Is a Minor Clinical Anastomotic Leak Clinically Significant after Resection of Colorectal Cancer?

Matthew G Tytherleigh, MD, FRCS, Les Bokey, MS, FRACS, Pierre H Chapuis, DS, FRACS, Owen F Dent, PhD

BACKGROUND: There are few reports comparing the variety and frequency of postoperative complications between patients with a major clinical leak requiring emergency abdominal reoperation and those with a minor leak diagnosed from clinical signs and managed expectantly without reoperation. This study examined the association between severity of leakage and 18 other postoperative complications, postoperative mortality, and length of postoperative hospital stay.

STUDY DESIGN: Data were drawn from a comprehensive, prospective hospital registry of 1,507 colorectal cancer resections involving an anastomosis from January 1995 to December 2006. Differences were evaluated by two-tailed Fisher's exact test, Student's *t*-test, or Mann-Whitney U test.

RESULTS: Leaks occurred in 54 patients (3.6%; 95% CI, 2.7% to 4.7%), comprising 21 major (1.4%; 95% CI, 0.9% to 2.1%) and 33 minor leaks (2.2%; 95% CI, 1.5% to 3.2%). Patients with a leak were significantly ($p < 0.01$) more likely than those without to have 11 of 18 other surgical and medical complications considered, although with few differences in complication rates between those with major and minor leaks. As compared with patients without leak, those with a leak (major or minor) had several of these complications rather than just one ($p < 0.001$) and greatly prolonged hospital stay ($p < 0.001$). Postoperative mortality was higher after major leaks than after minor leaks (4 of 21 and 0 of 33, respectively, $p = 0.019$).

CONCLUSIONS: A minor leak is not trivial. Apart from the fact that major clinical leakage necessitates urgent reoperation, there were few other differences between major and minor clinical leaks in the frequency of other complications. (J Am Coll Surg 2007;205:648–653. © 2007 by the American College of Surgeons)

A major clinical leak after resection and anastomosis for colorectal cancer (CRC) is a well-recognized surgical entity, as the patient presents with hypotension and tachycardia, temperature is elevated, there is local or generalized peritonitis, and possibly feculent or purulent discharge from a drain, wound, or the anus. Indication for abdominal reoperation in these patients is usually obvious. In contrast, there is a less severe form of leakage that can be termed a *minor clinical leak*[1-3] and is generally regarded as having few substantial consequences for the patient. Clinical signs in these patients are often very subtle. They include a mild elevation of temperature, slight tachycardia, postoperative ileus, and mild localized peritonism. Sometimes such a leak is confirmed on Gastrografin enema or CT scan. There is no absolute indication to reoperate and these patients are managed expectantly or conservatively. Occasionally, percutaneous drainage of an abscess can be necessary. This distinction has been recognized by Bruce and colleagues[4] in a systematic review in which they propose three categories of leak according to severity and need for intervention: radiologic leaks (asymptomatic), minor clinical, and major clinical, depending on the need for intervention or change in management. Comparisons between major and minor clinical leaks are seldom made in the literature; rather, these two types of leaks are almost invariably combined in analyses.

The aim of the study was to compare minor and major clinical leakage with respect to other immediate postoperative surgical and medical complications, postoperative mortality, and length of hospital stay and to compare these outcomes between patients with and without a leak in a large consecutive prospective series of patients having a resection with anastomosis for CRC.

METHODS

A prospective computerized clinical and pathologic database has been maintained on all patients undergoing resec-

Competing Interests Declared: None.

