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SURGICAL ENDOSCOPY
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Laparoscopic colectomy for colon adenocarcinoma

An 11-year retrospective review with 5-year survival rates

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Abstract
Background: Laparoscopic colectomy for the management of colon cancer remains a controversial therapeutic option, especially when the outcomes are compared with the historically accepted survival data and recurrence rates after open surgery. The purpose of this study was to evaluate the 5-year overall and disease-free survival rates after laparoscopic colon resection for invasive colon adenocarcinoma.
Methods: A total of 129 patients underwent consecutive laparoscopic colectomies for colon adenocarcinoma (between April 1992 and 2004 January) by a single surgeon at a single institution. Records were analyzed retrospectively and follow-up data was obtained. The Student *t*-test, Cox regression analysis, and Kaplan-Meier survival data were used for statistical analysis.
Results: After patients with noninvasive disease on final pathology were excluded, the study population comprised 88 patients who underwent laparoscopic colectomies for invasive colon cancer with >2 years of follow-up. Of these cases, 81 (93%) were amenable for complete follow-up at 11years (41 women and 40 men; mean age, 76 years). Mean follow-up was 61 months. There was one perioperative death (1.2%), and the overall postoperative morbidity rate was 13.6%. The average number of lymph nodes harvested was 10.1 (± 6). There were no port site recurrences. The Kaplan-Meier survival data were as follows for 5-year overall survival and 5-year disease-free survival, respectively stage I ($n = 34$) 89% and 89%; stage II ($n = 22$), 65% and 59%; stage III ($n = 19$), 72% and 67%; stages I–III combined, ($n = 75$), 77% and 73%.
Conclusions: For this specific cohort of patients undergoing curative laparoscopic colectomies for invasive colon adenocarcinoma, the mean follow-up was >5 years. Overall survival and disease-free survival for stage I, II, and III colon cancer as well as for stages I–III combined are favorable and comparable to historically acceptable open colectomy survival rates. Overall survival and disease-free survival after laparoscopic colectomy for invasive colon cancer is no worse, and perhaps better than, the previously reported rates for the same procedure done by an open technique.

Key words: Laparoscopy — Colectomy — Colon — Adenocarcinoma — Survival

There continues to be controversy over the application of laparoscopic techniques to the management of colonic diseases, despite the many studies documenting the advantages of minimally invasive surgery, including a shorter length of hospital stay, less pain, and an earlier return to normal activities [4, 12, 15]. The novel nature of this technology, slow development of appropriate laparoscopic skills, and perceived difficulty of colonic resection via the laparoscopic approach have all had a role in the delay of acceptance of this method. The role of laparoscopic surgery in colonic adenocarcinoma has been even more controversial [1–3, 13, 17]. Tumor and port site metastasis has been a major concern [20]. However, most surgeons now believe that these problems are no more serious than those that can occur in traditional open colon surgery [7, 16].

The goal of surgery in colon cancer is cure. The accepted survival rates for colon cancer patients who are resected via an open technique are based on years of retrospective accrual of data [18]. It seems prudent to judge the laparoscopic data against these norms. The generally accepted benchmarks are overall survival and disease-free survival.

We report the long-term follow-up data for our patients with invasive adenocarcinoma of the colon. This is a single surgeon's experience at the same institution over an 11-year period.

