

The Impact of Splenectomy on Outcome After Resection for Colorectal Cancer: A Multicenter, Nested, Paired Cohort Study

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PURPOSE: This study was designed to determine whether incidental splenectomy for iatrogenic injury affects long-term cancer-specific survival in patients having resection of an adenocarcinoma of the sigmoid or rectum.

METHODS: A retrospective case-matched review of patients undergoing surgery for colorectal cancer with incidental splenectomy between January 1, 1990 and December 31, 1999 was undertaken. Data were analysed for age, American Society of Anesthesiologists physical status, gender, disease stage, operation type, and outcome. These cases were matched with patients from the same center, of the same age and gender, with the same stage of disease and operation, who did not require a splenectomy at the time of their surgery.

RESULTS: Fifty-five patients were identified who had an iatrogenic splenectomy. Matched gender, stage, and American Society of Anesthesiologists-matched controls were identified. Follow-up from time of surgery to death or last follow-up ranged from 2 to 205 (median, 43) months. A Kaplan-Meier survival analysis using the Cox proportional hazards model to define the statistical significance found a significant difference between the groups favoring those without splenectomy (hazard ratio, 1.8; 95 percent confidence interval (CI), 1–3.3; $P=0.0399$). Cancer-specific survival at five years was 70 vs. 47 percent and at ten years was 55 vs. 38 percent.

DISCUSSION: Patients with colorectal cancer who had splenectomy as a result of iatrogenic damage of the spleen while undergoing resection of the sigmoid or rectum for adenocarcinoma had a significantly worse prognosis.

KEY WORDS: Spleen; Splenectomy; Colorectal cancer; Survival; Anterior resection.

Incidental splenectomy for iatrogenic injury at the time of colorectal resection is an infrequent but well recognized adverse event in patients who have left-sided colorectal resections. A splenectomy is recognized as having a significant immunomodulating effect, best described with regard to postsplenectomy sepsis and graft survival after renal transplant.¹ A variable effect of splenectomy has been described on survival after cancer surgery especially with regard to pancreatic, esophageal, and gastric cancer.^{2–7} In patients with these cancers, splenectomy is usually undertaken to achieve adequate cancer clearance or lymphadenectomy; a similar circumstance can occur in patients with colorectal cancer near the splenic flexure. The spleen, however, may be damaged during left-sided colon rectal resections during mobilization of the splenic flexure and require removal as a result.^{8–10}

Three studies have previously examined the effect of splenectomy on outcome after colorectal resection.^{8–10} Two studies have suggested that splenectomy impairs survival and one study has suggested that it makes no difference. These studies have variably included patients in whom the spleen was removed before surgery or in whom the spleen was removed because the cancer was at the splenic flexure. This study was designed to determine whether incidental splenectomy as a result of iatrogenic injury affects long-term survival in patients having resection of an adenocarcinoma of the sigmoid or rectum.

METHODS

A multicenter, retrospective database of patients undergoing surgery between January 1990 and December 1999 in five major New Zealand teaching hospitals was collected. A search of the clinical diagnostic and proce-

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Table 1. Descriptive data on patients with iatrogenic splenectomy and their matched controls

	<i>Iatrogenic splenectomy</i>	<i>Controls</i>	<i>P value</i>
No. of patients	55	55	
Median age (yr)	73 (45–90)	71 (43–89)	NS
Male/female ratio	34/21	34/21	NS
Stage of disease			
1	4	4	NS
2	32	32	
3	19	19	
4	nil	nil	
Blood transfusion*	range 0–3 median 0	range 0–4 median 0	NS
ASA			
1	5	4	NS
2	31	33	
3	16	16	
4	1	2	
5	1	0	
Site of primary			
Rectum	19	19	NS
Colon	36	36	

NS = nonsignificant; ASA = American Society of Anesthesiologists. * Data are numbers or medians with ranges in parentheses. • P>0.05.

diagnosis codes for colorectal cancer and splenectomy was undertaken at the clinical case mix centers at Auckland City, Christchurch, Dunedin, Middlemore, and Wellington Hospitals. All incidental splenectomies were identified with clinical case mix databases, were cross-referenced with hospitals pathologic audit and surgical audit databases. Only patients who had open operations were included.

