ORIGINAL ARTICLE

Radical lymph node resection of the retroperitoneal area for left-sided colon cancer

Antonios-Apostolos K. Tentes · Charalambos Mirelis · Charisios Karanikiotis · Odisseas Korakianitis

Abstract

Background/aims Radical lymph node resection of the retroperitoneal area for cancer of the left half of the colon has been strongly questioned. The purpose of the study was to investigate the effect of extended lymph node resection of the retroperitoneal area in left-sided colon cancer.

Materials and methods From 1993 to 2002, 124 patients with left-sided colon cancer were randomly elected to undergo either conventional left colectomy (62 patients) or left colectomy combined with radical lymphadenectomy (62 patients). Clinical features were correlated to survival, recurrences, hospital mortality, morbidity, and late urogenital morbidity. Survival was the end point of the study.

Results The groups were comparable for age, gender, physical status, TNM stage, tumor distribution, degree of differentiation, postoperative complications, chemotherapy, recurrences, sites of recurrence, and late urogenital morbidity ($p>0.05$). Hospital mortality was higher in conventional surgery group ($p=0.008$). Survival rates of 5 and 10 years did not differ significantly between the two groups ($p>0.05$), although there was a trend of improvement after radical lymphadenectomy. Stage III patients in radical lymphadenectomy group had significantly better survival over those in the conventional surgery group ($p=0.0406$).

Conclusions Radical lymph node resection of the retroperitoneal area is associated with the same rate of hospital morbidity, late urogenital morbidity, and total survival as is conventional surgery. It seems that there is a trend for improvement of survival particularly in stage III patients.

Keywords Colon cancer · Radical lymph node resection · Retroperitoneal area

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Introduction

The extent of lymph node resection for carcinomas of the left half of the colon is still controversial. The main concern of controversy is about high or low ligation of the inferior mesenteric artery. High ligation of the inferior mesenteric artery has not offered significant survival benefit in patients with metastasis to lymph nodes at this level [1]. It was supposed that if metastasis has reached at the origin of the inferior mesenteric artery, the disease has already spread beyond the limits of surgical cure. It was shown that extended lymph node resection increases survival in sigmoid lesions only [2]. Historical reports about extended lymph node resection for left-sided colon cancer are retrospective and include small number of patients. In these studies, left-sided colon and rectal carcinomas are almost always assessed together as a single entity [3, 4]. Therefore, the effect of radical lymph node resection for left-sided colon cancer has not been thoroughly interpreted. The purpose of the study is to investigate whether extended lymph node resection of the retroperitoneal area may affect survival in left-sided colon cancer patients.

Materials and methods

From 1993 to 2002, 124 consecutive patients with left-sided colon cancer were included in the study. The study was approved by the Ethical Committee of the Hospital and written consensus was given by the patients. The patients were randomized just before laparotomy to undergo either left colectomy combined with radical lymph node resection of the retroperitoneal area (LND group = 62 patients) or conventional left colectomy (CS = 62 patients). The inclusion criteria were: (1) patients able to tolerate major surgery (no evidence of recent myocardial infarction, cardiomyopathy, or acute pulmonary infection on chest X-ray), (2) tumor distally to splenic flexure and proximally to peritoneal reflection, (3) normal liver function, (4) urea blood level <50 mg/dl, (5) creatinine level <2 mg/dl, and (6) performance status >50% (according to Karnofsky performance status scale). The exclusion criteria were: (1) prior malignancy at risk for recurrence, (2) pregnancy, (3) presence of distant metastases, and (4) evidence of diffuse peritonitis.

The diagnosis was established by physical examination, complete hematological and biochemical examinations, tumor markers, colonoscopy and biopsy or barium enema, CT-abdominal scan, and bone scanning.

The patients' age; physical status (according to Karnofsky performance scale); tumor distribution; concomitant operations; the use of systemic adjuvant chemotherapy; the residual tumor; hospital morbidity and mortality; late urogenital morbidity; recurrences and sites of recurrence; T, N, and M stages (according to the International Union Against Cancer [5]); and histologic data were recorded in a designed form.