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Methods

Between April 1992 and January 2004, a single surgeon (B.A.S) at our institution performed 680 laparoscopy-assisted colectomies, 105 of which were performed for invasive colon adenocarcinoma. With institutional review board approval, a database was created by retrospectively reviewing hospital and office records of these patients. Follow-up data obtained by means of reviewing medical records, making telephone calls, and reviewing the Social Security Death Index (SSDI) were then entered into the database. Information recorded included patient demographics; age at operation; tumor location; type and duration of laparoscopic colectomy; length of hospital stay; final tumor pathology, including grade, number of nodes, and tumor stage (tumors were staged according to the American Joint Committee on Cancer TNM staging criteria); and perioperative morbidity and mortality. According to the pathology department at our institution, pathology specimens and nodal analysis were recorded in a standardized fashion. Management with adjuvant chemotherapy was noted, but specifics regarding type, duration, and dose were not. Finally, information on survival status and tumor recurrence was recorded. Disease recurrence was defined as evidence of locoregional (within the region of initial surgical resection) or distant (liver) disease and was identified by means of CT scan, positive emission tomography (PET), or colonoscopy. Recurrences had to be biopsy-proven. Levels of CEA were not followed. Length of follow-up was defined as the time between the date of operation and either the day of death or the most recent follow-up visit. Interval to recurrence was recorded from the date of operation to the date that a recurrent lesion was diagnosed. All of our results are shown in table form as well as being described in the text. Where appropriate, mean values are also reported.

To be included in the data analysis, patients had to have been operated on 24 months prior to March 2004. In addition, they had to have invasive colon adenocarcinoma on final pathology. Patients were excluded if the operation was performed <2 years prior to the writing of this paper or if the final pathology did not reveal invasive adenocarcinoma (no residual tumor identified or Tis). In addition, patients with concomitant inflammatory bowel disease and cancer as well as patients with rectal cancer were also excluded.

The purpose of this study was to evaluate the 5-year overall and disease-free (number of patients alive, without disease recurrence) survival data for this specific population of patients who had undergone an elective laparoscopic colon resection for invasive adenocarcinoma as performed by a single surgeon at a single institution. As compared to the acceptable survival rates for open colon resection, we hypothesized that our patients would have survival data as good as or better than those for the open procedure. In addition, we wanted to report our short-term and long-term morbidity and mortality data.

Operative procedures

All patients underwent a laparoscopy-assisted colectomy. Preoperatively, the patients received a dose of cephazolin and metronidazole, and all cases were performed under general anesthesia. Pneumoperitoneum to a pressure of 14 mmHg was used for all procedures. Prior to 1994, we performed our mobilization of the colon in a lateral-to-medial direction, followed by high ligation of the lymphovascular pedicle; however, from 1994 to 2004, we performed our colon mobilizations from medial to lateral, with early ligation of the lymphovascular pedicle. In all cases, we emphasized the no-touch technique, the use of a wound-protector, and the use of trocar stabilization by means of a suture or a tight skin incision. Extraction site length varied depending on the size of the colon tumor. At no time was the tumor squeezed through a small incision. The size of the incision was never measured.

Statistical analysis

The main end points of the study were overall and disease-free survival at the 5-year point. Statistical analysis was performed in March 2004. Cut-off points for the continuous variables were determined by their median values, and the groups were compared using the Students *t*-test, assuming unequal variance. Kaplan-Meier curves were used to show the survival rates for the cohort and then broken down by stage. Cox survival analyses were performed separately for stage, sex, age, and lymph node status, as well as with all the variables to allow us to analyze the multivariate associations of these variables with our end points and to obtain hazard ratios (HR). All calculations were done with SPSS software (ver. 10.0) and confirmed by our biomathematical sciences department.

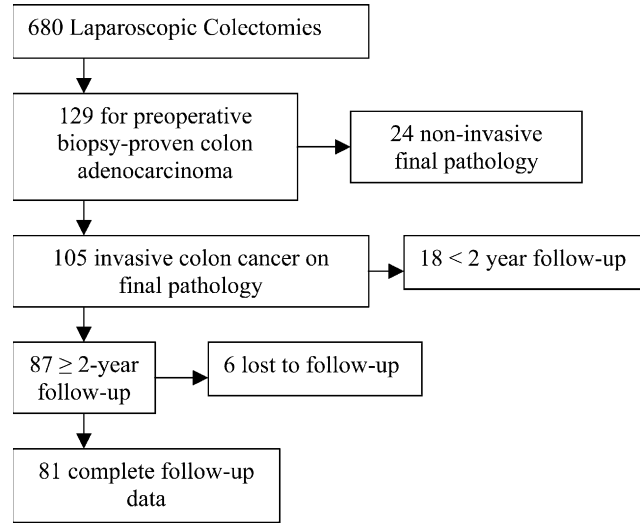


Fig. 1. Trial profile.