Data were collected for age and gender of the patient, disease site, International Union Against Cancer/American Joint Committee on Cancer UICC/AJCC stage of disease, American Society of Anesthesiologists physical status (ASA), blood transfusion data, and the outcome of the patient identified and hospital. Each case was matched with patients from the same center, gender, similar age (± 5 years), with the same stage and site (colon or rectum)

Table 2. Univariate/multivariate regression of factors related to overall survival

<i>Factor</i>	<i>Univariate regression</i>		
	<i>OR</i>	<i>95 percent CI</i>	<i>P value</i>
Site of primary (colon vs. rectum)	0.574	0.337, 1.34	0.278
Blood transfusion (yes vs. no)	1.019	0.526, 1.702	0.944
Stage (1 and 2 vs. 3 and 4)	1.942	1.215, 3.151	0.006

OR = odds ratio; CI = confidence interval.

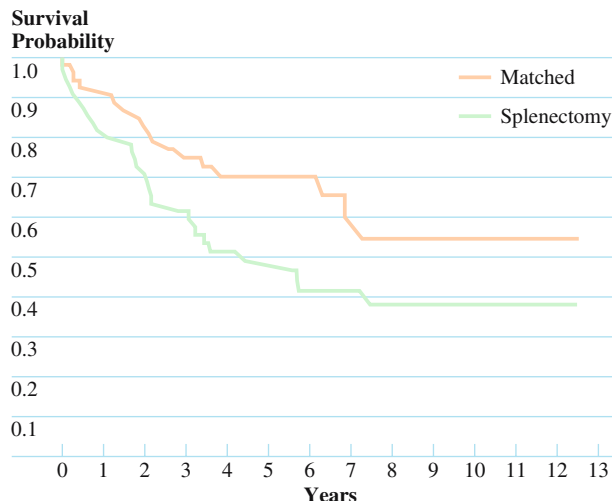
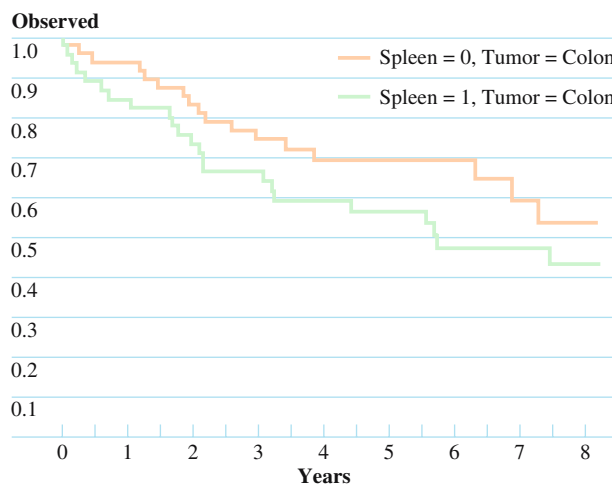


FIGURE 1. Colon and rectal cancer Kaplan-Meier survival analysis of cases and control (n=55; K-M spleen vs. no spleen; P=0.04).

of disease, the same preoperative ASA (± 1), and operation. The next patient in the indexed hospital who was operated on that fulfilled these criteria was selected for the control match.

The records of each patient were reviewed to ensure that the splenectomy was not undertaken for cancer clearance. Follow-up was possible on all patients for five years or death. Using the national unique identifier system means that all patients' major health events can be identified wherever they live within New Zealand. Although death could be confirmed with the national number system and the national deaths registrar, the cause of death was verified by reviewing the death certificate. Follow-up was recorded as the length of time

FIGURE 2. Colon cancer; Kaplan-Meier survival analysis of cases and control (n=36): colon cancers - spleen (spleen=0) vs. no spleen (spleen=1; P=0.37).



