Original article

Impact of anastomotic leak on long-term survival in patients undergoing gastrectomy for gastric cancer

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Background: **The impact of anastomotic leak (AL) on long-term outcomes after gastrectomy for gastric adenocarcinoma is poorly understood. This study determined whether AL contributes to poor overall survival.**

Methods: **Consecutive patients undergoing gastrectomy in a single high-volume unit between 1997 and 2016 were evaluated. Clinicopathological characteristics, oncological and postoperative outcomes were stratified according to whether patients had no AL, non-severe AL or severe AL. Severe AL was defined as anastomotic leakage associated with Clavien–Dindo Grade III–IV complications.**

Results: **The study included 969 patients, of whom 58 (6·0 per cent) developed AL; 15 of the 58 patients developed severe leakage. Severe AL was associated with prolonged hospital stay (median 50, 30 and 13 days for patients with severe AL, non-severe AL and no AL respectively; $P < 0·001$) and critical care stay (median 11, 0 and 0 days; $P < 0·001$). There were no significant differences between groups in number of lymph nodes harvested (median 29, 30 and 28; $P = 0·528$) and R1 resection rates (7, 5 and 6·5 per cent; $P = 0·891$). Cox multivariable regression analysis showed that severe AL was independently associated with overall survival (hazard ratio 3·96, 95 per cent c.i. 2·11 to 7·44; $P < 0·001$) but not recurrence-free survival. In sensitivity analysis, the results for patients who had neoadjuvant therapy then gastrectomy were similar to those for the entire cohort.**

Conclusion: **AL prolongs hospital stay and is associated with compromised long-term overall survival.**

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Introduction

Gastrectomy and lymphadenectomy are the cornerstone in curative treatment of patients with gastric adenocarcinoma. Total gastrectomy is frequently undertaken for proximal cancer, and this is advocated by some in the treatment of diffuse-type cancers[1,2]. Subtotal gastrectomy may be performed in patients with a more distal gastric cancer. Total gastrectomy may be associated with a higher incidence of anastomotic leak (AL) than subtotal gastrectomy[3], although perioperative morbidity and mortality rates may be the same[4]. AL represents a major complication, with a rate varying between 0 and 26 per cent, and a median of 5–8 per cent in recent major series. It is associated with increased postoperative morbidity and mortality[5–7].

Studies[8–10] of oesophageal and colorectal cancer have suggested that anastomotic leakage not only increases the risk of postoperative death but may also adversely affect long-term survival. However, studies evaluating the impact of AL on outcomes of subtotal or total gastrectomy for gastric cancer are scarce[11–13]. In 2010, Sierzega and colleagues[13] reported that AL following total gastrectomy was associated with significantly reduced long-term survival. However, this study included a historical cohort from 1999 to 2004, and lacked evaluation of the impact of severe AL associated with grade III–IV complications on long-term survival.

As such, the impact of AL on long-term outcomes of patients undergoing gastrectomy is not well established, and it is not known whether any difference exists between patients receiving neoadjuvant treatment and those having unimodal surgery. The aim of this study was to determine whether AL influences long-term survival following gastrectomy for gastric cancer. Sensitivity

analyses were undertaken for patients who had neoadjuvant therapy with surgery and those who had total gastrectomy alone.

Methods

Consecutive patients treated for gastric adenocarcinoma between January 1997 and December 2016 in the Northern Oesophagogastric Unit, Newcastle upon Tyne, were included. All patients were discussed at a multidisciplinary team meeting and subsequently received neoadjuvant chemotherapy followed by surgery (either total gastrectomy or subtotal gastrectomy) or had surgery as initial curative management. Patients were identified from a contemporaneously maintained database. The protocol was deemed as a service evaluation and therefore ethical approval was not required.

Pretreatment staging

All patients were staged according to standard protocols which included endoscopy with biopsy and thoracoabdominal CT. During the study, PET(–CT) evolved as a necessary component for patients being considered for radical (curative) treatment and endoscopic ultrasonography was used selectively. Neoadjuvant chemotherapy followed by surgery was the main treatment option in patients with histology proven locally advanced resectable cancer without metastases (cT1 N+ or cT3+ N0–3). Patients with tumour histology other than adenocarcinoma and those with metastatic disease at the time of the operation were excluded.

Treatment

Multiple neoadjuvant regimens were employed in the present study, determined by the standard of care and clinical trials recruiting at the time of treatment; patients treated earlier in the study interval were more likely to have surgery alone. Total gastrectomy or subtotal gastrectomy with D2 lymph node dissection was performed within 4–8 weeks after completion of neoadjuvant therapy.