Results

Within the 680 laparoscopic colectomies that we reviewed, we found a cohort of 129 patients who had undergone consecutive laparoscopy-assisted colon resections for preoperative biopsy-proven colon adenocarcinoma (Fig. 1). Because our goal was to review the long-term results of patients who had undergone laparoscopic colectomy for invasive colon adenocarcinoma only, we eliminated from this population any patient whose final pathology showed noninvasive cancer (this included pathology that showed carcinoma in situ [Tis] or pathology that showed no residual tumor at the inked polypectomy site [T0]). In addition, because most tumor recurrences occur <2 years after resection, we did not include in our study any of the patients who were resected <2 years prior to March 2004. Of the 87 patients who were eligible for our review, 81 (93%) were available for complete follow-up. The six patients lost to follow-up included one from the stage I group, two from the stage II group, and three from the stage III group. Of the three lost in the stage III group, all were operated on in either 1992 or 1993, two are alive as per the SSDI but cannot be located, and one is dead (this patient's cause of death is unknown). We therefore were able to study the long-term results for 81 patients who underwent laparoscopic colon resections for invasive colon cancer, of which 75 were performed with intent to cure (stages I–III).

The baseline characteristics of our patient population are shown in Table 1. Statistical data pertaining to the operation, length of hospital stay, and patient follow-up can be found in Table 2. The stage II and III

Table 1. Patient characteristics

	Laparoscopy-assisted colectomy (n = 81)
Mean age (yr)	
All stages	76.1 (41–94)
Stage I	73.0
Stage II	82
Stage III	78
Stage IV	69
Sex (male/female)	40/41
Tumor location	
Cecum	23
Ascending colon	14
Hepatic flexure	5
Transverse colon	1
Splenic flexure	3
Descending colon	8
Sigmoid colon	27
Intervention	
Right colectomy	42
Transverse colectomy	2
Left colectomy	12
Sigmoid/anterior resection	25
Mean no. of lymph nodes in resected specimen	
All stages	10.1 (1–26)
Stage I	10.7
Stage II	10.9
Stage III	8.7
Stage IV	7.7
Extent of primary tumor (TNM system)	
T1	23
T2	24
T3	28
T4	6
Lymph node metastasis (total patients)	(25)
N1	20
N2	5
Tumor stage (TNM system)	
I	34
II	22
III	19
IV	6
Histology	
Well-differentiated	28
Moderately differentiated	45
Poorly differentiated	8

Table 2. Variables and statistics

Variable	Mean (SD)	Median	Range
Operating time (min)	185 (51)	182	80–365
Length of hospital stay (d)	5.9 (2.5)	5	3–23
Follow-up (all stages) (mo)	61 (35)	56	1–133
Disease-free interval (stages I–III) (mo)	64 (34.7)	60	1–133
Age (yr)	76.1 (11)	79	41–94

patients were similar with respect to gender (p = 0.9), age (p = 0.36), follow-up time (p = 0.3), and number of nodes harvested (p = 0.2). Stage I patients were similar to stage II and III Patients with respect to gender (p = 0.3), follow-up time (p = 0.7), and number of nodes harvested (p = 0.2), but they were significantly different from stage II patients in terms of mean age (p = 0.006). The mean age of patients was as follows: stage I, 73 years; stage II, 82 years; and stage III, 78 years. Stage I and II patients were statistically similar with respect to age (p = 0.15). Although our groups were similar in terms of sex, we found it interesting to note that when analyzed using the Cox regression method, 5-year disease-free survival rate for women was 80% whereas for men it was only 65%. This difference was not statistically different (p = 0.09) (RR = 2.3, 95% CI 0.8 – 6.2).