Received January 14, 2007; Revised May 20, 2007; Accepted May 23, 2007.
From the Department of Colorectal Surgery, Concord Hospital and The University of Sydney, New South Wales, Australia.
Correspondence address: Owen F Dent, PhD, Department of Colorectal Surgery, Concord Hospital, NSW 2139, Australia. email: owen.dent@netspeed.com.au

ISSN 1072-7515/07/$32.00
doi:10.1016/j.jamcollsurg.2007.05.031

tion for CRC by members of the Concord Hospital colorectal surgical unit since 1971.[5] The data set contains information on patient characteristics, comorbidity, presentation, preoperative investigations, surgical management, complications, pathology, and followup to time of death or for at least 14 years and has the approval of the Sydney South West Area Health Ethics Committee. The database was revised in 1995 and several new variables on complications were added. The present study is restricted to resections between January 1995 and December 2006 to incorporate this wider range of morbidity variables. All clinical data were recorded and coded under the supervision of a single surgeon.

Resections at both elective and emergency operations were included. All patients undergoing an elective operation had a standard oral bowel preparation. All patients received standard antimicrobial cover at induction of anesthesia. All operations were performed by specialist colorectal surgeons.

A diverting stoma was constructed when the anastomosis showed clinical evidence of leakage on air testing. Most stomas were constructed for patients undergoing either low or ultra-low anterior resection. The decision to construct a stoma or not was made by the individual surgeon.

Anastomotic leaks were categorized as either major clinical leaks, with signs of generalized peritonitis requiring emergency abdominal reoperation, or minor leaks diagnosed on clinical signs and confirmed radiologically and managed expectantly without abdominal reoperation. Postoperative limited contrast radiology was not performed routinely.

A diagnosis of a wound complication was based on clinical identification of at least erythema, induration, abscess formation, or wound dehiscence. A patient with clinical features of an abscess, such as abdominal pain, urgency, diarrhea, tenesmus, fever, mass felt on rectal examination, leucocytosis, pus per rectum, or pus on drainage, and confirmed by CT scan, was defined as having a pelvic or abdominal abscess as appropriate. A patient with only abdominal pain or low-grade fever, or both, who was then investigated by CT scan, which demonstrated a minor collection that did not progress, was defined as having a pelvic hematoma. Diagnosis of a urinary complication included infection, urethral stricture, ureteric injury, or temporary or longterm bladder dysfunction. An infected vascular access line was diagnosed in the presence of phlebitis associated with a venous access cannula or a positive culture from the cannula site, or both. Renal failure and respiratory and cardiac complications covered a range of conditions that required management by a specialist in internal medicine. Acute drug withdrawal relates to patients with known drug dependency who manifested a psychotic state postoperatively, confirmed by a psychiatrist. Postoperative deaths were defined as deaths that occurred within 30 days of resection or before discharge from hospital after resection, but not including deaths from CRC, as these were deemed not to have resulted from the operation or its sequelae. All complications and other characteristics examined in this study were sought in every patient, and their presence or absence was recorded explicitly. There were no missing data for any variable.

Statistical analysis

Differences between percentages in contingency tables were evaluated by Fisher's exact test as implemented in SPSS 14.0 (SPSS Inc). Because of the exploratory multiple comparisons between types of leaks across a large number of complications (Table 1), the convention of setting a conservative level for statistical significance to reduce the possibility of type I errors was followed, in this case, $p < 0.01$. Elsewhere, when testing differences in postoperative mortality, number of complications, hospital stay, diverting stomas, and some other comparisons, there were implicit hypotheses underlying the tests, and the conventional significance level of $p < 0.05$ was used. The two continuous variables, number of complications, and hospital stay were bell-shaped for patients who had a leak. A number of complications were reverse J-shaped, and hospital stay was strongly positively skewed for patients who did not have a leak. Differences between means of bell-shaped distributions were assessed by *t*-test, and differences between medians for reverse J-shaped or skewed distributions as compared with the bell-shaped distributions were tested by Mann-Whitney U test. All tests were two-tailed. Ninety-five percent confidence intervals for percentages were calculated using StatXact 5 (Software Corp).

RESULTS

Of 1,854 consecutive resections for CRC performed between January 1995 and December 2006, an anastomosis was constructed in 1,507 (81.3%). Fifty-four resections were performed at urgent operation. There were 867 male and 640 female patients, with a median age of 70 years (range 24 to 96 years). Tumor site and type of operation are detailed in Table 2.

