Gastric Cancer (2002) 5: 29–34

Original article

D2 or not D2? The gastrectomy question

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Abstract

Background. **The best reported long-term survival following surgery for gastric cancer is from centers performing radical D2 gastrectomy. Yet comparative studies from European centers report higher rates of postoperative complications following D2 gastrectomy than after the less radical D1 gastrectomy, without any benefit in survival. We aimed to compare the outcome after modified D2 gastrectomy (preserving spleen and pancreas where possible), performed by specialist surgeons, with that after conventional D1 gastrectomy performed by general surgeons for gastric cancer in a large United Kingdom cancer unit.**

Methods. **Two groups of patients were studied: a historical control group of 245 consecutive patients with gastric cancer, of whom 50 underwent a potentially curative D1 resection (median age, 69 years; 35 males) was compared with 200 consecutive patients, 72 of whom underwent a potentially curative D2 resection (median age, 71 years; 47 males).**

Results. **Among the 122 patients judged to have curable cancers, patients who underwent a D2 gastrectomy had lower operative mortality (8.3% vs 12%; $\chi^2 = 0.48$; $P = 0.50$) and experienced fewer complications (28% vs 36%; $\chi^2 = 0.93$; $P = 0.35$) than patients who underwent a D1 gastrectomy. Cumulative survival at 5 years was 56% after D2 resections, compared with 11% after D1 resections ($P < 0.00001$). In a multivariate analysis, only the stage of disease (stage I, hazard ratio [HR], 0.068; $P = 0.0001$; stage II, HR, 0.165; $P = 0.001$; stage III, HR, 0.428; $P = 0.053$) and the level of lymphadenectomy (HR, 0.383; $P = 0.00001$) were independently associated with the duration of survival.**

Conclusion. **Modified D2 gastrectomy without pancreaticosplenectomy, performed by specialist surgeons, can improve survival after R0 resections without increasing operative morbidity and mortality, when compared with D1 gastrectomy performed by general surgeons.**

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Originally presented at the Seventh UEGW meeting, Rome, November 1999, and at the Fourth International Gastric Cancer Congress, New York 2001.
Received: July 24, 2001 / Accepted: November 19, 2001

Key words Gastric cancer · Surgery · Lymphadenectomy

Introduction

Gastric cancer is now the second commonest cancer worldwide, accounting for 11 000 deaths per year in the United Kingdom alone [1]. Although surgery remains the prime therapeutic modality, opinion over the optimum resection for patients with gastric cancer remains divided, and the literature polarized.

The impressive outcome after D2 gastrectomy published in large retrospective series from Japan [2–5] has not been reproduced in randomized comparative studies from Europe [6–9]. The two largest randomized studies both report significantly greater operative morbidity and mortality associated with an extended D2 lymphadenectomy when compared with the less aggressive D1 lymphadenectomy, and have failed to demonstrate any survival advantage for a D2 resection. Many of the serious complications associated with D2 resections, however, were associated with resections of the pancreas and spleen [6,7]. Moreover, the best-long term survival was observed in patients undergoing D2 resections without pancreatico-splenectomy [8].

In Britain, patients with gastric cancer tend to be older, more overweight, and less fit than those in Japan [10]. Furthermore, such patients often have diverse and complex clinical needs, best addressed by a site-specific multi-disciplinary team. Surgery for upper gastrointestinal malignant disease in Britain and much of the West, has by tradition, been performed by general surgeons, and, despite sporadic reports to the contrary [10–12], the prognosis for patients diagnosed with gastric cancer remains poor. The tedious and demanding nature of D2 lymphadenectomy, harnessed to limited subspecialist development [13], means that the D1 perigastric lymphadenectomy remains the most commonly performed

operation for gastric cancer. The aim of our study, therefore, was to investigate whether a modified D2 gastrectomy (preserving pancreas and spleen where possible), and allied to a specialist multidisciplinary team approach, might improve the outcome when compared with the traditional D1 gastrectomy performed by general surgeons working outside this framework. The setting was a large District General Hospital in South Wales, serving a population of 480 000.