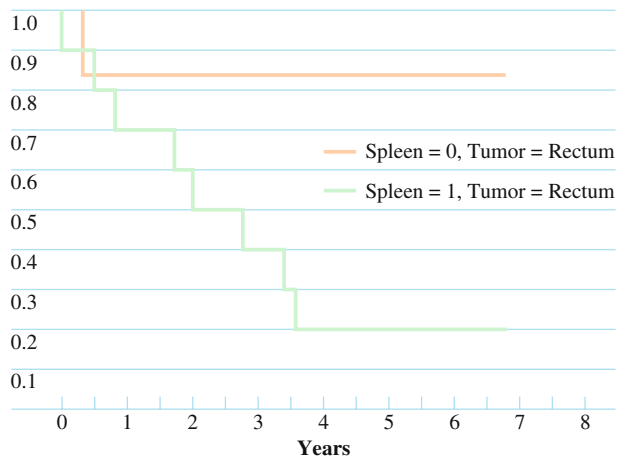


FIGURE 3. Rectal cancer; Kaplan-Meier survival analysis of cases and control (n=19): rectal cancers - spleen (spleen=0) vs. no spleen (spleen=1; P=0.03).

from operation until the patient died or was discharged from follow-up by their doctors. Cases in which the patients subsequently died after discharge from follow-up, the follow-up period was deemed to have been terminated when discharged from such by their medical team.

Statistical analysis was performed by using SPSS® version 11.0 (SPSS Inc., Chicago, IL). Fisher’s exact tests were used to compare categorical variables and ANOVA was used to compare age. Survival curves were generated by the Kaplan-Meier method. Univariate survival comparisons were performed by using the log-rank test. Multivariate survival analyses were performed by using a Cox proportional hazards model. All probability values reported are two-sided, with P<0.05 used to denote statistical significance. Approval was obtained from hospital ethics committees for this study.

RESULTS

The analysis was based on 55 cases of iatrogenic splenectomy and their matched controls (Table 1) identified during a ten-year period from the five centers

around New Zealand from January 1, 1990 to December 31, 1999. There were more than 10,000 colorectal resections for adenocarcinoma undertaken in these hospitals during this time.

The date of death or the date of the last known follow-up was used as the end point for the analysis (the last follow-up was December 31, 2004 or a minimum 5 years from operation). Follow-up from time of surgery to death or last follow-up ranged from 2 to 205 (median, 43) months.

Overall, patients with colorectal cancer who had splenectomy as a result of iatrogenic damage of the spleen while undergoing resection of the sigmoid or rectum for adenocarcinoma had a significantly worse prognosis, independent of stage (Table 2), and ASA; however, subgroup analysis of patients into colon or rectum failed to confirm this independently for colon or rectal cancers most likely because of the small sample size (Type 2 error). A Kaplan-Meier survival analysis (Fig. 1) was performed using the Cox proportional hazards model to define the statistical significance of any difference in cancer-specific survival between the two groups. There was a significant difference between the groups favoring those without splenectomy (hazard ratio, 1.8; 95 percent CI, 1–3.3; P=0.0399). The analysis found: for all patients with colon and rectal cancers (spleen vs. no spleen; P=0.03), for patients with colon cancers (spleen vs. no spleen; P=0.37; Fig. 2), and for patients with rectal cancers (spleen vs. no spleen; P=0.03; Fig. 3).

DISCUSSION

Patients with colorectal cancer who have splenectomy as a result of iatrogenic damage of the spleen while undergoing resection of the sigmoid or rectum for adenocarcinoma had a significantly worse prognosis, independent of stage of disease. Incidental splenectomy may have an immunomodulating effect after colorectal resection. When splenectomy is undertaken in most other cancer surgery, it is to obtain surgical cancer clearance or adequate lymphadenectomy. There are few studies on the influence of splenectomy on colorectal cancer out-

Table 3. Studies of outcome after splenectomy in colorectal cancer

Study	Year	No.	Type	Findings
Davis et al. ⁸	1988	68	Case-controlled	Patients after splenectomy do worse Deceased survival in Dukes C No difference in Dukes B
Varty et al. ⁹	1993	21	Case-controlled	No significant difference, but trend for patients after splenectomy doing worse 45 vs. 59 percent survival at 5 years
Konstadoulakis et al. ¹⁰	1999	25	Case-controlled	No significant difference, but trend for patients after splenectomy doing worse 30 vs. 50 percent survival at 5 years
Present study		55	Case-controlled	Patients after splenectomy do worse (P=0.0399)

comes. Upper gastrointestinal cancers, especially gastric and pancreatic cancers, seem to be the most commonly reported. In noncolorectal surgery, such as surgery for pancreatic, esophageal, or gastric cancer, splenectomy has been suggested to impair survival.²⁻⁸

In colorectal surgery, except for splenic flexure cancers, splenectomy is usually undertaken to control bleeding from iatrogenic trauma. Of the three previous studies on this (Table 3), two studies have suggested that splenectomy impairs survival and one study has suggested that it makes no difference.