Table 3. Tumor recurrence and mortality in patients with nonmetastatic colon cancer

	Laparoscopy-assisted colectomy (n = 75)
Type of recurrence	
Liver metastasis	4
Locoregional relapse	2
Port site recurrence	0
Overall tumor recurrence	6 (8%)
Mean time to recurrence (mo)	23
Cause of death	
Perioperative mortality	1 (1.2%)[b]
Tumor progression	4 (5.3%)
Other[a]	17 (22.5%)

[a] Stroke (n = 2), myocardial infarction (n = 2), Alzheimer's disease (n = 1), respiratory failure (n = 1), brain tumor (n = 1), lung adenocarcinoma (n = 1), "natural causes" (n = 9). Average age of those who died without disease recurrence was 84 years for stage II patients and 88 years for stage III patients.
[b] Calculated from total study population (n = 82)

Mean length of hospital stay was 5.9 days (range, 3–23). We had one perioperative death in 1992 in a stage I patient, making our overall operative mortality rate 1.2%. This perioperative death was secondary to an anastomotic leak and sepsis, with multilorgan failure and cardiac arrest on postoperative day 23. Our overall 30-day perioperative morbidity rate for the 81 patients was 13.6 % and included wound infection (n = 3), urinary tract infection (n = 2), endoluminally bleeding staple line (n = 2), partial small bowel obstruction (n = 2), pneumonia (n = 1), and deep venous thrombosis (n = 1). The two patients with postoperative bleeding were managed nonoperatively with blood transfusions, one with 4 U and one with 2 U of packed red blood cells. In 1993, one postoperative patient required a laparoscopic exploration for a prolonged small bowel obstruction, and a tight kink was found near the anastomosis. This patient recovered well from the second procedure and was discharged home on day 80 Finally, in 1992, one conversion to open (1.2%) was needed to safely identify the location of the inked tumor.

Complete follow-up data was obtained for 93% of our patients, and the mean follow-up period was 61 months (median, 56; range, 1–133). There were tumor recurrences in 6 patients, for an overall rate of 8%. The presence of nodes (p = 0.006) was significantly associated with tumor recurrence in the univariate analysis.

Table 4. Tumor recurrence

No.	Primary tumor	Grade	Recurrence location	Disease-free interval (mo)	Status	Intervention for recurrence	Total follow-up (mo)
1	T2, N1	WD	Liver	12	Alive	Hepatectomy/chemotherapy	34
2	T2, N1	WD	Liver	23	Dead	None	32
3	T3, N0	MD	Liver	31	Dead	None	48
4	T3, N0	PD	Locoregional	45	Alive	Chemotherapy	50
5	T3, N2	PD	Liver	12	Dead	Hepatectomy/ Chemotherapy	21
6	T3, N2	PD	Locoregional	17	Dead	Chemotherapy	29

WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated

Table 5. Long-term cancer- and non–cancer-related mortality during the 11-year study period

	Overall mortality (%)	Cancer-related mortality (%)
Overall ($n = 81$)	34	12
Of those with intent to cure ($n = 75$)	29	5
Stage I	21[a]	0
Stage II	40	4.3
Stage III	32	15.8
Stage IV	100	100

[a] Includes one perioperative death secondary to anastomotic leak

The mean time to remain disease-free (disease-free interval) for those patients resected with intent to cure was 64 months (median, 60; range, 1–133). Of the six tumors that did recur, the mean time to recurrence was 23 months. There were no anastomotic recurrences. Complete data on these patients can be found in Tables 3 and 4. There were no disease recurrences in the stage I patients; however, there was evidence of disease recurrence two of the 22 patients (9%) with stage II cancer and four of the 19 patients (21%) with stage III cancer. Among these patients with disease recurrence, there were no port- site recurrences and no peritoneal seeding.

Long-term mortality was also analyzed (Table 5). A careful review of the overall long-term mortality stratified by stage compared to the deaths that occurred specifically from tumor recurrence (cancer-related mortality) showed that there was a large difference between the overall mortality and cancer-related mortality for the Stage II patients. This finding may be due in part to the statistical difference in age between this group and the overall mean.