Patients and methods

Two groups of patients were studied. Between January 1990 and September 1995, 245 consecutive patients with adenocarcinoma of the stomach were treated by five consultant general surgeons in the Department of Surgery at the Royal Gwent Hospital. Clinical and pathological information for this group of patients was obtained by review of their case notes. The median age of this group of patients was 67 years (range, 47–87 years) and 166 were male. The definition of a potentially curative resection was that all visible tumor was removed and that both proximal and distal resection margins were free of tumor on histological examination. Potentially curative resection was possible in 50 of them (median age, 69 years [range, 59–77 years]; 35 males). This comprises our historical control group (D1). Between October 1, 1995 and January 31, 2000, 200 consecutive patients were treated by a single surgeon (W.G.L.) with an interest in esophagogastric cancer, after an executive decision by the Department of Surgery at the Royal Gwent Hospital to increase surgical subspecialization and develop the subspeciality of upper gastrointestinal surgery. This latter surgeon had received 2 years specialist training as Lecturer in Surgery under the supervision of Professor David Johnson at the University of Leeds Department of Surgery, United Kingdom. The median age of this group of patients was 71 years (range, 35–93 years), and 129 were male. Potentially curative resection was possible in 72 (36%) of them (median age 71 years [range, 44–83 years]; 47 males). This comprises our comparison group (D2).

Surgical treatment

Since 1995 our policy has been to perform a modified radical D2 resection with extended lymphadenectomy, but preserving the pancreas and spleen where possible, as described by Sue-Ling et al. [10]. Preoperative staging was done with the aid of both spiral computerized tomography and laparoscopy. All tumors were staged in accordance with the 1987 unified international gastric cancer staging classification [14], until 1997, when we adopted the recently published TNM classification of malignant tumours [15]. The details of the patients who underwent potentially curative resection, together with their American Society of Anesthesiologists (ASA) grade and stage of disease, are shown in Table 1. The details of their surgery are shown in Table 2.

Table 1. Details of the patients who underwent potentially curative surgery

	D1	D2
Number	50	72
Age (years)	69 (59–77)	71 (63–75)[a]
Sex (M:F)	35:15	47:25
Stage of disease		
I	5 (10)	14 (19)
II	9 (18)	15 (21)
IIIA	36 (72)	19 (26)
IIIB		14 (19)
IV		10 (14)
ASA grade		
I	7 (14)	3 (4)
II	28 (56)	37 (51)
III	10 (20)	29 (40)[b]
IV	5 (10)	3 (4)

Figures are numbers of patients, with percentages shown in parentheses
ASA, American Society of Anesthesiologists
[a] Median, with interquartile ranges in parentheses
[b] $\chi^2 = 5.579$; $P = 0.018$

Table 2. Details of the surgery in patients who underwent a potentially curative resection

	D1 ($n = 50$)	D2 ($n = 72$)
Operation		
Subtotal gastrectomy	30	37
Total gastrectomy	13	31
Esophagogastrectomy	7	4
Splenectomy	9	4
Distal pancreatectomy + Sx	0	4
Transverse colectomy	0	10[a]

Figures are numbers of patients
Sx, Splenectomy
[a] $\chi^2 = 7.564$; $P = 0.006$

Follow-up

Patients who underwent D2 resections were reviewed every 3 months for the first year and every 6 months thereafter. Only 1 of the 122 patients was lost to follow-up, and 90 patients were followed up for a minimum of 5 years or until death (50 D1; 40 D2). The median duration of follow-up in the D2 group was 36 months (range, 12 to 72 months). Endoscopy and computed tomography were arranged if recurrent disease was suspected. Causes of death were sought from case notes, pathology records, and general practitioners' records.

Statistical analysis

Statistical analysis appropriate for nonparametric data was used. Grouped data were expressed as median (interquartile range). Groups were compared with the Mann-Whitney *U* test for unpaired data. Nominal data were analyzed by means of Fisher's exact test [16]. Cumulative survival was calculated by the life table method of Kaplan and Meier [17]. Differences in survival times between groups of patients were analyzed by the log rank method [18]. Cox's proportional hazards model was used to assess the prognostic value of individual variables. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 10 (SPSS, Chicago, IL, USA).

