



## Gastric cancer surgery – a balance of risk and radicality

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### ABSTRACT

**INTRODUCTION** The aim of this study was to determine whether tailoring the extent of resection would allow radical gastric cancer surgery to be performed safely in a UK population.

**PATIENTS AND METHODS** A total of 180 consecutive patients (median age 70 years; male:female ratio 2:1) undergoing resection for gastric adenocarcinoma with curative intent were studied. Extent of lymphadenectomy was based upon pre-operative and intra-operative staging, and balanced against the patient's age and fitness.

**RESULTS** In the study group, 83 patients underwent subtotal or distal partial gastrectomy and 97 patients underwent total or proximal partial gastrectomy. Operative procedures were: D1 lymphadenectomy ( $n = 62$ ); modified (spleen and pancreas preserving) D2 lymphadenectomy ( $n = 73$ ); D2 lymphadenectomy ( $n = 42$ ); and extended resection ( $n = 3$ ). TNM classification was: stage 1 ( $n = 45$ ); stage 2 ( $n = 37$ ); stage 3 ( $n = 61$ ); and stage 4 ( $n = 37$ ). Of the patients, 48 developed postoperative complications including 17 patients with a major surgical complication. The in-hospital mortality was 1.7% (3 of 180). Predicted mortality according to POSSUM and P-POSSUM was 21.4% and 7.8%, respectively. Disease-specific 5-year survival according to stage was 85.4%, 64.2%, 33.3%, and 6.9%.

**CONCLUSIONS** By tailoring the extent of resection and balancing risk and radicality, gastric cancer surgery can be performed with low mortality in Western patients.

### KEYWORDS

Stomach neoplasms – Gastrectomy – Lymph node excision

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For many years, the Japanese have reported improved long-term outcome with increasingly radical surgery for gastric cancer.<sup>1</sup> The wide-spread adoption of radical gastric cancer surgery and D2 lymphadenectomy in the West has been prevented by two factors. First, the lack of demonstrated benefit for radical lymphadenectomy in Western studies, and second concerns regarding the high postoperative morbidity and mortality. Whereas large Japanese and Eastern series have recently reported outstanding mortality rates of less than 1%,<sup>2,5</sup> the UK Medical Research Council and Dutch D1 versus D2 trials identified rates of 13% and 10% for gastrectomy with D2 lymphadenectomy, respectively.<sup>4,5</sup> A criticism of these trials was the low volume of the recruiting centres and relative inexperience of surgeons in performing radical gastric resections. In particular, there was considerable morbidity associated with the additional resection of spleen and pancreas as part of a D2 lymphadenectomy. However, despite increasing experience and the development of specialist

centres in the West, recent large UK audits still report mortality rates in the region of 10%.<sup>6,7</sup>

Whilst Eastern centres clearly use excellent surgical technique and peri-operative care, the most important difference between the East and West appears to be the population undergoing resection.<sup>8</sup> Western patients are, on average, 10 years older, have a higher incidence of cardiovascular disease, are significantly more overweight and have a higher risk of thrombo-embolic complications. There is also an increasingly higher proportion of proximal tumours in the West, where total gastrectomy has been associated with a mortality of twice that of a subtotal resection.

It appears that radical surgery can produce some survival benefit but that this will vary with the stage of disease.<sup>9</sup> If the benefit is small, this may be offset completely by the increased mortality. Only when the benefits of radical resection outweigh the increased risks can it be considered standard practice. There is a concern that a surgical philosophy

based on less radical surgery will deny some patients a chance of cure, or at least prolonged survival. Procedures based on a rational approach that balances risk and radicality, with a variable lymphadenectomy and preservation of the spleen and pancreas may, therefore, be most appropriate for the UK population. Multiple factors influence such operative tactics including evidence of spread, patient health, age, and build; therefore, these procedures need to be tailored to the individual patient. The aim of this study was to determine whether such an approach would allow this surgery to be performed with a low morbidity and mortality in a UK population.