Clinical anastomotic leaks were identified in 54 patients (3.6%; 95% CI, 2.7% to 4.7%), comprising 21 major leaks (1.4%; 95% CI, 0.9% to 2.1%) and 33 minor leaks (2.2%; 95%, CI 1.5% to 3.1%). Site distribution of leaks is shown in Table 3. Occurrence of leaks of either kind did not differ significantly between hand-sewn and stapled anastomoses (8 of 275 [2.9%] and 46 of 1,232 [3.7%], respectively; p =

Table 1. Association Between Anastomotic Leak and Postoperative Complications

	No leak		Minor leak		Major leak		Any leak		p Values			
Complications	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**No leak versus minor leak**	**No leak versus major leak**	**Minor versus major leak**	**No leak versus any leak**
Wound complication	113	7.8	3	9	9	43	12	22	0.739	< 0.001	0.006	0.001
Septicemia	42	2.9	5	15	6	29	11	20	0.003	< 0.001	0.305	< 0.001
Pelvic abscess	3	0.2	14	42	9	43	23	43	< 0.001	< 0.001	1.000	< 0.001
Pelvic hematoma	12	0.8	9	27	4	19	13	24	< 0.001	< 0.001	0.536	< 0.001
Intraabdominal abscess	6	0.4	5	15	10	48	15	28	< 0.001	< 0.001	0.014	< 0.001
Urinary	103	7.1	11	33	3	14	14	26	< 0.001	0.188	0.202	< 0.001
Renal failure	6	0.4	0	0	1	5	1	2	1.000	0.096	0.389	0.226
Respiratory	216	14.9	13	39	13	62	26	48	< 0.001	< 0.001	0.163	< 0.001
Cardiac	183	12.6	7	21	11	52	18	33	0.180	< 0.001	0.037	< 0.001
Deep venous thrombosis	20	1.4	3	9	0	0	3	6	0.013	1.000	0.274	0.046
Pulmonary embolus	34	2.3	2	6	2	10	4	7	0.189	0.091	0.638	0.044
Cerebrovascular accident	6	0.4	0	0	2	10	2	4	1.000	0.005	0.147	0.031
Infected vascular access line	45	3.1	2	6	2	10	4	7	0.281	0.143	0.638	0.095
Prolonged postoperative ileus	166	11.4	11	33	12	57	23	43	< 0.001	< 0.001	0.009	< 0.001
Small bowel obstruction	46	3.2	3	9	2	10	5	9	0.092	0.147	1.000	0.033
Confusion	121	8.3	5	15	8	38	13	24	0.193	< 0.001	0.100	< 0.001
Acute drug withdrawal	14	1.0	0	0	1	5	1	2	1.000	0.194	0.389	0.423
Multisystem failure	15	1.0	0	0	4	19	4	7	1.000	< 0.001	0.019	0.004

0.506), and this was true for major and minor leaks separately.

Table 1 shows the frequency of 18 surgical and medical complications in patients without a leak, as compared with their frequency in patients with a minor leak, a major leak, and minor and major leaks combined. Seven complications were considerably more common among patients who had a minor clinical leak than among those with no leak. These were the sepsis-related complications of septicemia, pelvic abscess, pelvic hematoma, and intraabdominal abscess, plus urinary and respiratory complications and prolonged postoperative ileus. Eleven complications were more common among patients who had a major leak than those with no leak. Again, these included sepsis-related complications with the addition of a wound complication, plus respiratory and cardiac complications, stroke, prolonged postoperative ileus, confusion, and multisystem failure. There were significant differences in rates between patients with a major leak and those with a minor leak in only two complications: wound complication and prolonged postoperative ileus.