All the patients underwent standard resection of the left colon (distal third of the transverse colon-descending-sigmoid colon down to the peritoneal reflection) by the same surgical team. In the LND group, high ligation of the inferior mesenteric vein was possible after complete mobilization of the Treitz ligament. The inferior mesenteric artery was ligated at its origin from the aorta with en bloc resection of the lymphatic bearing tissue from periaortic and inferior vena cava regions between the ureters from the left renal vein down to the bifurcation of the common iliac arteries. Bilateral preservation of the thoracolumbar sympathetic chain was always attempted in patients with preoperatively documented normal urogenital function. Postmenopausal women underwent routinely resection of the ovaries en bloc with the specimen. In the CS group the same steps were followed without resection of the aorto-caval lymphatic tissue. The reconstruction of the gastrointestinal tract was made with end-to-end colorectal anastomosis. Stage III patients were assigned to receive six cycles of adjuvant systemic chemotherapy with

5-fluorouracil (500 mg/m^2) combined either with leuco-vorin (200 mg/m^2) or isovorin (175 mg/m^2).

All the resected specimens were staged according to TNM system and classified for the degree of differentiation. Complete resection of the macroscopically visible tumor was considered as R_0 resection.

The patients were assessed in 6-month intervals for the first 5 years and once a year later with physical examination, hematological and biochemical examinations, tumor markers, and CT scan, and recurrences were recorded. Barium enema and colonoscopy were performed once a year if the patients complained of serious problems. The patients were asked to complete a special questionnaire

Table 1 General characteristics

	LND group	CS group	*p* value
Age	68.8±10.3	71.4±13.4	>0.05
Gender (men/women)	(21/41)	(28/34)	>0.05
Physical status (Karnofsky performance scale)			>0.05
90–100%	56	48	
70–80%	5	14	
50–60%	1	0	
Tumor distribution			>0.05
Left colic flexure	3	2	
Descending colon	7	6	
Sigmoid colon	52	54	
Concomitant surgery	49	40	>0.05
T			>0.05
T_1	1	3	
T_2	9	8	
T_3	46	41	
T_4	6	10	
N			>0.05
N_0	33	34	
N_1	19	20	
N_2	10	8	
M			>0.05
M_0	59	57	
M_1	3	5	
Stage			>0.05
I	4	19	
II	28	25	
III	27	23	
IV	3	5	
Degree of differentiation			>0.05
G_1	29	28	
G_2	28	29	
G_3	5	5	
Morbidity	11	18	>0.05
Mortality	1	9	0.008
Adjuvant chemotherapy	30	28	>0.05
Recurrences	17	18	>0.05
Sites of recurrence			>0.05
Distant	12	13	
Locoregional	5	5	

with regard to their urogenital status 7–8 months after initial surgery. Retrograde ejaculation, erectile dysfunction for previously potent men and pain, and discomfort or dryness during sexual activity for women were recorded as sexual disorders. Voiding problems or low urinary tract infection was recorded for both men and women as urinary morbidity.

Statistical analysis

Statistical analysis was made using Statistical Package for Social Sciences. The study of relationships between variables was made using χ^2 (Pearson's correlation). Survival analysis was performed using the Kaplan–Meier method and comparison of curves with the log–rank test. Cox regression analysis made possible the multiple analysis of survival and logistic regression analysis was used to calculate the clinical factors related to recurrence. P values <0.05 were considered significant. The postoperative deaths were not excluded from the survival analysis. The end point of the study was survival.