Surgical technique

Resections involved an open approach with radical *en bloc* D2 lymphadenectomy. Patients with proximal tumours and those diagnosed with linitis plastica underwent total gastrectomy. Patients with a distal tumour where adequate clearance could be achieved had subtotal gastrectomy. *En bloc* nodal dissection of the hepatic artery, coeliac axis, left gastric artery, proximal and distal splenic artery, and, when indicated, splenic hilum nodal lymphadenectomy were carried out routinely. A proximal retrocolic oesophagojejunal anastomosis was created using a 25-mm anvil in patients undergoing total gastrectomy, and a two-layer handsewn proximal gastrojejunal anastomosis in those undergoing subtotal gastrectomy. The distal jejunojejunal anastomosis was handsewn in two layers approximately 40 cm downstream of the proximal anastomosis.

Management of anastomotic leakage

In this unit, AL was managed conservatively throughout, with the use of enteric feeding by means of a nasojejunal tube, drainage to control sepsis and antibiotics. Reoperation was not usually undertaken for AL. Routine contrast swallows were not performed as part of postoperative patient management. In patients undergoing total gastrectomy, with the most vulnerable anastomosis, a feeding nasojejunal tube was placed at the time of surgery and left *in situ* until AL had been ruled out clinically. This allowed enteral nutrition in the event of leakage. Exceptionally total parenteral nutrition was given if enteral access could be achieved and there was concern about a prolonged period without nutrition. An endoprosthesis (stent) was not used routinely.

Pathology and tumour staging

Histopathological reporting was carried out by specialist gastrointestinal pathologists using a pro forma. This was in accordance with guidelines produced by the Royal College of Pathologists[14], which included tumour type and differentiation, depth of tumour infiltration and tumour regression. The total numbers of nodes from each location and nodal metastases were recorded, along with information on the presence of extracapsular, lymphatic, venous and perineural invasion. Lymph node groups were dissected from the specimen by the operating surgeon and analysed separately by the pathologist[14]. The pathological stage was determined according to the AJCC TNM staging system (8th edition)[15].

Definition of anastomotic leak

AL was defined as a full-thickness gastrointestinal defect involving either the anastomosis (oesophagojejunal or gastrojejunal in the case of subtotal gastrectomy, and jejunojejunal), irrespective of presentation or method of identification. AL was confirmed using either contrast swallow, CT or endoscopy. Leakage associated with grade III–V complications, according to the Clavien–Dindo grading system[16,17], was defined as severe AL, and that

associated with less severe complications (grade I–II) as non-severe AL. All patients who died within 30 days of surgery were excluded from the adjusted analyses of long-term survival, consistent with previous studies[9,18].

Follow-up and definition of recurrence

Patients were followed up until death or 10 years. Patients were seen at 3–6-month intervals in the first 2 years, every 6 months for the next 2 years, and annually thereafter. Recurrence of disease was based on clinical grounds and confirmed endoscopically or radiologically. The minimum follow-up was 30 months.

Statistical analysis

Categorical variables were compared using the χ^2 test. Non-normally distributed data were analysed using the Mann–Whitney *U* test. Survival was estimated by Kaplan–Meier analysis and curves were compared using the log rank test. Cox proportional hazards models were used for multivariable analyses. Patients who received neoadjuvant therapy before oesophagectomy and those who underwent total gastrectomy were included in separate subgroup analyses. $P < 0{\cdot}050$ was considered statistically significant. Data analysis was performed using R version 3.2.2, with TableOne, ggplot2, Hmisc, Matchit and survival packages (R Foundation for Statistical Computing, Vienna, Austria) as described previously[10,19].

Results

All patients

Baseline characteristics

This study included 969 patients who underwent either total gastrectomy (419) or subtotal gastrectomy (550) for adenocarcinoma of the stomach. Of these, 250 (25·8 per cent) received neoadjuvant chemotherapy. From 2006 onwards, the rate of neoadjuvant therapy was 39·1 per cent (244 of 624), with annual rates ranging from 23·1 to 49·2 per cent. Clinicopathological data are shown in *Table 1*. The median age of all patients was 71 (i.q.r. 63–76) years, and 634 (65·4 per cent) were men. In this cohort, 32 patients (3·3 per cent) had linitis plastica. Of 58 patients who developed AL, 43 had non-severe and 15 had severe leakage. Of patients undergoing total gastrectomy, 49 (11·7 per cent) developed AL, which was severe in 14. Among patients undergoing subtotal gastrectomy, nine (1·6 per cent) developed AL, which was severe in only one patient. Among the entire cohort there were a total of nine leaks from the jejunojejunal anastomosis, all in patients who had subtotal gastrectomy. One patient underwent stent placement for a leak, with stent removal after 3 weeks. Reoperation was necessary for leakage in only one patient in this cohort. Of the patients who developed AL, six (10 per cent) died in hospital, of whom five had severe leaks.

AL and severe AL were more likely to occur after total than subtotal gastrectomy ($P < 0{\cdot}001$). Severe AL was more prevalent among patients who had surgery alone than in those who received neoadjuvant therapy and surgery. There were no significant differences in leak rate according to age, sex, BMI, ASA fitness grade, lymph node yield or longitudinal (R1) margin involvement.