When major and minor clinical leaks were combined, 11 complications were considerably more common among patients with a leak than in those without (Table 1). These were sepsis-related complications of septicemia, pelvic abscess, pelvic hematoma, intraabdominal abscess, and wound complications; plus urinary, respiratory, and cardiac complications; prolonged postoperative ileus; confusion; and multisystem failure. An additional four would have been significant if the 0.05 significance level had been used rather than the more conservative 0.01 level. These were deep venous thrombosis, pulmonary embolus, cerebrovascular accident, and small bowel obstruction. Three complications did not show a substantial association with any category of leakage. These were renal failure, infected vascular access line, and acute drug withdrawal.

Total load of complications

For all patients, total number of complications (of 18 considered) ranged from 0 to 11, with a median of 0 and a reverse J-shaped distribution (55.7% had no complications). For patients with a minor leak, the number of complications ranged from 0 to 9, with a median of 3 and a mean of 2.8. For those with a major leak, the number of complications ranged from 0 to 11, with a median of 4 and a mean of 4.7. Patients with either kind of leak had markedly more complications than those with no leak (Mann-Whitney, $p < 0.001$), although those with a minor leak

Table 2. Tumor Site and Type of Operation

	n (N = 1,507)	%
Tumor site		
Cecum	182	12.1
Ascending colon	223	14.8
Hepatic flexure	54	3.6
Transverse colon	121	8.0
Splenic flexure	30	2.0
Descending colon	48	3.2
Sigmoid colon	356	23.6
Rectum 12−18.9 cm	177	11.7
Rectum 8−11.9 cm	212	14.1
Rectum 0−7.9 cm	104	6.9
Operation		
Right hemicolectomy	477	31.7
Transverse colectomy	8	0.5
Left hemicolectomy	56	3.7
Sigmoid colectomy	31	2.1
Segmental colectomy	11	0.7
Extended colectomy	102	6.8
Total colectomy	7	0.5
High anterior resection	342	22.7
Low anterior resection	212	14.1
Ultra-low anterior resection	248	16.5
Complex	13	0.9

had fewer complications than those with a major leak (*t*-test, $p = 0.008$).

Postoperative mortality

Postoperative mortality in patients with a leak (minor or major) was 4 of 54 (7%; 95% CI, 3% to 17%). There was no difference in postoperative mortality rate between patients with a minor leak (0 of 33 [0%]; 95% CI, 0% to 9%) and those without leak (29 of 1,453 [2.0%]; 95% CI, 1.3% to 2.9). Mortality rate for those with a major leak (4 of 21 [19%]; 95% CI, 7% to 40%) was significantly higher than either those with no leak ($p < 0.001$) or those with a minor leak ($p = 0.019$).

Hospital stay

Median postoperative hospital stay was significantly longer for patients with a minor leak than for those with no leak (19 days and 10 days, respectively, $p < 0.001$) and also longer for those with a major leak (median 29 days, $p < 0.001$) compared with no leak. Patients with a major leak stayed significantly longer than those with a minor leak ($p = 0.017$).

Diverting stomas

A diverting stoma was constructed for 408 resections (27.1%); mostly for ultra-low and low anterior resections (227 of 248 [91.5%] and 109 of 212 [51.4%], respectively). There was no significant variation in the proportion of patients having a stoma, broken down by 3-year periods during the course of the study ($p = 0.678$). Overall leak rate was significantly higher in patients who had a diverting stoma than in those who did not (7.8%; 95%, CI, 5.4% to 10.9 and 2.0%; 95% CI, 1.3% to 3.0, respectively). A major leak was no more likely to develop in patients who had a diverting stoma than those who did not (1.7%; 95%, CI, 0.7% to 3.5 and 1.3%; 95% CI, 0.7% to 2.1, respectively). A minor leak was more likely to develop in those with a diverting stoma (6.1%; 95% CI, 4.0% to 8.9 and 0.7%; 95% CI, 0.3% to 1.4, respectively).