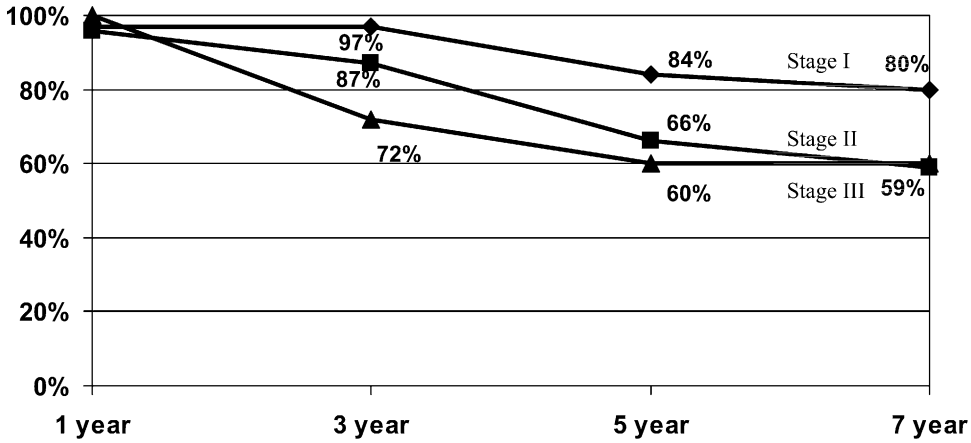
Life table (actuarial) survival data can be found in Fig. 2, but a finer way of reporting survival rates is by Kaplan-Meier curves. As derived using Kaplan-Meier methods, our 5-year overall and disease-free survival rates are shown in Table 6, with accompanying Kaplan-Meier curves shown in Fig. 3–5. The 5-year overall survival rate for the entire group resected with intent to cure (Stages I–III) was 77%, with a mean survival of 99.6 months (95% CI, 88.4–110.8). The 5-year overall disease-free survival rate for the entire group resected with intent to cure (stages I–III) was 73%, with a mean disease-free survival of 96.9 months (95% CI, 85.6–108). When we stratifed the survival curves by stage, the observed 5-year overall survival rates for stage I, stage II, and stage III were 89%, 65%, and 72% respectively (NS). The 5-year disease-free survival rates for the three stages were 89%, 59%, and 67%, respectively (NS).

Our Cox regression analysis showed that compared to stage I, stages II and III each trended toward a significant association with a decreased 5-year disease-free survival ($p = 0.8$). The hazard ratio (HR) for stage II was 3.9 (95% CI = 1.0–14.8); for stage III, was 4.3 (95% CI, 1.1–17.4). In addition, Cox regression analysis showed us that in this series, age was significantly correlated with a decrease in 5-year disease-free survival ($p < 0.01$) and a decrease in 5-year overall survival ($p < 0.05$). In the multivariate Cox regression analysis, age was significantly and independently associated with both 5-year disease-free survival ($p < 0.01$) and overall survival ($p < 0.05$), while sex (female > male) trended toward significance ($p = 0.8$).