Results

Stage of disease at presentation

Over the study period of 10 years, the proportion of patients in whom potentially curative resection was possible increased significantly, from 20% of patients with gastric cancer in 1990 to 1994, to 36% of patients with gastric cancer in 1995 to 2000 (χ^2 13.452; $P = 0.0001$). Similarly favorable changes were seen in the proportion of patients who had early stage of disease, from 10% of all patients with gastric cancer who underwent surgery in the first 5-year period, to 19% of all such patients in the last 5-year period ($\chi^2 = 2.002$; $P = 0.157$). This trend toward earlier diagnosis of gastric cancer coincided with a 50% increase in the number of upper gastrointestinal endoscopies performed, from 2283 procedures in 1995 to 3418 in 2000.

Operative mortality and morbidity

The ASA grades of the patients who underwent potentially curative surgery are shown in Table 1. Operative morbidity was 36% after D1 gastrectomy, compared with 28% after D2 gastrectomy ($\chi^2 = 0.93$; $P = 0.335$). Details of the major operative morbidities are shown in Table 3. Operative mortality 30 days after operation was 12% (6 of 50 patients) after the traditional D1 gastrectomy, compared with 8.3% overall (6 of 72 patients) after a modified D2 gastrectomy ($\chi^2 = 0.477$; $P = 0.504$). None of the patients who died after a D2 gastrectomy had undergone a splenectomy or pancreatectomy.

Learning curve

The operative morbidity and mortality after D2 gastrectomy, with respect to sequence within the consecutive series, is shown in Fig. 1. Operative mortality after D2 gastrectomy was considerably lower for the last 32 patients (3.1%) than for the first 40 patients (12.5%), although this decrease was not significant ($\chi^2 = 2.045$; $P = 0.153$).

Table 3. Operative morbidity

	D1	D2
Anastomotic leak	4 (4)	2 (1)
Respiratory sepsis	6 (2)	9 (2)
Wound infection	4	3
Myocardial infarct	1	2 (1)
Pulmonary embolus	3	2 (2)
Cerebrovascular accident	0	1
Renal failure	0	1
Total morbidity	18	20

Figures are numbers of patients
Operative deaths are shown in parentheses

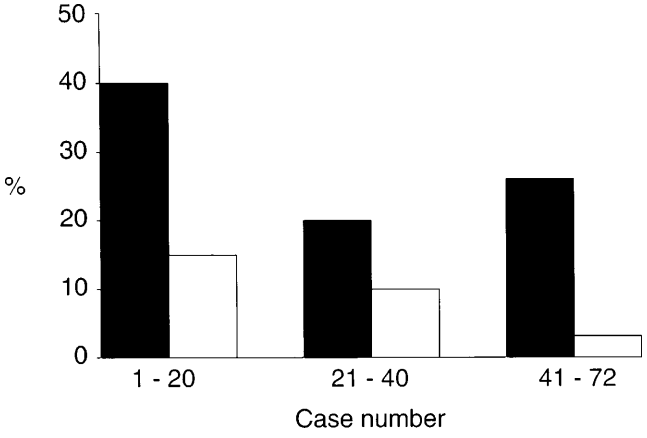

Fig. 1. Learning curve of operative morbidity (*black bars*) and mortality (*white bars*) after D2 gastrectomy, related to sequence within the consecutive series

Survival

Corrected cumulative survival by treatment, calculated by life table analysis, is shown in Fig. 2. Cumulative survival for the 50 patients who underwent a D1 gastrectomy was 11% at 5 years. In contrast, survival for the 72 patients who underwent a D2 gastrectomy was 56% at 5 years ($P < 0.00001$). The median follow-up (or time to death) after D1 gastrectomy was 19 months (range, 1.3–137 months) compared with a median follow up of 34 months (range, 9–72 months) after D2 gastrectomy. The factors found to be significantly associated with the duration of survival on univariate analysis are shown in Table 4.