## Patients and Methods

Between October 1992 and September 2005, 200 patients underwent gastric resection with a curative intent in this unit. The 180 consecutive patients who underwent gastrectomy for adenocarcinoma of the stomach form the basis of this study. This study describes all patients undergoing surgery with an intention to cure and thus includes some in whom more advanced disease was only identified at laparotomy and in whom macroscopic (R2 resection) or microscopic residual disease (R1 resection) was left behind. Patients undergoing intended palliative operations on the basis of pre-operative staging are not included. The indication for gastrectomy for the other 20 patients was gastrointestinal stromal tumour ( $n = 11$ ), lymphoma ( $n = 5$ ), carcinoid ( $n = 2$ ), and peptic ulcer disease ( $n = 2$ ). During the last 2 years of the study period, 11 selected patients with locally advanced adenocarcinoma received peri-operative chemotherapy with epirubicin, cisplatin, and 5-fluorouracil.<sup>10</sup>

## Surgical procedure

### DISTAL TUMOURS

An 80% subtotal gastrectomy with a Roux-en-Y reconstruction was routinely performed for adenocarcinoma of the distal and middle thirds of the stomach with a palpable 7-cm free margin from the oesophagogastric junction. The Japanese Research Society for Gastric Cancer description of nodal stations was used.<sup>11</sup> All patients underwent at least a D1 lymphadenectomy with resection of the perigastric nodal stations. A D2 lymphadenectomy required the additional *en bloc* resection of lymph nodes along the left gastric artery (station 7), common hepatic artery (station 8), and coeliac axis (station 9). If any nodal station was omitted (most frequently the common hepatic artery or origin of left gastric artery), then this was classified as a D1 lymphadenectomy. A more limited 50% distal gastrectomy was carried out in selected elderly patients and a D1 lymphadenectomy was performed in these cases. All tumours reaching or above the incisura underwent a formal subtotal gastrectomy.

### PROXIMAL TUMOURS

A total gastrectomy with a Roux-en-Y reconstruction with or without a jejunal pouch was performed for adenocarcinoma involving the proximal third of the stomach. A D2 lymphadenectomy required resection of nodal stations 1–11, including splenectomy and distal pancreatectomy for complete removal of nodes at the splenic hilum (station 10). It was classified as a modified D2 lymphadenectomy for a proximal cancer if only nodes along the splenic artery were resected with preservation of the spleen and pancreas. If any other nodal station was omitted, this was classified as a D1 lymphadenectomy. For certain early tumours, a proximal partial gastrectomy was performed creating a gastric tube with preservation of the vagal fibres to the distal stomach.