Discussion

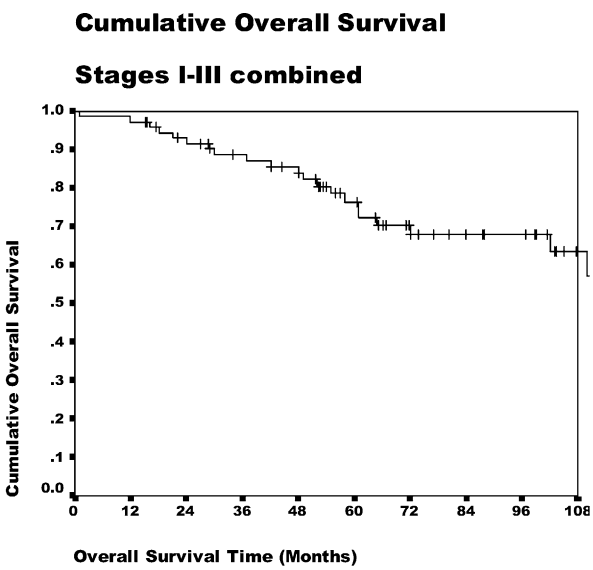
Our main goal was to study the survival of patients undergoing laparoscopy-assisted colon resection for invasive adenocarcinoma as performed by a single surgeon at a single institution. Both carcinoma of the rectum and carcinoma in patients with inflammatory bowel disease were excluded. We had 81 patients available for complete follow-up, of whom 75 had been operated on with intent to cure (stages I–III). Although no patient who presented to this surgeon with a curable colon adenocarcinoma was excluded from laparoscopic surgery, it is important to note that the relatively small number of patients and the retrospective nature of the study subject these results to possible statistical biases, including both selection and sample biases.

The generally accepted standards of reporting for the American Society of Colon and Rectal Surgeons and the American Cancer Society are 5-year overall survival and 5-year disease-free survival (cancer-free survival). Overall 5-year survival was 77%, with 89% for stage I, 65% for stage II, and 72% for stage III The Surveillance, Epidemiology, and End Results (SEER) database [18] for open surgery between the years 1992 and 1999 shows an overall 5-year survival rate of 62.3%. For the age group >75 years, the overall 5-year survival rate was 60.5%. The mean age of this study group was 76.3 years. Therefore, the 5-year overall survival in this series com-



	1 year	3 year	5 year	7 year	Mean survival (months) (95% CI)
Stage I	97%	97%	84%	80%	110 (96-125)
Stage II	96%	87%	66%	59%	90 (72 – 107)
Stage III	100%	72%	60%	60%	89 (65-113)
Stage IV	50%	--	--	--	16.3

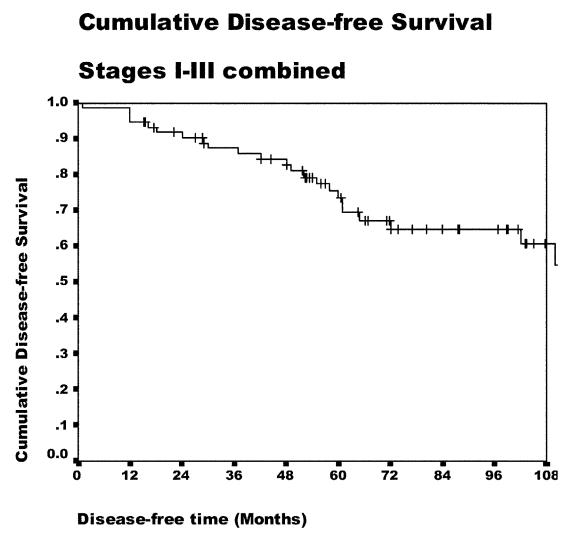
Fig. 2. Life table (actuarial survival).



month	0	12	24	36	48	60	72	84	96	108
Number at risk	75	73	64	56	50	37	26	22	19	10

Mean survival (months)	95% CI
99.6	88.4 - 110.8

A



month	0	12	24	36	48	60	72	84	96	108
Number at risk	75	72	63	57	51	37	26	22	19	10

Mean survival (months)	95% CI
96.9	85.6 – 108.0

B

Fig. 3. **A** Kaplan-Meier estimates of overall survival. Stages I–III combined. **B** Kaplan-Meier estimates of disease-free survival. Stages I–III combined.

pares favorably to the data for the open procedure. The 5-year disease-free survival was 73%, with 89% for stage I, 59% for stage II, and 67% for stage III. According to the SEER database for open surgery, the overall 5-year cancer-free survival rate for local disease (stages I and II) is 91%, whereas the rate for regional disease (stage III) is 68%. Therefore, the 5-year cancer-free survival rate in this series was no different from that after open surgery. In addition, the 5-year cumulative overall survival rates for stage II and stage III were equivalent in this series ($p = 0.55$). (Fig. 2). This has already been demonstrated in the randomized trial reported by lacy et al. in *The Lancet* in 2002, as well as several other prospective and retrospective reviews [5, 8, 9].