Postoperative outcomes

Patients with severe or non-severe ALs had higher rates of other complications than patients with no AL, specifically cardiac (33, 12 and 6·0 per cent respectively; $P < 0{\cdot}001$) and pulmonary (67, 16 and 6·4 per cent; $P < 0{\cdot}001$) complications. In addition, severe or non-severe ALs were also associated with a longer critical care stay (median 11 *versus* 0 *versus* 0 days; $P < 0{\cdot}001$) and longer stay in hospital (median 50, 30 and 13 days; $P < 0{\cdot}001$).

Overall and recurrence-free survival

Severe and non-severe ALs were both associated with shorter longer-term survival (median 24·2 and 40·9 months respectively *versus* 59·8 months in the no-leak group; $P = 0{\cdot}013$) (*Fig. 1a*). In adjusted Cox regression analysis, only severe AL was associated with poor long-term survival (hazard ratio (HR) 3·96, 95 per cent c.i. 2·11 to 7·44; $P < 0{\cdot}001$) (*Tables 2* and *3*). There were no significant differences in recurrence-free survival between groups with severe or non-severe AL compared with the no-leak group for the entire cohort (*Fig. 2a* and *Table 4*; *Table S1*, supporting information).

Neoadjuvant treatment followed by surgery

Baseline characteristics

Clinicopathological variables of the 250 patients who had neoadjuvant treatment followed by surgery are shown in *Table S2* (supporting information). Of these, 19 patients (7·6 per cent) developed an AL, which was severe in one. This severe leak occurred in a patient who had total gastrectomy. There were no in-hospital deaths among patients with leakage. However, patients with non-severe or severe AL had a significantly prolonged hospital stay compared with those without leakage (median 28·5, 22 *versus* 12 days respectively; $P < 0{\cdot}001$).

Overall and recurrence-free survival

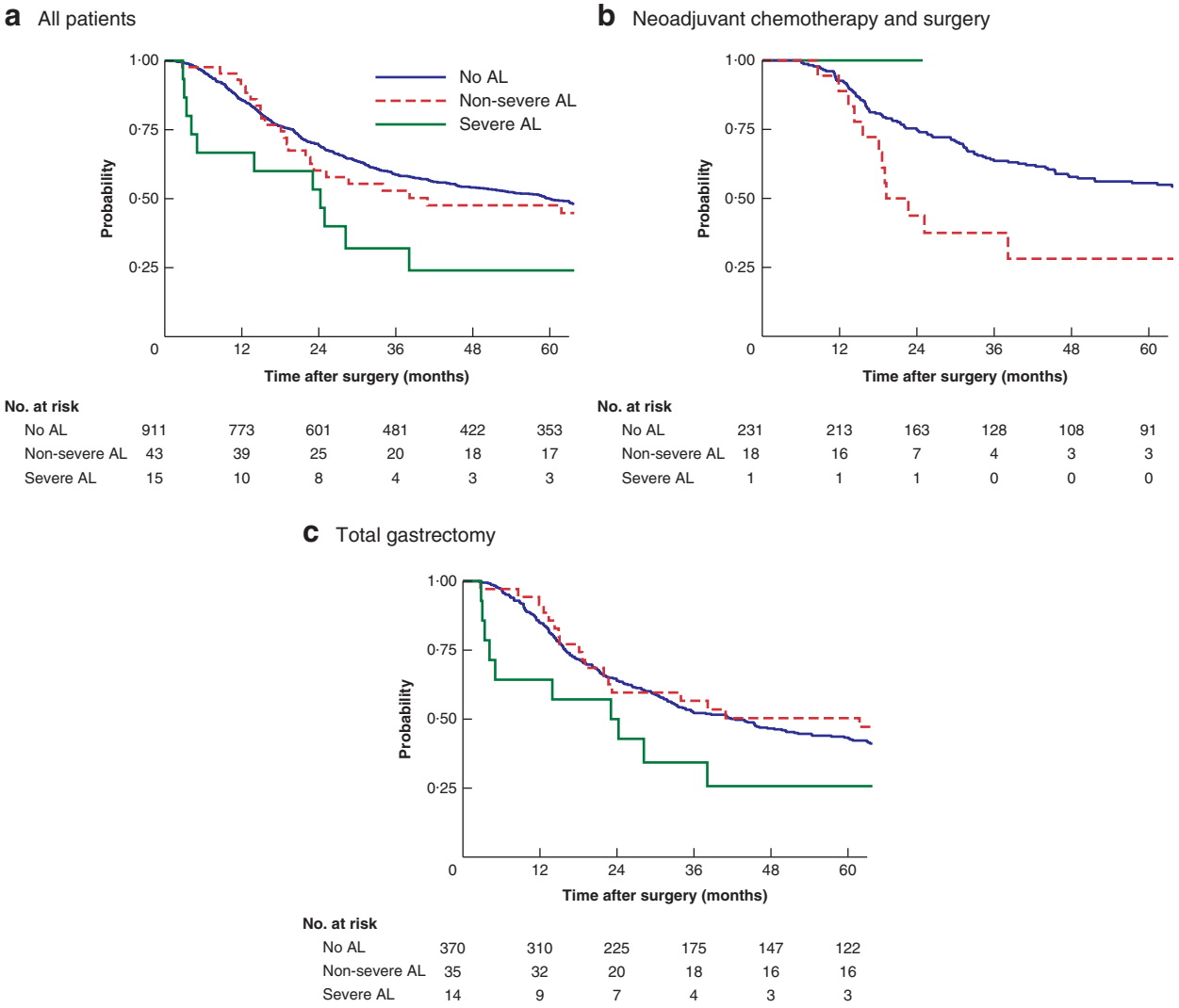
Overall survival was significantly shorter in those who experienced non-severe or severe leakage compared with