Multivariate analysis

The prognostic variables entered into the model were age, sex, stage of the tumor, location of the tumor, type

Table 4. Univariate analysis of factors associated with duration of survival

Factor	χ^2	*P* value
Age	1.93	0.7495
Sex	0.60	0.4383
ASA grade	2.24	0.524
Site of tumor	1.19	0.7556
Type of gastrectomy	1.10	0.578
Pancreatectomy	0.04	0.8486
Splenectomy	8.24	0.0041
Stage of disease	17.30	0.0006
Surgeon	24.03	0.0005
D1 lymphadenectomy	17.55	0.00001

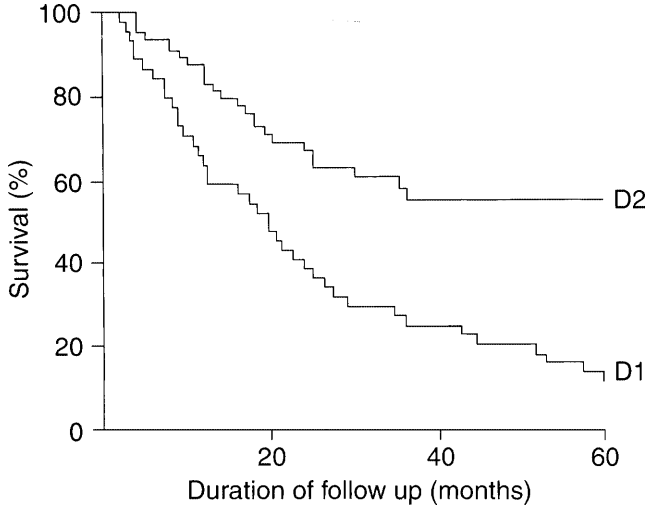

Fig. 2. Corrected survival curves for patients who underwent potentially curative resection. Log rank $\chi^2 = 17.55$; $P = 0.00001$. Operative deaths were excluded

of gastrectomy (subtotal or total), level of lymphadenectomy, and level of the resection of the spleen and pancreas. Forward and backward stepwise regression were used. Stage of disease (stage I, hazard ratio was 0.068; 95% confidence interval [CI], 0.017–0.273; $P = 0.0001$; stage II, hazard ratio was 0.165; 95% CI, 0.055–0.501; $P = 0.001$; stage III, hazard ratio was 0.428; 95% CI, 0.181–1.012; $P = 0.053$) and level of lymphadenectomy (hazard ratio, 0.383; 95% CI, 0.228–0.644; $P = 0.00001$) were found to be the most important predictors of outcome as determined by Cox's proportional hazards model (global χ^2 for the model was 34.583; $P = 0.0001$).

Discussion

The findings of this study demonstrate that the techniques originally described by Japanese surgeons [2–4] can be introduced, with modification, both safely and effectively into a British Cancer Unit. The proportion of all patients for whom potentially curative resection was possible doubled during the 1990s, even though no significant favorable shift toward earlier pathological stages occurred in the patients undergoing surgery. Moreover, this was achieved without a concomitant increase in postoperative complications. Operative morbidity fell from 36% to 28%, and operative mortality from 12% to 8.3%, while survival at 5 years improved fivefold, from 11% to 56%.

Clearly, this is not a randomized control trial and the number of patients is relatively small, but, nevertheless, it does demonstrate what can be achieved by specialist care in a large District General Hospital in Britain. The improved outcome cannot be explained by poorer than average results in our historical control group, as our results in the early 1990s did not differ significantly from those reported by Allum et al. [19] in 1989 in a large population-based study. In this latter study, fewer than 1% of patients had stage I disease (compared with 2% at our hospital), and curative resection was possible in only 25% of patients (compared with 20%). Operative mortality was 16% after potentially curative resection (compared with 12%), and 5-year survival was 12% (compared with 11%). The surgical management of patients with gastric cancer in our hospital was, therefore, probably in keeping with that in most other centers in the United Kingdom at that time. Nonetheless, the operative mortality in our control group (12%) and that in the study of Allum et al. [19] (16%) were considerably higher than the 4%–7% described following D1 gastrectomy in the most recent randomized controlled trials [6–9]. However, these latter studies universally fail to mention the ASA grade of the patients studied, which, in our study, is clearly relevant, as no fewer than 30% of the patients who underwent D1 lymphadenectomy, and 44% of the patients who underwent D2 lymphadenectomy (39% overall) had significant associated comorbidity, resulting in an ASA classification of grade three or more.

