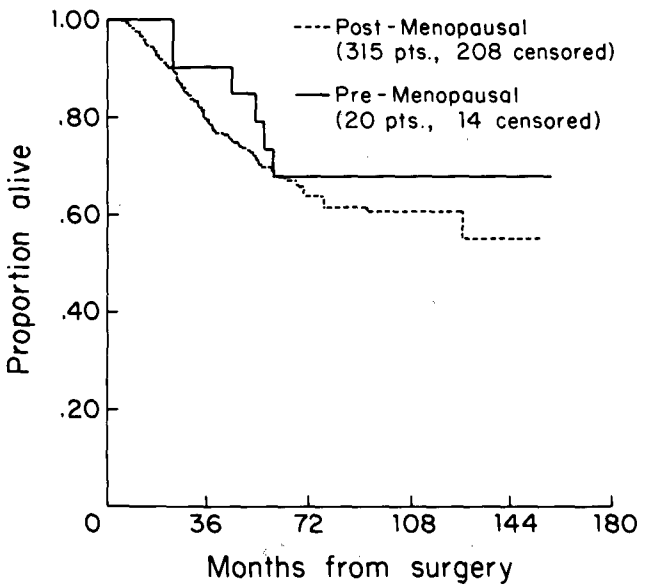

FIG. 5. Effects of menstrual status on survival of patients undergoing prophylactic oophorectomy in surgery for large-bowel cancer. No significant difference observed.

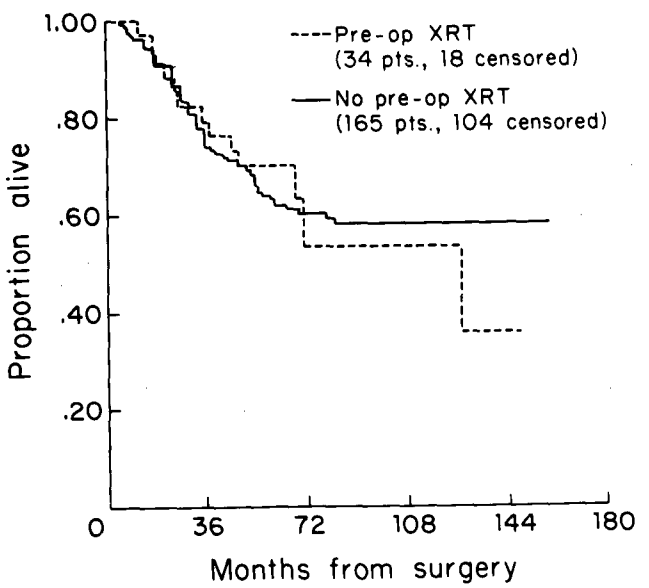

FIG. 6. Effects of having received preoperative pelvic irradiation on survival after prophylactic oophorectomy during surgery for large-bowel cancer. No significant effect observed.

The purpose of this paper was scrutiny of the role of oophorectomy in the salvage of patients with ovarian micrometastases, the effects of oophorectomy on the clinical course of colorectal cancer, and the subsequent hazards of leaving behind intact ovaries in women undergoing large-bowel resection for carcinoma. In our experience, no salvage or survival benefit in large-bowel cancer was achieved by prophylactic oophorectomy. The recent large experience of Blamey *et al.*[15] supports this view. Nevertheless, a small protective benefit against subsequent ovarian cancer may have been achieved. This one benefit of oophorectomy in postmenopausal women seems to outweight either the risk or the effort involved in conferring this limited protection.

In the absence of any appreciable benefit *vis-a-vis* the colonic carcinoma from the universal application of prophylactic oophorectomy, we define the clinical population in whom adjunctive oophorectomy would be of clinical value as falling into one of the following circumstances:

1. Therapeutic oophorectomy is indicated for large-bowel cancer patients when there is gross evidence of benign or malignant ovarian disease present at initial laparotomy. This includes direct extension of colorectal carcinoma to the ovary removable by *en bloc* salpingo-oophorectomy for cure.
2. In postmenopausal women, prophylactic oophorectomy is indicated as the optimal protection against ovarian cancer, and is probably the most compelling reason for performing bilateral oophorectomy.
3. In the absence of data, the indications for oophorectomy in premenopausal women undergoing resection for large-bowel cancer are less defined. For those premenopausal women with a defined high risk of cancer (*i.e.* cancer family syndromes, prior history of breast, bowel or gynecologic cancers) or in patients with a strong family history for cancers at these sites, bilateral prophylactic oophorectomy should be considered. Some younger women who are cured of their cancer may still choose to bear children.

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DICRAG is a code word ("coden") used by the Chemical Abstract Service to identify the journal.