For patients in whom a leak (minor or major) developed, there was no difference in the number of complications between those who had a stoma and those who did not (mean 3.3 and 4.0, respectively; $p = 0.919$). This was true for minor and major leaks separately ($p = 0.453$ and $p = 0.332$, respectively).

For patients who had a leak (minor or major), there was no difference in length of postoperative stay between those who had a stoma and those who did not (mean 29.4 and 28.9 days, respectively; $p = 0.936$), and this was true for both minor and major leaks separately ($p = 0.934$ and $p = 0.159$, respectively).

DISCUSSION

Anastomotic leakage is a complex topic and, during several decades, many studies have investigated possible risk factors for leak and have addressed the problem of ameliorating this complication— in particular, by use of a temporary diverting stoma. These issues are not the concern of the present study. Rather, the aim was to examine the variety

Table 3. Type of Leak by Tumor Site

	Rectum						Colon	
	0–7.9 cm (n = 104)		8–11.9 cm (n = 212)		12–18.9 cm (n = 177)		(n = 1,014)	
	n	%	n	%	n	%	n	%
No leak (n = 1,453)	88	84.6	196	92.5	172	97.2	997	98.3
Minor clinical leak (n = 33)	9	8.7	12	5.7	4	2.3	8	0.8
Major clinical leak (n = 21)	7	6.7	4	1.9	1	0.6	9	0.9

and frequency of surgical and medical complications associated with anastomotic breakdown, regardless of whether a diverting stoma was constructed or not. In particular, the intention was to assess the commonly held view that a so-called minor clinical leak is an insignificant event when compared with a full-blown leak requiring urgent abdominal reoperation. This study has shown that the consequences of any clinical leak, minor or major, were multiple and serious, as compared with patients without a leak; that frequency of most complications taken individually did not differ substantially between minor and major leaks; and that the principal difference lay in the considerably higher rates of respiratory and cardiac complications in patients with the latter.

Patients with only minor leakage had a high rate of septic complications, including septicemia, pelvic and intraabdominal abscess, and infected pelvic hematoma. They also had a high rate of urinary and respiratory complications and prolonged postoperative ileus. Importantly, many of these patients had not just one but several of these complications and the postoperative hospital stay required to resolve their problems was lengthy, although considerably shorter for patients with a minor leak than those with a major leak (median 19 and 29 days, respectively). These results indicate that minor clinical leakage is not trivial.

Frequency of septic and other complications in patients with a major leak was high, as would be expected; in addition, cardiac and respiratory complications and stroke, confusion, and multisystem failure were more likely to develop in those with a major leak than those without a leak. These additional complications undoubtedly arise from a greater degree of peritoneal contamination and, possibly, from exposure to the potential hazards of a second laparotomy.

It is possible that this study failed to detect more differences in complication rates between minor and major leaks because of the small number of leaks (33 and 21, respectively) and low power. Because of the very low frequency of leaks, a far greater number of patients would be required to detect what might be regarded as a clinically significant difference. For example, if a true difference in the rate of septicemia of at least 10% (between 15% in minor leaks and 25% in major leaks) was deemed to be clinically important and assuming a significance level of $p < 0.05$ and a power of 0.8, at least 266 patients would be required in each group in order not to miss this difference. At the major leak rate of 1.4%, 19,000 resections with anastomosis would be required; and for a smaller, clinically significant difference, a considerably larger number would be needed. Such numbers could only be attained in very extensive multiinstitution studies extending several years. We believe that our experience is worth reporting at this stage, as it points to what might be found in other settings similar to our own. Results could differ away from the environment of a specialist unit in a tertiary referral hospital where all operations are performed by colorectal surgeons.

When patients with either a minor or major leak were combined into a single group, it was shown that complications tended to be multiple; if a patient had 1, he was likely to have at least 2 or 3 others and, in some patients, up to 11. Only 11% of patients with a leak had no other complication among the 18 considered. Patients with a minor leak had fewer complications in total than those with a major leak (mean 2.8 and 4.7, respectively).