### DECISION-MAKING PROCESS

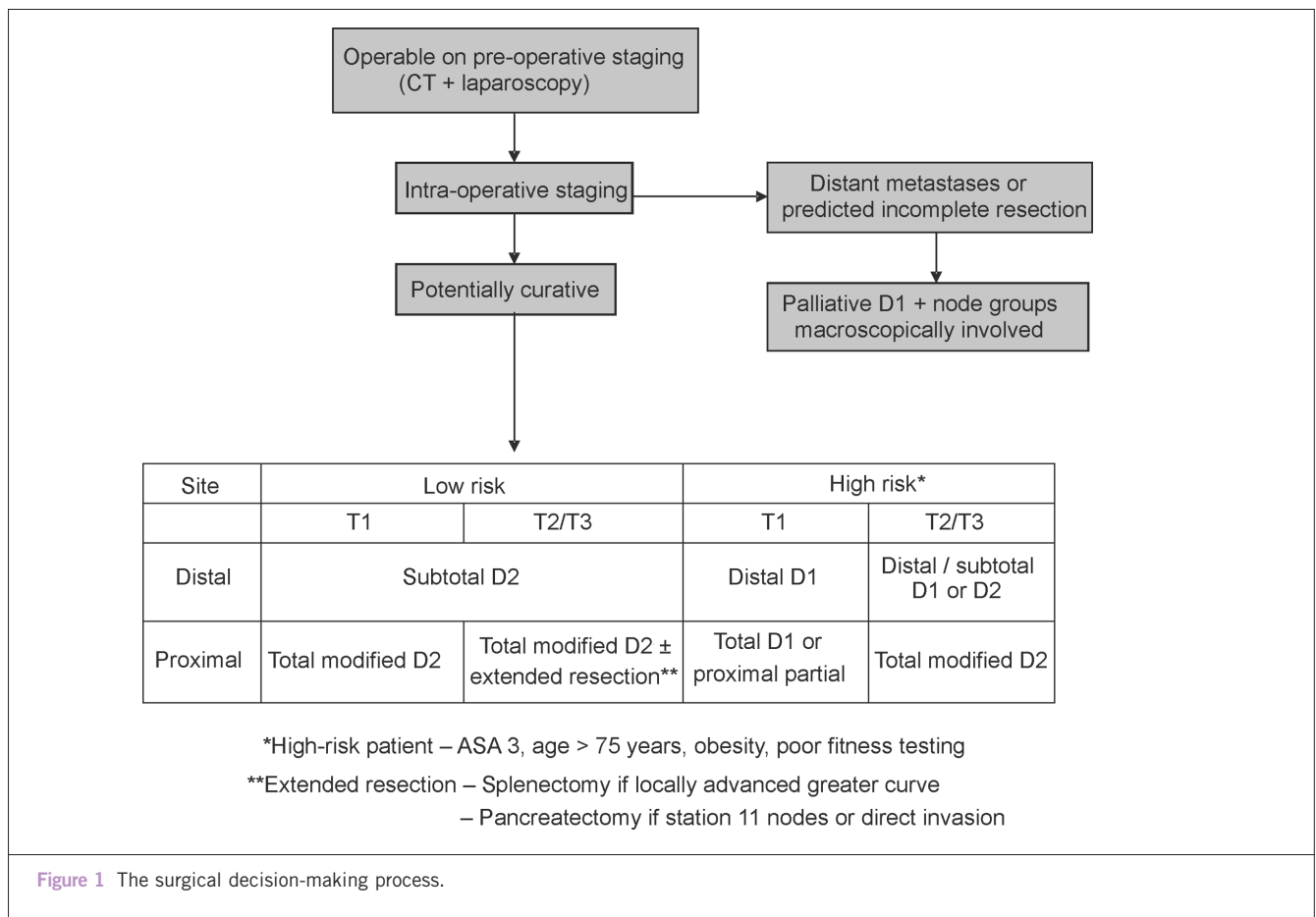
The extent of resection and *en bloc* lymphadenectomy was planned based upon pre-operative and intra-operative staging and balanced against the age and health of the patient. The algorithm for this decision-making process is given in Figure 1. For a low-risk patient, the standard procedure for a distal tumour was a subtotal gastrectomy with D2 lymphadenectomy, and for a proximal tumour a total gastrectomy with modified D2 lymphadenectomy. Splenectomy to allow resection of station 10 nodes was restricted to selected larger tumours involving the greater curve or fundus of the stomach. A limited distal gastrectomy was performed for certain high-risk patients staged as having early disease or found to have more advanced disease unlikely to benefit from radical surgery. There are inevitably individual cases that have not followed the algorithm because of intra-operative findings and decision-making appropriate to the circumstances of the case.

### Peri-operative care

Postoperatively, patients deemed to be high risk due to co-morbidity were managed initially in a high dependency unit. Epidural analgesia was routinely used and early mobilisation was encouraged. The nasogastric tube was removed on the first postoperative day and patients allowed 25 ml water per hour from this time. Following subtotal gastrectomy, oral fluids were routinely re-introduced on day 3 and diet on day 5 when the duodenal stump drain was removed. Following total gastrectomy, the anastomotic and duodenal stump drains were routinely removed on days 5 and 6 following re-introduction of oral fluids and diet, respectively. Routine postoperative contrast swallows were not performed.

### Follow-up

Pathological staging of tumours was according to the revised TNM classification.<sup>12</sup> Patients were reviewed



clinically every 3 months for 2 years and every 6 months thereafter. Complete follow-up until 5 years or death was available for 175 patients. The remaining two patients declined follow-up but were known to be well from communication with the general practitioner. Where there was a suspicion of recurrent disease, patients underwent further investigation initially with computed tomography and video-endoscopy. The diagnosis of disease recurrence was based on histological proof or definite radiological evidence.