Results

All the patients in both groups underwent R_0 resection. The mean number of retrieved lymph nodes in the CS group was 10 (6–41) and in the LND group 19 (16–61) ($p=0.048$). As demonstrated in Table 1, the groups were comparable except for hospital mortality ($p=0.008$). The hospital mortality in the LND group was 1.6% (one patient) and in the CS group 14.5% (nine patients). Although 18 patients in the CS group and 11 patients in the LND group developed complications, the difference was not significant (Table 2). In both groups, stages III and IV patients completed their treatment receiving systemic chemotherapy. In the LND group, 24 oophorectomies, 3 splenectomies, 7 segmental resections of the small bowel, 3 cholocystectomies, and 12 hernia repairs were performed concomitantly. In the CS group, 18 oophorectomies, 4 splenectomies, 4 segmental resections of the small bowel, 4 cholocystectomies, and 10 hernia repairs were performed concomitantly ($p>0.05$).

Table 2 Postoperative complications

	LND group (no. of patients)	CS group (no. of patients)
Respiratory	2	2
Cardiovascular	3	4
Anastomotic failure	1	3
Septic	2	4
Renal	0	1
Wound infection	3	4

Histopathology

Complete histopathologic report was available for all the resected specimens. Three patients in the LND group and five in the CS group were classified as M_1 because of the presence of limited peritoneal spread. Peritoneal dissemination was detected intraoperatively. The limited extent of the peritoneal spread made impossible a precise preoperative staging. Peritoneal implants were found either at the greater omentum or at small bowel loops directly invaded by the primary tumor. In these cases greater omentectomy or limited intestinal resection was performed en bloc with the specimen and no visible tumor was left behind. No synchronous colorectal tumor (polyp or cancer) was detected in the specimens. Two patients in the LND group were detected as having disease in lymph nodes of the retroperitoneal area. One of them died because of liver metastases within 2 years after initial surgery and the other is still alive 10 years after initial treatment.

Follow-up

No patient was lost during follow-up. Recurrence was detected in 34 patients (27.4%). One of them was stage I (LND group), 5 were stage II (1 in LND and 4 in CS group), 23 were stage III (11 in LND and 12 in CS group), and 5 were stage IV (3 in the LND group and 2 in the CS group). During follow-up 12 patients in the LND group were recorded with distant metastases and 4 with locoregional metastases. In the CS group 14 patients were recorded with distant and 4 with locoregional metastases. The distant metastases were multiple liver or pulmonary lesions and they were considered nonresectable. The patients in both groups with distant metastases were treated with systemic chemotherapy. Resection of locoregional recurrence was attempted in two patients of the LND group and the others denied any further treatment. By univariate analysis it was demonstrated that there was no difference in recurrences between the groups ($p=0.569$), either for locoregional ($p=0.6943$) or for distant recurrences ($p=0.6521$). Multivariate analysis showed that stage was the only clinical factor independently influencing recurrence ($p<0.0001$).

Six patients (9.7%) in the CS group developed late urogenital morbidity. Retrograde ejaculation was present in one man. Two women and three men suffered from

Table 3 Urogenital morbidity

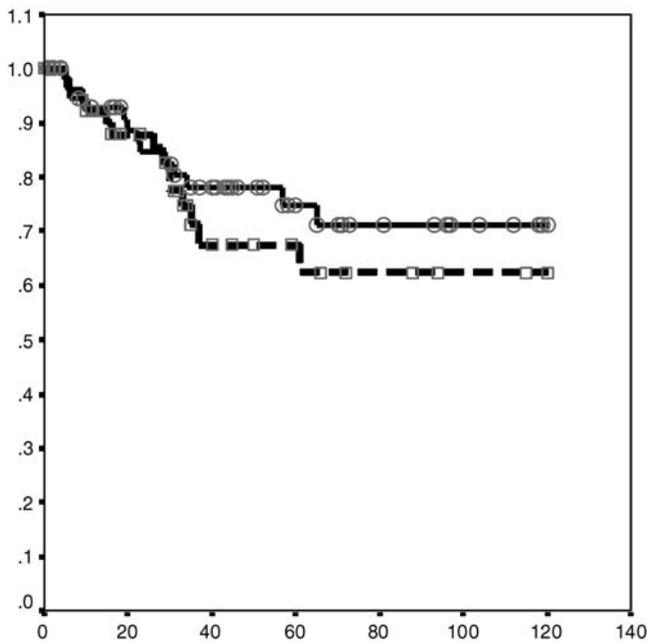|	LND group (no. of patients)	CS group (no. of patients)
Ejaculatory	2	1
Low urinary tract infections	5	5