Table 1 Clinicopathological characteristics of patients undergoing gastrectomy for gastric cancer stratified by anastomotic leakage

	No AL ($n = 911$)	Non-severe AL ($n = 43$)	Severe AL ($n = 15$)	All patients ($n = 969$)	P†
Age at presentation (years)*	70 (63–76)	71 (66–75)	72 (67·5–78)	71 (63–76)	0·665‡
Sex					0·873
M	596 (65·4)	29 (67)	9 (60)	634 (65·4)	
F	315 (34·6)	14 (33)	6 (40)	335 (34·6)	
BMI (kg/m^2)*	25·2 (22·6–28·4)	24·8 (22·7–27·3)	23·5 (20·1–28·5)	25·2 (22·6–28·4)	0·475‡
ASA fitness grade					0·658
I–II	486 (53·3)	26 (60)	8 (53)	520 (53·7)	
III–IV	425 (46·7)	17 (40)	7 (47)	449 (46·3)	
Year of operation					0·069
1997–2006	372 (40·8)	14 (33)	10 (67)	396 (40·9)	
2007–2016	539 (59·2)	29 (67)	5 (33)	573 (59·1)	
Treatment type					0·013
NAC + surgery	231 (25·4)	18 (42)	1 (7)	250 (25·8)	
Surgery only	680 (74·6)	25 (58)	14 (93)	719 (74·2)	
Operation type					< 0·001
Subtotal gastrectomy	541 (59·4)	8 (19)	1 (7)	550 (56·8)	
Total gastrectomy	370 (40·6)	35 (81)	14 (93)	419 (43·2)	
Pathological AJCC stage					0·038
I	343 (41·1)	11 (26)	9 (60)	363 (40·6)	
II	302 (36·2)	24 (56)	5 (33)	331 (37·1)	
III	190 (22·8)	8 (19)	1 (7)	199 (22·3)	
Missing	76	0	0	76	
Tumour grade					0·636
Well/moderately differentiated	381 (45·2)	20 (53)	6 (50)	407 (45·6)	
Poorly differentiated/anaplastic	462 (54·8)	18 (47)	6 (50)	486 (54·4)	
Missing	68	5	3	76	
No. of lymph nodes examined*	28 (21–38)	30 (22·5–40·5)	29 (19·5–33·0)	28 (21–38)	0·528‡
Resection margin status					0·891
R0	852 (93·5)	41 (95)	14 (93)	907 (93·6)	
R1	59 (6·5)	2 (5)	1 (7)	62 (6·4)	
Lymphovascular invasion					0·207
No	402 (44·1)	18 (42)	10 (67)	430 (44·4)	
Yes	509 (55·9)	25 (58)	5 (33)	539 (55·6)	
Venous involvement					0·110
No	520 (57·1)	21 (49)	12 (80·0)	553 (57·1)	
Yes	391 (42·9)	22 (51)	3 (20·0)	416 (42·9)	
Perineural involvement					0·243
No	469 (51·5)	17 (40)	9 (60)	495 (51·1)	
Yes	442 (48·5)	26 (60)	6 (40)	474 (48·9)	
Extracapsular spread					0·007
No	773 (84·9)	30 (70)	15 (100)	818 (84·4)	
Yes	138 (15·1)	13 (30)	0 (0)	151 (15·6)	
Duration of critical care stay (days)*	0 (0–1)	0 (0–2)	11 (2–14)	0 (0–2)	< 0·001‡
Total duration of hospital stay (days)*	13 (10–17)	30 (21–42)	50 (41·5–68)	13 (10–18)	< 0·001‡
Overall complications					< 0·001
No	566 (62·1)	0 (0)	0 (0)	566 (58·4)	
Yes	345 (37·9)	43 (100)	15 (100)	403 (41·6)	
Surgical-site infection					0·734
No	837 (91·9)	40 (93)	13 (87)	890 (91·8)	
Yes	74 (8·1)	3 (7)	2 (13)	79 (8·2)	
Pulmonary complications					< 0·001
No	853 (93·6)	36 (84)	5 (33)	894 (92·3)	
Yes	58 (6·4)	7 (16)	10 (67)	75 (7·7)	
Cardiac complications					< 0·001
No	856 (94·0)	38 (88)	10 (67)	904 (93·3)	
Yes	55 (6·0)	5 (12)	5 (33)	65 (6·7)	

Values in parentheses are percentages unless indicated otherwise: *values are median (i.q.r.). AL, anastomotic leak; NAC, neoadjuvant chemotherapy. †χ^2 test except ‡Mann–Whitney U test.