### Statistical analysis

Data were collected prospectively using a Microsoft Access database and analysed to determine the postoperative morbidity and mortality, and long-term outcome of these patients. Patient and tumour characteristics including the American Society of Anesthesiologists (ASA) grade and Physiological and Operative Severity Score for enumeration of Mortality and Morbidity (POSSUM) and Portsmouth predictor equation (P-POSSUM) were analysed. Chi-squared or Fisher's exact tests were used to compare categorical data. Survival data were demonstrated using Kaplan–Meier curves and the Log-Rank test was used to

determine the equality of survival curves.  $P < 0.050$  was considered to indicate statistical significance.

## Results

### Patient characteristics

The study cohort undergoing gastrectomy for adenocarcinoma comprised 118 males and 62 females with a median age of 70 years (range, 26–88 years). The mean ASA grade of these patients was 2.18 (SD 0.681). Of these, 44 patients were current smokers (24.4%), 84 patients were ex-smokers (46.7%) and 52 patients were non-smokers (28.9%).

### Tumour characteristics

The details of tumour location are summarised in Table 1. Overall, 83 patients (46.1%) underwent subtotal gastrectomy ( $n = 56$ ) or distal partial gastrectomy ( $n = 27$ ), including six patients with tumours of the body of the stomach. The remaining 97 patients (53.9%) underwent total ( $n = 89$ ), complete ( $n = 6$ ), or proximal partial ( $n = 2$ ) gastrectomy for tumours involving the proximal stomach. Twenty resections (11.1%), comprising four subtotal gastrectomies, six distal partial gastrectomies, and ten total

**Table 1 Tumour Location**

Tumour location	No. of patients (%)
Antrum	58 (32.2)
Body/antrum	19 (10.6)
Body	17 (9.4)
Cardia/body	19 (10.6)
Cardia	46 (25.6)
Cardia/oesophagus	5 (2.8)
Gastric remnant (stomal region)	6 (3.3)
Linitis plastica (most/all stomach)	10 (5.6)

gastrecomies were deemed to have been palliative (R1 or R2) procedures on the basis of operative findings or histology. The details of tumour stage are summarised in Table 2.

#### Extent of lymphadenectomy

Sixty-two patients (34.4%) underwent a D1 lymphadenectomy, including all 27 distal partial gastrectomies (Table 2). Seventy-three patients (40.6%) underwent total

gastrecomy with a modified D2 lymphadenectomy. Forty-two patients (23.3%) underwent a D2 lymphadenectomy, 37 in association with a subtotal gastrectomy.

Thirty patients (16.7%) underwent splenectomy, all in combination with a total gastrectomy, 24 for oncological reasons and six as a result of intra-operative haemorrhage. This included seven patients (3.9%) who underwent combined distal pancreatectomy and splenectomy. Three of these patients underwent an extended procedure with resection of other organs, colon in one patient and a wedge resection of the liver in two patients.

#### Postoperative complications

There were three postoperative deaths during the study period, an in-hospital or 30-day mortality of 1.7% (3 of 180; Table 3). The mortality following total or proximal partial gastrectomy was 2.1% (2 of 97). One patient died of multiple organ failure on the seventh postoperative day secondary to a leak at the oesophagojejunal anastomosis requiring reoperation following a modified D2 resection. The second patient died from sepsis and multiple organ failure on the nineteenth postoperative day following a super-extended D2 resection. This patient developed intra-operative haemorrhage from the spleen during initial dissection of an advanced gastric stump cancer, necessitating what was

**Table 2 Surgical procedure and stage of disease**

Procedure	Distal partial gastrectomy (n = 27)	Subtotal gastrectomy (n = 56)	Total/Complete/proximal partial gastrectomy (n = 89/6/2)	Overall (%)
D1	27	18	17	62 (34.4)
Modified D2	0	0	73	73 (40.6)
D2	0	37	5	42 (23.3)
Extended D2	0	1	2	3 (1.7)
Stage 1	7	16	22	45 (25.0)
Stage 2	3	16	18	37 (20.6)
Stage 3	8	16	37	61 (33.9)
Stage 4	9	8	20	37 (20.6)

**Table 3 In-hospital or 30-day mortality rates according to procedure**

Procedure	Adenocarcinoma	Other	Total (%)
Subtotal/distal gastrectomy	1/83	0/13	1/96 (1.0)
Total/complete/proximal gastrectomy	1/67	0/3	1/70 (1.4)
Total gastrectomy & splenectomy	0/23	0/1	0/24 (0)
Total gastrectomy & pancreatectomy/splenectomy	1/7	0/3	1/10 (10)
Total	3/180	0/20	3/200 (1.5)