Fig. 1 Survival rates of 5 and 10 years for patients undergoing extended lymph node resection (*continuous line*) or conventional surgery (*dotted line*)
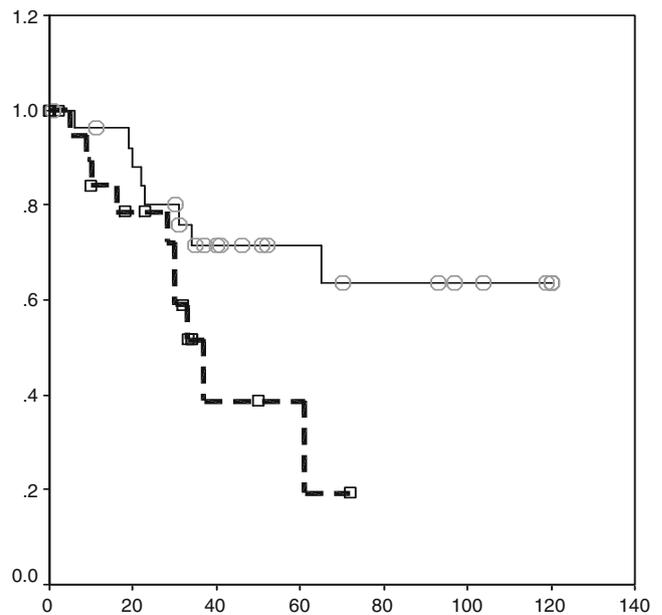

Fig. 2 Survival rates of 5 and 10 years for stage III patients undergoing extended lymph node resection (*continuous line*) or stage III patients undergoing conventional surgery (*dotted line*)

frequent low urinary tract infections. Seven patients (11.3%) in the LND group complained for late urogenital symptoms. Two men complained for retrograde ejaculation. Two men and three women complained for frequent low urinary tract infections. Late urogenital morbidity was not different between the two groups ($p>0.05$) (Table 3).

Survival

Mean survival time for the LND group was 94 ± 6 months [95% confidence interval (CI) = 82–106] and for the CS group was 86 ± 8 months (95% CI = 17–100). Although the 5-year survival rate for the LND group was 75% and for the CS group 67%, the difference was not significant

$(p=0.4341)$ (Fig. 1). By univariate analysis, it was demonstrated that age, gender, physical status, the use of adjuvant chemotherapy, tumor location, histologic type of the resected specimens, and stages I and II were not related to survival ($p>0.05$) (Table 4). Only T ($p=0.0325$), N ($p<0.0001$), and the degree of differentiation ($p=0.0081$) were related to survival. In addition, it was found that the 5-year survival rate in LND group stage III was 70% and in CS group stage III 19% ($p=0.0406$) (Fig. 2).

By multivariate analysis it was shown that the individually prognostic clinical factors of survival were T ($p=0.006$) and N ($p=0.003$) (Table 5).

Discussion

The extent of lymph node resection in left-sided colon cancer still remains an issue of controversy [6]. Lymphatic metastasis in colorectal cancer is almost always likely to follow an orderly pattern of spread from the distal paracolic nodes to the more proximal nodes [2]. Skip metastases are found in less than 5% because bypassing of a node or a group of nodes is an infrequent event [7, 8]. This option supports the concept that extended lymphadenectomy with

Table 4 Univariate analysis for survival

Factor	p value
Age	0.2617
Gender	0.8729
Physical status	0.4505
Tumor distribution	0.6739
Concomitant surgery	0.5579
T	0.0325
N	0.0000
M	0.6238
Degree of differentiation	0.0081
Adjuvant chemotherapy	0.9785
Stage I	0.2207
Stage II	0.2293
Stage III	0.0406