Overall leak rate was higher in patients who received a diverting stoma than in those who did not; a minor leak was more likely to develop than a major leak in those with a stoma, suggesting that the stoma very likely was effective in preventing the more drastic outcome. Mean number of complications among the 18 considered was not lower for those who had a stoma, whether for any leak or for major or minor leaks separately, and length of hospital stay of patients with a stoma did not differ by type of leak.

Postoperative mortality in patients with anastomotic leakage from colorectal anastomoses has varied considerably, from 39%,[6] 36%,[7] and 33%[8] in earlier reports, to levels between 0% and 5% more recently.[9-12] In the present study, postoperative mortality rate of 7% in such patients was similar to that in the latter reports. It is difficult to make comparisons, because of the widely differing case-mix and surgical techniques among studies.

The lengthy postoperative stay of patients with anastomotic breakdown places a great demand on hospital beds. These patients require higher-intensity nursing, involving greater specialization, higher acuity, and more one-to-one support of patients; and a range of other resources, including specialist consultations, imaging, pathology, and medications. The end result of this is a substantial access block to beds and resources for patients awaiting elective colorectal operations. The need to avoid these consequences emphasizes the importance of training in good anastomotic technique.

Presentation of major leakage is well known and overt. Presentation of minor leakage is often very subtle and requires a strong index of suspicion. Despite this, our study has shown that once most patients with a major leak have had an urgent operation to control the leak, their subsequent course was not dissimilar to that of patients with a minor leak, who were as likely to have substantial complications, although with a lower postoperative death rate. Minor leakage is not trivial and should not be taken lightly.

Author Contributions

Study conception and design: Tytherleigh, Bokey, Chapuis, Dent
Acquisition of data: Bokey, Chapuis, Dent
Analysis and interpretation of data: Tytherleigh, Bokey, Chapuis, Dent
Drafting of manuscript: Tytherleigh, Bokey, Chapuis, Dent
Critical revision: Tytherleigh, Bokey, Chapuis, Dent

REFERENCES

1. Isbister WH. Anastomotic leak in colorectal surgery: a single surgeon's experience. A N Z J Surg 2001;71:516–520.
2. Killingback M, Barron P, Dent O. Elective resection and anastomosis for colorectal cancer: a prospective audit of mortality and morbidity 1976−1998. A N Z J Surg 2002;72:689–698.
3. Chambers WM, Mortensen NJ. Postoperative leakage and abscess formation after colorectal surgery. Best Pract Res Clin Gastroenterol 2004;18:865–880.
4. Bruce J, Krukowski ZH, Al-Khairy G, et al. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 2001;88:1157–1168.
5. Newland RC, Chapuis PH, Pheils MT, Macpherson JG. The relationship of survival to staging and grading of colorectal cancer. A prospective study of 503 cases. Cancer 1981;47:1424–1429.
6. The Consultant Surgeons and Pathologists of the Lothian and Borders Health Board. Lothian and Borders large bowel cancer project: immediate outcome after surgery. Br J Surg 1995;82:888–890.
7. Irvin TT, Goligher JC. Aetiology of disruption of intestinal anastomoses. Br J Surg 1973;60:461–464.
8. Schrock TR, Deveney CW, Dunphy EJ. Factors contributing to leakage of colonic anastomoses. Ann Surg 1973;177:513–518.
9. Nesbakken A, Nygaard K, Lunde OC. Outcome and late functional results after leakage following mesorectal excision for rectal cancer. Br J Surg 2001;88:400–404.
10. Averbach AM, Chang D, Koslowe P, Sugarbaker PH. Anastomotic leak after double-stapled low colorectal resection. Dis Colon Rectum 1996;39:780–787.
11. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355–358.
12. Byrn JC, Schlager A, Divino CM, et al. The management of 38 anastomotic leaks after 1,684 intestinal resections. Dis Colon Rectum 2006;49:1346–1353.