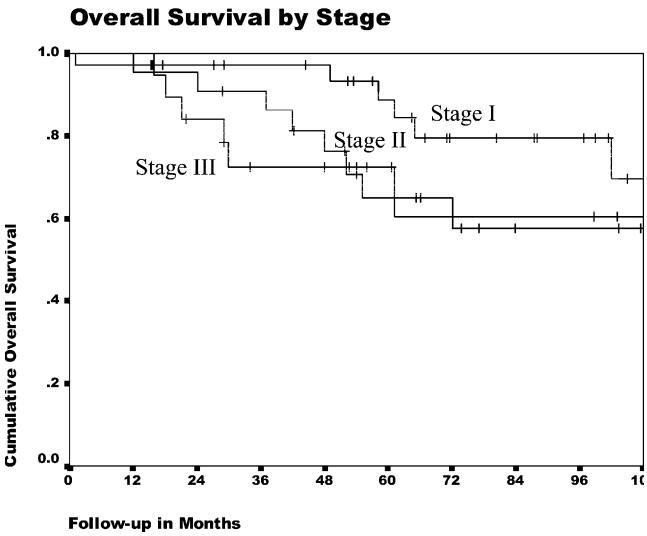


Fig. 4. Kaplan-Meier estimates of overall survival stratified by stage.

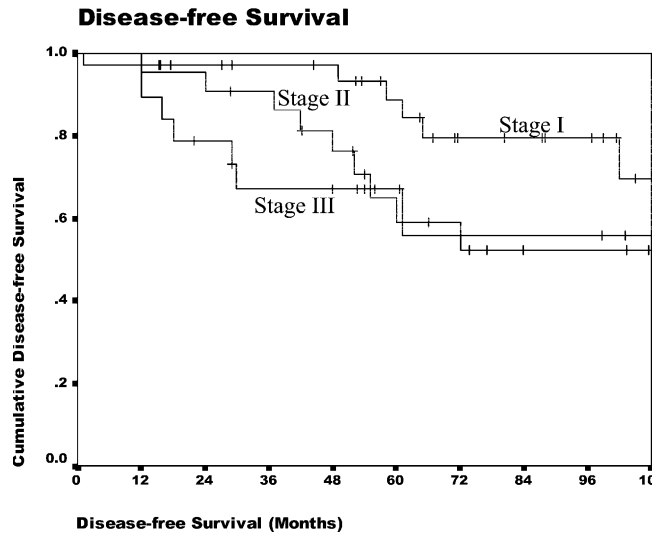


Fig. 5. Kaplan-Meier estimates of disease-free survival stratified by stage.

Table 6. Kaplan-Meier survival data

Stage	*n*	5-year overall survival (%)	Mean overall survival (mo) (95% CI)	5-year disease-free survival (%)	Mean disease-free survival (mo) (95% CI)
All (I–IV)	81	71	93.2 (81.8–104.7)	69	90.8 (79.2–102.3)
Intent-to-cure (I–III)	75	77	99.6 (88.4–110.8)	73	96.9 (85.6–108.0)
I	34	89	110.7 (96.5–124.8)	89	110.7 (96.5–124.0)
II	22	65	88.4 (70.0–106.7)	59	85.0 (67.0 – 103.0)
III	19	72	90.0 (66.4–113.8)	67	84.2 (59.6–108.7)

Note the higher overall and 5-year disease-free survival rates in stage III patients in this series (72% and 67%, respectively). This is an extremely favorable result. However, there was a single non–cancer-related death of a patient in the stage III group just beyond 60 months (60.5 months). Therefore, it is worth stating that the overall and 5-year disease-free survival rates for stage III patients dropped at 61 months to 60% and 56%, respectively. The notable difference in overall and 5-year disease-free survival at 60 and 61 months created simply by the addition of this single death must be attributed, at least in part to, the small number of patients in the particular cohort. The mean follow-up was 61 months (range, 1–133). The patient with only 1 month of follow-up was the one who died perioperatively, and he was included in the evaluation. It is important to emphasize that only patients with invasive cancer of the colon were included in this study. All Tis patients and patients who had invasive cancer in polypectomy specimens but no residual tumor in the colectomy specimen were excluded from the analysis.