**Table 4 Postoperative complications**

Complication	Number of patients (%)
<b>Major surgical complications</b>	<b>17 (9.4)</b>
Anastomotic leakage	6
Abdominal haemorrhage	1
Intra-abdominal abscess	5
Empyema of pleural cavity	1
Pancreatic fistula	2
Ischaemic colitis	1
Intestinal obstruction	1
<b>Minor surgical complications</b>	<b>5 (2.8)</b>
Wound infection	4
Infected jejunostomy site	1
<b>Medical complications</b>	<b>33 (18.3)</b>
Respiratory	13
Cardiovascular	12
Renal impairment	3
Transient ischaemic attack	1
Urinary tract infection	2
Pressure sores	2
Thrombo-embolic	0

ultimately a palliative resection. The mortality was 1.8% (1 of 56) following subtotal gastrectomy. This patient died of a myocardial infarction on the first postoperative day following a D2 subtotal gastrectomy with no evidence of a surgical complication at post mortem. There were no deaths following distal partial gastrectomy (0 of 27). There were no deaths following gastric resection for indications other than adenocarcinoma (0 of 20), giving an overall mortality of 1.5% (3 of 200).

Postoperative complications were identified in 48 patients (26.5%; Table 4), including eight patients who required admission or re-admission to the critical care unit during the postoperative period. Major surgical complications developed in 17 patients (9.4%) including six patients with an anastomotic leak (3.3%). This included two duodenal stump leaks following a distal partial and a subtotal gastrectomy, and four leaks from the oesophagojejunal anastomosis. Five patients required repeat laparotomy to divide obstructing adhesions, to resect ischaemic transverse colon, to drain a duodenal stump leak and an oesophagojejunal leak adequately (patient died), and to debride necrotic pancreas following a D2 total gastrectomy. One further patient who had undergone total gastrectomy with distal pancreatectomy and splenectomy required a thoracotomy

to drain an empyema of the pleural cavity secondary to a leak of the oesophagojejunal anastomosis within the mediastinum.

Medical complications developed in 33 patients (18.3%) predominantly respiratory (pneumonia or respiratory failure), and cardiovascular problems (myocardial infarction, angina, atrial fibrillation; Table 4). This included the patient who died following a myocardial infarction. Of note, no patients were identified as having developed deep vein thrombosis or pulmonary embolism.

The overall median hospital stay for all 180 patients was 10 days (range, 6–75 days). The median hospital stay for patients who developed a complication was 15 days (range, 6–75 days) and 10 days (range, 6–20 days) for those who did not develop a complication. The median stay was 11 days (range, 7–75 days) following total gastrectomy and 10 days (range, 6–39 days) following subtotal or distal partial gastrectomy.

#### POSSUM

The physiological POSSUM score was 11–14 for 37 patients (20.6%), 15–19 for 72 patients (40.0%) and  $\geq 20$  for 71 patients (39.4%). The mean physiological score was 18.7 (SD 4.44), and the mean operative score was 19.8 (SD 5.32). The POSSUM score predicted complications for 121 patients (67.0%; SD 0.166) compared to observed complications for 48 patients, an observed-to-predicted ratio of 0.40 ( $\chi^2 = 59.4$ ;  $P < 0.0001$ ). The POSSUM score predicted mortality for 39 patients (21.4%; SD 0.128) compared to the three observed deaths, an observed-to-predicted ratio of 0.08 ( $\chi^2 = 54.9$ ;  $P < 0.0001$ ). The P-POSSUM equation for mortality predicted 14 deaths (7.8%; SD 0.084), an observed-to-predicted ratio of 0.21 ( $\chi^2 = 7.47$ ;  $P = 0.006$ ).

#### Outcome data

The long-term outcome data are based upon the 177 patients who were discharged from hospital following resection for gastric adenocarcinoma. The median follow up was 805 days (range, 39–4818 days). During follow-up, 110 patients (62.1%) died including 72 patients with recurrent gastric adenocarcinoma, and 38 patients of other causes without evidence of recurrent disease. A further two patients are currently alive with proven recurrence.