Fig. 1 Impact of anastomotic leaks on overall survival after gastrectomy for gastric cancer



a All patients, **b** neoadjuvant chemotherapy and surgery and **c** total gastrectomy. AL, anastomotic leak. **a** $P = 0{\cdot}013$, **b** $P = 0{\cdot}034$, **c** $P = 0{\cdot}077$ (log rank test).

patients without AL (21·0, not reached and 77·4 months respectively; $P = 0{\cdot}034$) (*Fig. 1b*). As only one patient developed a severe AL, it was not possible to include this as a co-variable. In Cox regression analysis, non-severe AL was not an independent predictor of overall survival (*Table 3*; *Table S3*, supporting information). There was a significant difference in recurrence-free survival between the three groups in unadjusted analysis (*Fig. 2b*). However, there were no significant differences in recurrence-free survival between either AL group compared with the no-leak group in adjusted Cox regression analysis (*Table 4*; *Table S4*, supporting information).

Total gastrectomy

Baseline characteristics

Clinicopathological data for the 419 patients who had total gastrectomy are shown in *Table S5* (supporting information). Of these, 49 (11·7) per cent developed AL, which was severe in 14. Rates of in-hospital death were significantly higher in patients who developed a severe leak than in those with a non-severe leak or no AL: five of 14 (36 per cent), one of 35 (3 per cent) and three of 370 (0·8 per cent) respectively; $P < 0{\cdot}001$). Hospital stay was significantly prolonged in patients with non-severe or severe leaks compared with

Table 2 Cox regression analysis of overall survival of patients undergoing gastrectomy for gastric cancer

	Univariable analysis		Multivariable analysis	
	Hazard ratio‡	*P*	Hazard ratio‡	*P*
Age at presentation (years)†	1·01 (1·01, 1·02)	0·001	1·02 (1·01, 1·03)	< 0·001
Sex				
M	1·00 (reference)		1·00 (reference)	
F	0·95 (0·81, 1·13)	0·585	0·93 (0·75, 1·14)	0·467
BMI (kg/m^2)†	0·96 (0·94, 0·98)	< 0·001	0·97 (0·95, 0·99)	0·002
ASA fitness grade				
I–II	1·00 (reference)		1·00 (reference)	
III–IV	1·59 (1·36, 1·86)	< 0·001	1·42 (1·16, 1·73)	0·001
Year of operation				
1997–2006	1·00 (reference)		1·00 (reference)	
2007–2016	0·80 (0·68, 0·94)	0·008	0·85 (0·67, 1·07)	0·169
Treatment type				
NAC + surgery	1·00 (reference)		1·00 (reference)	
Surgery only	1·26 (1·04, 1·54)	0·021	1·03 (0·80, 1·33)	0·826
Operation type				
Subtotal gastrectomy	1·00 (reference)		1·00 (reference)	
Total gastrectomy	1·27 (1·08, 1·49)	0·003	1·38 (1·13, 1·69)	0·002
Pathological AJCC stage				
I	1·00 (reference)		1·00 (reference)	
II	2·45 (1·99, 3·01)	< 0·001	1·96 (1·52, 2·54)	< 0·001
III	5·05 (4·02, 6·33)	< 0·001	3·20 (2·32, 4·42)	< 0·001
Tumour grade				
Well/moderately differentiated	1·00 (reference)		1·00 (reference)	
Poorly differentiated/anaplastic	1·40 (1·18, 1·65)	< 0·001	1·21 (0·99, 1·47)	0·061
No. of lymph nodes examined†	0·99 (0·99, 1·00)	0·062	0·99 (0·98, 1·00)	0·003
Resection margin status				
R0	1·00 (reference)		1·00 (reference)	
R1	2·83 (2·16, 3·71)	< 0·001	1·92 (1·35, 2·74)	< 0·001
Lymphovascular invasion				
No	1·00 (reference)		1·00 (reference)	
Yes	2·31 (1·95, 2·74)	< 0·001	1·26 (1·00, 1·58)	0·051
Venous involvement				
No	1·00 (reference)		1·00 (reference)	
Yes	2·21 (1·88, 2·59)	< 0·001	1·21 (0·97, 1·52)	0·090
Perineural involvement				
No	1·00 (reference)		1·00 (reference)	
Yes	2·92 (2·47, 3·44)	< 0·001	1·47 (1·17, 1·85)	0·001
Extracapsular spread				
No	1·00 (reference)		1·00 (reference)	
Yes	2·38 (1·94, 2·93)	< 0·001	1·31 (0·99, 1·74)	0·057
Anastomotic leakage				
No AL	1·00 (reference)		1·00 (reference)	
Non-severe AL	1·17 (0·80, 1·70)	0·418	0·95 (0·61, 1·49)	0·829
Severe AL	2·13 (1·25, 3·63)	0·005	3·96 (2·11, 7·44)	< 0·001