The Mayo Clinic study of 68 patients operated on for colorectal cancer between 1966 and 1980, who had a splenectomy before or concurrently with the resection, was reported in 1988 as showing that splenectomy was associated with a significant decrease in survival at five years in patients with regional (Dukes Stage C) disease but not in patients with localized (Dukes Stage B) disease.⁸ This was a case-matched series similar to the present study with the healthy control subjects with concurrent disease being matched with each study patient for age, gender, stage of disease, and date of operation. There was 100 percent follow-up. Between splenectomy patients and healthy control subjects, there was no difference in the site of primary disease (rectum *vs.* colon), number of patients receiving adjuvant therapy, purpose of resection (cure *vs.* palliation), or extent of regional disease.

The report from England of 21 patients who had a concurrent splenectomy with resection of colorectal cancer between 1970 and 1988 found that splenectomy with resection of colorectal cancer increases the risk of postoperative sepsis but did not influence long-term survival.⁹ In this study the patients were matched individually with disease-control patients based on age, gender, site of tumor, Dukes stage, tumor differentiation, and date of the operation. Significantly more patients in the splenectomy group (n=11) developed postoperative infective complications than in the control group (n=4; McNemar test: $P=0.03$). Five-year overall actuarial survival was 45 percent in the former group and 59 percent in the latter (log-rank test: $\chi^2=1.07$; $P=0.24$). Similarly, five-year disease-free survival in 17 patients with Dukes B and C cancers who had curative resections did not differ between the groups (log-rank test: $\chi^2=0.08$; $P>0.25$).

The study case-matched study from Greece published in 1999 found that for 25 patients, splenectomy significantly increased the number of infective postoperative complications in patients with colonic cancer.¹⁰ Although there was a trend for shorter disease-free survival after splenectomy, it seems that splenectomy had no impact on survival.

The present study is unique. The New Zealand national individual patient number system, clinical case mix data collection, and the national cancer register and the deaths register allows unique ability to tract patients,

hence the 100 percent follow-up. This study, however, has a number of weaknesses naturally enough on this topic. It is not randomized, it is multicenter, and required a ten-year period to obtain adequate patient numbers. The patient study group is heterogenous; however, the control group is matched for the hospital, age, gender, ASA, and operation which helps control for this factor. The length of study time was long (starting 1990) and cancer therapy changed during this period, such as with the introduction of chemotherapy in the early 1990s for node-positive disease. The absence of perioperative adjuvant therapy details and absence of cause of death details (systemic distant *vs.* local recurrence) also are weaknesses that distract from the significance of the results. The subgroup analysis that has been undertaken is another possible weakness because of the small sample size,^{11,12} although overall patients who had splenectomy had a significantly worse prognosis, and subgroup analysis of patients into colon or rectal did confirm this independently for rectal cancers but failed to do so for colon cancers most likely because of the small sample size (Type 2 error).

From the above-mentioned reports, splenectomy seems to have a negative impact on survival in patients with cancer. In many patients with upper gastrointestinal cancers, this may be an effect of stage shift with more extensive surgery because of local invasion or lymphadenectomy. It seems that patients with colorectal cancer who have splenectomy as a result of iatrogenic damage of the spleen while undergoing resection of the sigmoid or rectum for adenocarcinoma have a significantly worse prognosis, independent of the stage of their disease.

CONCLUSIONS

Incidental splenectomy should be considered a poor prognostic feature. If future studies confirm this difference in mortality, it may be appropriate to consider this in the decision about the role of postoperative chemotherapy in patients who have incidental splenectomy. It is likely that there will never be enough cases in centers with high-quality surgery to undertake a randomized, controlled trial in patients with incidental splenectomy; however, given the magnitude of the difference between the patient groups, further cohort studies may confirm these findings.

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