The overall 5-year survival for all 177 patients was 38.4% with a median survival of 1124 days ( $\pm 233.3$  days). The overall stage-specific, 5-year survival was 68.2%, 54.2%, 25.3% and 5.9%, respectively (Fig. 2). Although 18 of 45 patients with stage 1 disease died during follow-up, only 5 of these patients, all with stage 1b disease, had recurrence. The disease-specific, 5-year survival was: stage 1a, 100%; stage 1b, 80.5%; stage 2, 64.2%; stage 3, 33.3%; and stage 4, 6.9% (Fig. 3). The disease-specific, 5-year survival for patients with distal tumours ( $n = 82$ ) was 67.1% compared

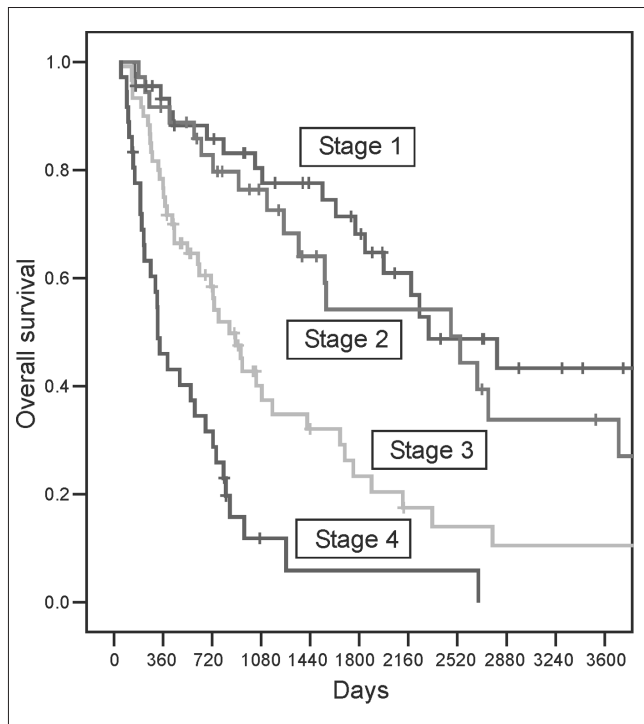


Figure 2 Overall stage-specific survival (n = 177).

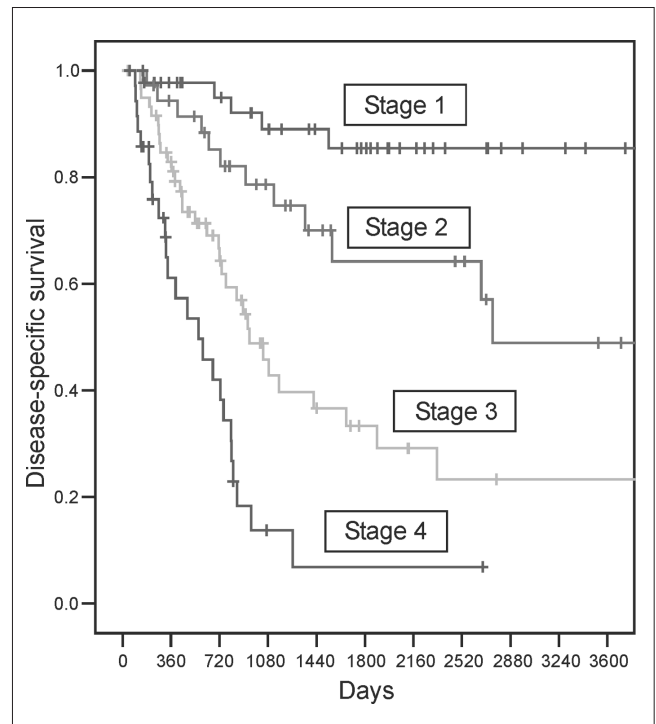


Figure 3 Disease-specific survival according to TNM stage (n = 177).