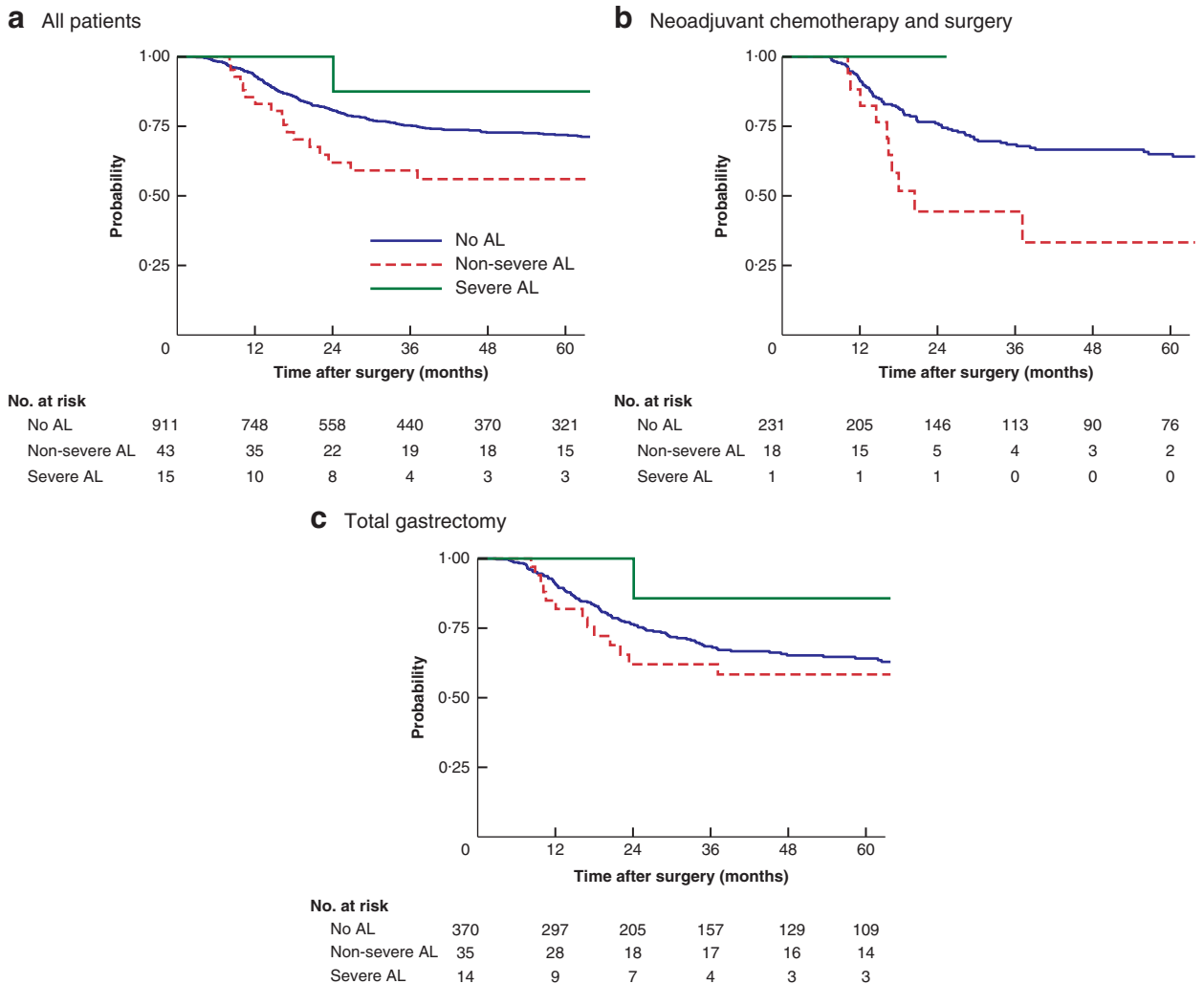
*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.); ‡values in parentheses are 95 per cent confidence intervals. NAC, neoadjuvant chemotherapy; AL, anastomotic leak.