As shown in Fig. 2, cumulative overall survival, as expressed in a life table, can be followed out to 7 years in this series. Clearly, our survival data compare favorably to the open data. According to the actuarial data, the mean survival (in months) is 110 (95% CI, 96–125) for stage I, 90 (95% CI, 72–107) for stage II, 89 (95% CI, 65–113) for stage III, and 16.3 for stage IV. Considering the advanced age of the patients in this series, these numbers compare very favorably to the open data as well. In addition, it is worth mentioning that at 7 years, the stage II and III patients had similar survival rates that were not statistically different ($p = 0.5$)

Table 3 lists the cancer recurrences and the causes of death in the 75 patients treated with intent to cure. So far, there are four cancer-related deaths (5.3%), but there is one patient with a late recurrence presently being treated with chemotherapy (Table 4). This patient's recurrence was documented 45 months after operation. She was stage II, and she was not treated with chemotherapy postoperatively. There was one patient (stage III) treated with chemotherapy who developed a metastatic lesion in the right lobe of the liver. He was resected, and he has no evidence of disease 22 months after the liver resection. The other four patients with recurrent disease have all died. No stage I patient has died of recurrent disease. There were no port site metastases in any of the stage I, II, or III patients. We and others believe that the incidence of port site recurrence is the same as for open surgery [6, 19]. Meticulous attention to technique during performance of the operation is the key to the prevention of port site recurrence. The non–cancer-related deaths were, as expected, in an older population. There were two patients who died with noncolon cancers. The only perioperative death (1.2%) occurred early in the series, and it was secondary

to an unrecognized leak that developed after a right hemicolectomy.

Although the primary aim of this study was to look at survival, there was a notable lack of perioperative complications given the advanced age of the patients in our study population (mean, 76.3 years). There were three wound infections (3.7%), two partial small bowel obstructions (2.4%), two anastomotic staple line bleeds (2.4%), one case of pneumonia (1.2%), and one deep venous thrombosis (1.2%). One of the patients with small bowel obstruction needed repeat laparoscopy to lyse adhesions. This was a relatively simple procedure, but the total length of hospital stay for this patient was consequently prolonged (8 days vs a mean of 5.9 days). The one conversion to open (1.2%) was secondary to a failure of India ink tattoo injection in terms of localization of the tumor. Although the preoperative location was supposed to be the ascending colon, in fact it was the splenic flexure. Proper preoperative or intraoperative localization is imperative. On that note, there were no conversions based on surgical technique, and the relatively low incidence of conversions may be related to the operating surgeon's level of experience.

The number of lymph nodes identified in the resected specimens can vary based on the location of the tumor and the diligence of the pathologist [10]. There are multiple studies demonstrating the adequacy of lymph node retrieval in laparoscopy-assisted colon resection [4, 11, 12, 14]. The mean number of lymph glands retrieved in this series was 10.1. We previously reported a comparison of laparoscopic vs open surgery at our institution, and the lymph node retrieval in this series is similar [6]. The resection margins were not measured, but the primary surgeon deemed the resection to be adequate in every case. Clear margins were documented in every patient by the pathologist. In fact, there were no local anastomotic recurrences of cancer in this series.

In conclusion, the retrospective nature of this work and the relatively small number of patients represent drawbacks to this study. However, it does demonstrate that, with adequate laparoscopic skills, the survival rate after laparoscopy-assisted colon resection is not only comparable to but perhaps even better than the results for the open procedure. Morever, it is noteworthy that the stage II and stage III patient in this series had similar 5-year survival rates.

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