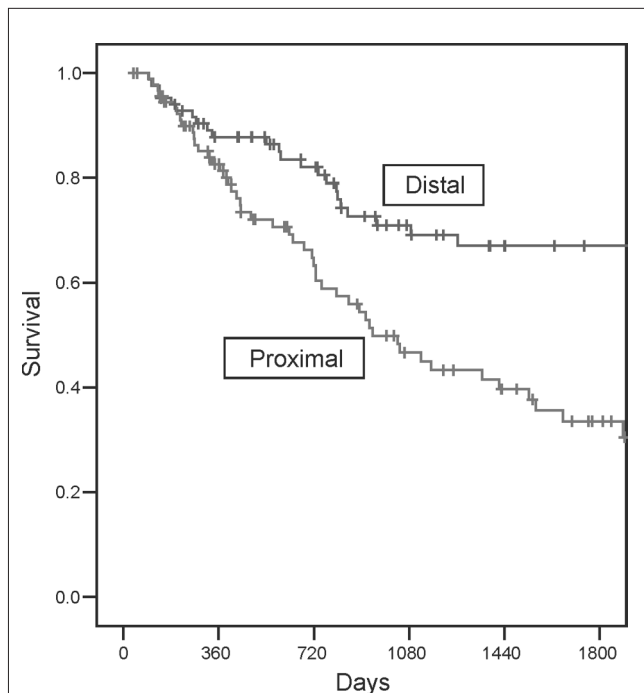


Figure 4 Disease-specific survival for adenocarcinoma of the distal (n = 82) and proximal stomach (n = 95).

to only 31.1% for tumours involving the proximal stomach (n = 95; Log-Rank 13.71; P = 0.0002; Fig. 4).

Discussion

The wide-spread adoption of radical gastric cancer surgery and D2 lymphadenectomy in the West has been prevented by concerns regarding the high associated morbidity and mortality. Only when the benefits of radical resection are shown to outweigh the increased risks of more extensive resection will this become standard practice. Western randomised trials<sup>4,5</sup> and recent multicentre UK audits<sup>6,7</sup> continue to report unacceptably high mortality rates in the region of 10%. There are now reports from specialist European centres with a mortality rate of less than 5%, and even below 2%.<sup>13,14</sup> This study, including a majority of patients undergoing total gastrectomy, demonstrates that by using a tailored and rational approach, radical gastric cancer surgery can be performed with low mortality in a UK population.

Although the overall in-hospital mortality of 1.7% begins to approach results reported by high-volume, specialist centres in the East,<sup>1-3</sup> it might never be possible to replicate fully their outcome data in a Western population.<sup>8</sup> This consecutive series represents a typical, unselected, UK population with a median age of 70 years and a mean ASA grade of 2.18 compared to 57 years and 1.6 in the Korean series.<sup>5</sup> The level of cardiorespiratory co-morbidity is also certainly

higher, as Kodera *et al.*<sup>2</sup> reported only one cardiac complication in 525 Japanese patients, a figure that is unrecognisable in any published Western series. This series also includes a higher proportion of proximal tumours than Eastern studies, remembering that total gastrectomy has been associated with a mortality almost twice that of a subtotal resection.<sup>6</sup> Reports from Eastern centres tend not to use, or even refer to, validated risk-assessment tools making true comparison between the populations difficult. Although the POSSUM and even P-POSSUM scoring systems have been criticised for over predicting mortality as they did significantly in this series, they do at least allow for accurate comparative audit between centres. A high physiological POSSUM score of  $\geq 20$  was found in 39.4% of patients compared to only 20% of patients in the ASCOT multicentre audit where it was identified to be an independent predictor of mortality.<sup>6</sup>

Despite careful case selection, the higher associated comorbidity of Western patients both increases the risk of non-surgical complications and lowers patients' ability to survive major surgical complications when they occur. In order to minimise mortality and morbidity, a rational approach to the radicality of surgery was utilised. Throughout the study, spleen and pancreas were preserved wherever possible as resection of these organs is recognised to increase the risk of complications. During the study period, such resections were specifically identified as predictors of poor postoperative outcome by the MRC and Dutch trials.<sup>4,5</sup> There have been concerns that splenectomy may also compromise long-term survival,<sup>15</sup> and a recent randomised trial from Korea confirmed that there is no survival benefit associated with performing routine splenectomy for proximal gastric cancer.<sup>16</sup>