Table 3 Impact of anastomotic leakage on overall survival

		Unadjusted analysis		Adjusted analysis	
	Median survival (months)*	Hazard ratio†	*P*	Hazard ratio†	*P*
All patients					
No AL	59·8 (51·6–67·3)	1·00 (reference)		1·00 (reference)	
Non-severe AL	40·9 (22·7 to NR)	1·17 (0·80, 1·70)	0·418	0·95 (0·61, 1·49)	0·829
Severe AL	24·2 (5·0 to NR)	2·13 (1·25, 3·63)	0·005	3·96 (2·11, 7·44)	< 0·001
NAC + surgery					
No AL	77·4 (51·6–115·0)	1·00 (reference)		1·00 (reference)	
Non-severe AL	21·0 (18·1 to NR)	2·13 (1·17, 3·89)	0·013	1·32 (0·66, 2·62)	0·431
Severe AL	NR (NR to NR)	–		–	
Total gastrectomy					
No AL	42·4 (33·4–54·3)	1·00 (reference)		1·00 (reference)	
Non-severe AL	61·8 (22·7 to NR)	0·98 (0·65, 1·50)	0·935	0·93 (0·56, 1·53)	0·778
Severe AL	23·7 (5·0 to NR)	1·88 (1·08, 3·29)	0·027	4·06 (2·02, 8·14)	< 0·001

Values in parentheses are *ranges and †95 per cent confidence intervals. AL, anastomotic leak; NR, not reached; NAC, neoadjuvant chemotherapy.

Fig. 2 Impact of anastomotic leaks on recurrence-free survival after gastrectomy for gastric cancer



a All patients, **b** neoadjuvant chemotherapy and surgery and **c** total gastrectomy. AL, anastomotic leak. **a** $P = 0{\cdot}051$, **b** $P = 0{\cdot}027$, **c** $P = 0{\cdot}380$ (log rank test).

Table 4 Impact of anastomotic leakage on recurrence-free survival

		Unadjusted analysis		Adjusted analysis	
	Median survival (months)*	Hazard ratio†	*P*	Hazard ratio†	*P*
All patients					
No AL	NR (NR to NR)	1·00 (reference)		1·00 (reference)	
Non-severe AL	NR (23·4 to NR)	1·72 (1·05, 2·83)	0·030	1·31 (0·74, 2·32)	0·349
Severe AL	NR (NR to NR)	0·37 (0·05, 2·66)	0·325	0·65 (0·09, 4·81)	0·677
NAC + surgery					
No AL	NR (NR to NR)	1·00 (reference)		1·00 (reference)	
Non-severe AL	NR (23·4 to NR)	2·37 (1·22, 4·59)	0·011	1·51 (0·71, 3·23)	0·287
Severe AL	NR (NR to NR)	–		–	
Total gastrectomy					
No AL	NR (NR to NR)	1·00 (reference)		1·00 (reference)	
Non-severe AL	NR (23·4 to NR)	1·20 (0·67, 2·13)	0·541	1·18 (0·61, 2·29)	0·618
Severe AL	NR (NR to NR)	0·31 (0·04, 2·22)	0·243	0·80 (0·10, 6·14)	0·828

Values in parentheses are *ranges and †95 per cent confidence intervals. AL, anastomotic leak; NR, not reached; NAC, neoadjuvant chemotherapy.

those without leakage (median 30, 55 and 14 days respectively; $P < 0·001$).

Overall and recurrence-free survival

Overall survival was shorter in those who experienced severe AL than in those with no leak, but not those with non-severe leakage (23·7, 61·8 and 42·4 months for patients with severe AL, non-severe AL and no leak respectively; $P = 0·077$) (*Fig. 1c*). In Cox regression analysis, severe AL was an independent predictor of overall survival (HR 4·06, 95 per cent c.i. 2·02 to 8·14; $P < 0·001$), but non-severe leak was not (*Table 3*; *Table S6*, supporting information). There were no significant differences in recurrence-free survival between patients with severe or non-severe AL and patients without AL (*Fig. 2c* and *Table 4*; *Table S7*, supporting information).

Impact of postoperative complications on survival

All patients

In total, 403 of 969 patients (41·6 per cent) developed postoperative complications. Patients who had a postoperative complication had significantly shorter overall survival (median 41·4 *versus* 64·9 months; $P = 0·002$) (*Fig. S1a*, supporting information). In adjusted Cox regression analysis, postoperative complications were associated with poor long-term survival (HR 1·30, 95 per cent c.i. 1·07 to 1·58; $P < 0·001$) (*Table S8*, supporting information). Kaplan–Meier analysis of the impact of postoperative complications on recurrence-free survival is shown in *Fig. S2a* (supporting information). Complications were not associated with recurrence-free survival in adjusted Cox regression analysis (*Table S9*, supporting information).

Neoadjuvant treatment followed by surgery

In this group, 96 of 250 patients (38·4 per cent) developed postoperative complications. Patients who had a postoperative complication had significantly shorter overall survival (median 38·1 *versus* 112·2 months; $P = 0·003$) (*Fig. S1b*, supporting information) and recurrence-free survival (*Fig. S2b*, supporting information). In adjusted Cox regression analysis, postoperative complications were associated with worse long-term survival (HR 1·69, 95 per cent c.i. 1·11 to 2·59; $P = 0·015$) (*Table S10*, supporting information) and also worse recurrence-free survival (HR 2·04, 1·23 to 3·38; $P = 0·006$) (*Table S11*, supporting information).