Table 5 Multivariate analysis for survival

Variable	Hazard ratio	p value
T	3.088	0.013
N	1.836	0.003

high ligation of the inferior mesenteric artery is not necessarily required in colorectal cancer and conventional lymph node resection without high ligation of the inferior mesenteric artery may be considered a potentially curative operation. However, detailed examination of colectomy and abdominoperineal resection specimens has revealed that when colorectal cancer metastasis blocks regional nodes then lymph flow is directed to alternative routes involving nodes at atypical locations known as retrograde or lateral metastases [1]. This option supports the concept that extended lymphadenectomy may be required if a potentially curative result is attempted.

The initial study about high ligation of the inferior mesenteric artery combined with radical lymph node resection of the retroperitoneal space stated that high ligation was the key point for the increase of survival in patients with left-sided colon cancer [9]. A later study stated that radical lymphadenectomy combined with high ligation of the inferior mesenteric artery was the clinical factor that improved survival [10]. The majority of later studies did not demonstrate any increase in overall survival [11, 12]. Only one study reported a significant survival benefit in sigmoid cancer patients undergoing extended lymph node resection [2]. Historical reports showed that the reduction of local recurrences was possible by radical resection of the lymphatic network [2]. Even if the risk of locoregional recurrence may be reduced, radical resection of the lymph nodes could not affect the occult or microscopic nonnodal metastatic tumor. This observation fits with the data showing that surgery helps prevent locoregional recurrences while having no effect on overall survival [13]. This observation was not reproduced in the present study once both locoregional and distant metastases were not different for LND and CS group. In addition, no difference in the total number of recurrences was found.

The results of the study demonstrate that radical lymph node resection in patients with left-sided colon cancer does not offer a survival benefit although there is a trend for improvement of survival after radical lymph node resection. In fact, no difference in survival was demonstrated in stages I and II. However, in stage III, the LND group was shown to have a statistically significant survival over the CS group. This was the result of univariate analysis but was not reproduced by multivariate analysis, which means that extended lymph node resection of the retroperitoneal area is not an independent prognostic variable of survival. On the other hand, Cox regression analysis showed that only T and N are the factors that independently influence survival.

In this study, the number of stage III patients was small (27 in LND group and 23 in the CS group) and probably another study including larger number of patients is required to establish whether these patients may be offered a survival benefit by lymph node resection of the retroperitoneal area. However, in clinical practice no diagnostic test can properly select left colon cancer patients stage III preoperatively.

Bilateral oophorectomy was always performed en bloc with the resected left colon although it has never been justified as a standard step of colon cancer treatment in postmenopausal women.

The study demonstrated that hospital mortality was lower after radical surgery. Surprisingly, this is in agreement with the results of other studies [2]. It is generally believed that hospital morbidity and mortality is not different between conventional and radical surgery, although a few studies report a higher incidence when radical surgery is performed [14].

During extended lymphadenectomy injury of the hypogastric nerves in the retroperitoneal space along the peritoneal reflection of the sigmoid mesentery may result in late urogenital morbidity, which becomes obvious in previously potent adult men as ejaculatory dysfunction [15]. The thoracolumbar sympathetic chain and the hypogastric nerves are in close anatomic proximity to resection lines in extended lymphadenectomy. Permanent injury to the nerve plexus may occur during surgery even when conventional surgery is performed because during left colon mobilization there is a possibility of avulsion of these structures [16]. Therefore, approximately equal number of patients in both groups developed late urogenital morbidity that was particularly obvious in previously potent men as retrograde ejaculation. Ejaculation is regulated by the sympathetic nervous system from T_{11} to L_2, an anatomic structure that is amenable to injury during left colon mobilization and explains the results.

Conclusions

Radical resection of the lymphatic network of the retroperitoneal space is associated with the same morbidity as conventional surgery and the same rate of late urogenital complications. Radical retroperitoneal lymph node resection does not seem to offer any survival benefit when it is compared to conventional surgery although there is a trend of improvement in survival particularly in stage III patients.

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