Less radical surgery was also performed in selected high-risk elderly or unfit patients in order to prevent complications for those least able to tolerate them (Fig. 1). This included some obese patients where radical lymphadenectomy is technically difficult and has been associated with increased morbidity.<sup>17,18</sup> This was particularly the case for patients with either very early or locally advanced disease, where the potential survival benefit of more radical surgery would have been least.<sup>9</sup> For these patients, a subtotal gastrectomy was performed with a more limited lymphadenectomy in order to optimise postoperative recovery and functional outcome. In high-risk or very elderly patients with distal tumours, a partial gastrectomy with a D1 lymphadenectomy was usually chosen. No patient had less than a D1 lymphadenectomy performed. As the extent of resection was deliberately selected according to patient factors, no direct comparison between the results of D1 and D2 lymphadenectomy was performed.

The rates of major surgical and non-surgical complications were 9.4% and 18.3%, respectively. The basic principle for these patients was to recognise complications early and

deal with them in a pro-active way. It is likely that the low mortality of the present study reflects a combination of the rational approach to the radicality of surgery and meticulous postoperative care, as both the surgical and non-surgical complication rates and the risk of dying from a complication are considerably lower than in Western trials and the ASCOT audit.<sup>4-6</sup> Importantly, the combined anastomotic and duodenal stump leak rate, repeatedly shown to be the commonest surgical cause of mortality, was low at 3.3%, and only one of six leaks resulted in a death. This mirrors the experience of the NCCH in Tokyo<sup>19</sup> where the risk of dying following an anastomotic leak was only one-third of the 43.1% reported by the Dutch trial.<sup>5</sup>

In addition to achieving a low postoperative mortality, it is important to demonstrate that long-term outcome is not being compromised by tailoring the extent of surgery. The overall 5-year survival of 38% is comparable to the results for chemotherapy plus surgery (36%) rather than surgery alone (23%) in the recently published MAGIC trial.<sup>10</sup> The overall 5-year survival rates of 54.2% for stage 2 and 23.3% for stage 3 compare favourably with the D2 limbs of the MRC and Dutch trials.<sup>20,21</sup> The stage 2 data are also comparable to the 56.7% for the D2 limb of the German gastric cancer study, the subgroup they proposed gained greatest benefit from lymphadenectomy.<sup>9</sup> The outcome for patients with stage 4 disease is clearly poor and this reflects the inclusion of 20 patients who ultimately underwent a palliative (R1/R2) resection even though a curative resection had been planned pre-operatively. Although the 5-year survival rate of 68.2% for stage 1 disease is comparable to the MRC and Dutch trials,<sup>20,21</sup> it does not match the 87% reported by the Leeds group.<sup>22</sup> However, complete follow-up data have been collected and it is known that only 5 of 18 deaths, all in patients with stage 1b disease, were related to gastric cancer. The disease-specific survival was 100% and 80.5% for stage 1a and 1b disease, respectively. These results suggest that, overall, patients were not disadvantaged in the long-term as a result of tailored surgery.

The prognostic importance of tumour site was expected, as proximal gastric cancer has previously been shown to behave more aggressively than distal gastric cancer.<sup>23,24</sup> Nevertheless, the relatively poor outcome of patients with proximal tumours requires further evaluation and whether certain patients with locally advanced proximal tumours would benefit from more radical surgery cannot be excluded by this study. There is a need to determine whether any additional survival benefit of splenectomy to remove station 10 nodes for these patients is offset by additional mortality and long-term morbidity. Following the positive findings of the MAGIC trial,<sup>10</sup> there is an increasing use of peri-operative chemotherapy, nevertheless, it is widely recognised that, if newer multidisciplinary approaches are to be effective, it is vital that the surgery is of the highest quality.

## Conclusions

This study supports a tailored approach to gastric cancer surgery that balances risk and radicality. It provides further evidence to show we should be moving away from the D2 versus D1 debate, and that each operation has a place depending on the stage of the cancer and the age and fitness of the patient. The favoured procedure for distal tumours is a D2 lymphadenectomy and for proximal tumours a modified D2 lymphadenectomy with preservation of the pancreas and spleen. A more limited D1 resection is appropriate for high-risk or very elderly patients, particularly those with early or locally advanced disease. This approach can allow gastric cancer surgery to be performed with low mortality in a UK population, and does not appear to compromise long-term survival.

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