Total gastrectomy

Among 419 patients who had total gastrectomy, 207 (49·4 per cent) developed postoperative complications. Patients who had a postoperative complication had significantly shorter overall survival (median 34·2 *versus* 47·4 months; $P = 0·011$) (*Fig. S1c*, supporting information). However, in adjusted Cox regression analysis, postoperative complications were associated with worse overall survival (HR 1·39, 95 per cent c.i. 1·04 to 1·86: $P = 0·026$) (*Table S12*, supporting information). Postoperative complications were not associated with worse recurrence-free survival (*Fig. S2c* and *Table S13*, supporting information).

Discussion

In this study, patients who developed severe AL had significantly worse overall survival than those who did not. However, AL was not associated with worse recurrence-free survival. The overall rate of anastomotic leak in this cohort

of patients, who all underwent Roux-en-Y reconstruction, was 6·0 per cent. Nearly all identified leaks were from the proximal anastomosis, and there was a much higher leak rate after total gastrectomy. In addition, AL was associated with a longer postoperative hospital stay. The in-hospital mortality rate was 33 per cent (5 of 15) among those with a severe leak, 2 per cent (1 of 43) for those with a non-severe leak and 0·7 per cent (6 of 911) in those who did not experience a leak. This study confirmed previous findings[20] that postoperative complications are associated with significantly worse long-term overall survival.

Previous studies[21–23] of gastrointestinal malignancies demonstrated that postoperative complications may have either a positive or negative impact on long-term survival, although few studies[6,11–13] analysed the influence of AL in patients with oesophagogastric cancers. As they usually included both oesophageal and gastric tumours and various types of resection, interpretation of the results is difficult. The results are generally contradictory, suggesting either no influence of early morbidity on long-term survival[6,11] or poorer survival rates[12]. A multicentre observational study[24] of gastric cancer carried out between 1986 and 1989 suggested that surgical complications may significantly affect long-term outcome in a relatively homogeneous population. The cohort comprised 1654 patients who underwent gastric resections in 19 surgical university hospitals in Germany and Austria, including 1176 who had total or extended total gastrectomy. AL was diagnosed in 134 patients (8·1 per cent), although no details were provided regarding the type of resection. The relative risk of leakage in multivariable survival analysis of the whole patient population was 2 per cent. However, as the multivariable analysis excluding perioperative mortality failed to retain anastomotic failure in the model, the authors concluded that the effects of leakage were solely due to increased early death[24].

AL has been associated with impaired long-term survival in other gastrointestinal procedures for malignancy. A multicentre study[9] indicated that AL influenced long-term survival in patients with oesophageal cancer, and another[25] suggested this might be true in rectal cancer, but not colonic cancer. The present study showed a clear association between AL and poorer outcome in the entire cohort and also among those who received neoadjuvant treatment. Although development of AL may affect patients by preventing them from receiving adjuvant treatment, other factors may be involved in this poorer outcome. One possibility is that AL occurs in those with poorer disease biology; in essence AL is more likely in patients with a more aggressive tumour that is likely to recur. This was not borne out by recognized prognostic markers such as disease stage and the quality of surgery performed, with similar lymph node yields between groups and similar positive resection margin rates. Perhaps the more concerning possibility is that AL itself plays some part in influencing long-term prognosis. It has been suggested previously that AL permits shedding of cells from the gut lumen, which can contribute to local recurrence. This does not necessarily explain the increased rate of distant recurrence[8,26,27], but it could be that an immunosuppressive effect produced by a leak enables disease recurrence.

Although the present study is unable to explain this association, it seems likely that the systemic inflammatory response syndrome (SIRS) caused by leakage may be important[28]. Given that various inflammatory mediators (tumour necrosis factor α, interleukin 1β and interleukin 6) and their receptors control cell motility, invasiveness and survival, it seems reasonable that SIRS induced by anastomotic failure may promote proliferation and metastasis of circulating cancer cells and those in the tumour bed. The notion that poorer long-term outcome is associated with a leakage-related inflammatory response has been suggested in oesophagogastric and rectal cancer[29,30]. Other studies[31,32], however, have failed to confirm the detrimental effects of postoperative fistulas on disease-free survival and recurrence rates in non-gastric cancers. Further work is required to understand these differences.

The main limitation of this study was that the data were from a single institution; although they were collected contemporaneously, the bias of a retrospective study may still exist. It could be argued that such data are not generalizable to other populations. However, given the large number of patients, the standardized preoperative decision-making and surgical technique, they may also help act as a benchmark for comparison. Linitis plastica is an important subgroup that may require further analysis to evaluate the impact of AL on survival. In this study, the number of patients with linitis plastica was small, so a meaningful analysis was not possible.

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Supporting information

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