The reluctance of Western surgeons to adopt extended lymphadenectomy is understandable in the light of the recently published Medical Research Council (MRC) ST01 trial of D1 versus D2 resection for gastric cancer [6,8] and the Dutch study of Bonenkamp et al. [7,9]. Both studies have reported mortality rates following D2 gastrectomy that are very similar, at 13% and 10%, respectively, and each study provides good evidence that the excess mortality is accounted for by splenectomy (with or without the resection of the pancreas) rather than by the extended lymphadenectomy. Moreover, in the MRC ST01 trial, the best survival was obtained in patients who underwent D2 resections without pancreatico-splenectomy. The incidence of lymph node

metastases along the splenic artery and splenic hilum is reported to vary from 15% to 27% [20–22], but the level-two lymphadenectomy with pancreatico-splenectomy performed in the MRC ST01 trial harvested, on average, only four more nodes than the number harvested after D1 gastrectomy. Many of these nodes can be cleared with preservation of the pancreas and spleen, and impressive results, with low morbidity and mortality and improved survivals, have already been reported with spleen-preserving D2 gastrectomy [23].

Both the MRC ST01 trial and the Dutch trial have received criticism over the relative inexperience of many different surgeons performing D2 lymphadenectomy, and the existence of any possible relationship between caseload and operative mortality remains controversial. The transitional learning curve from a D1 to a D2 gastrectomy, described by surgeons in Leeds, was long, with 10 years elapsing before their operative mortality fell to 5% [10]. Our results parallel this finding of a typical learning curve. Surgical subspecialization reduced operative mortality from 12% to 3.1% over a period of 5 years, although the stage of gastric cancer remained advanced and postoperative morbidity was persistent and common. The initial high operative mortality occurred despite the principal author's previous experience in a large-volume specialist unit at the University of Leeds. This finding again emphasises that maintaining low operative mortality is not simply a matter of specialized operative technique, but that it also requires specialized anesthetic and postoperative care from an experienced multidisciplinary team.

Clinical outcomes for common cancers vary widely in different hospitals [24], and gastric cancer is no exception. Moreover, survival figures for all the common cancers in Britain remain well below the European average [25]. The duration of follow-up of our patients after D2 gastrectomy is currently modest, and comparisons of survival with those in major European centers are of limited value because of unknown and uncontrolled variables, such as methods of case selection, patients' characteristics, and the surgical methods used. Nevertheless, outcome for patients with gastric cancer in our own center has improved over the past decade, and the suggestion that the introduction of more radical surgery might increase operative morbidity and mortality, and thus nullify any survival advantage, has proven to be false [6,7]. Furthermore, our cumulative survival curve (Fig. 2) compares well with the best results reported in Britain by Sue-Ling et al. [10].

In conclusion, the MRC ST01 trial did not dismiss the possibility that a D2 gastrectomy without pancreatico-splenectomy may be better than a standard D1 resection. The practical problem that we face in Britain is that the majority of our patients continue to have advanced stage III and IV disease at presentation, and the randomization of otherwise fit patients who clearly have disease within lymph node groups 7 to 9, to D1 gastrectomy (groups 1–6 only), may be difficult to justify on ethical grounds in any future trials. The exact role of D2 gastrectomy within a framework of greater subspecialization and a multidisciplinary team approach remains unclear at present, but our own experience is encouraging and suggests that, in otherwise fit patients with gastric cancer, without distant metastatic disease, a modified D2 gastrectomy, preserving pancreas and spleen where possible, and performed by specialist surgeons, has advantages over the traditional standard D1 gastrectomy, performed by the majority of British general surgeons. We believe that this approach is likely to become the standard in the future surgical treatment of gastric cancer.

Acknowledgments We should like to acknowledge the contribution of the following Consultant General Surgeons who all treated numbers of patients who underwent a D1 gastrectomy in the early 1990s at the Royal Gwent Hospital: Mr. D. Eric Sturdy, MS, FRCS, Consultant Surgeon, Royal Gwent Hospital; Mr. Gwylim Griffith, OBE, FRCS, Consultant Surgeon and ex Medical Director Glan Hafren N.H.S. Trust; The late Mr. Martin Price Thomas, FRCS, Consultant Surgeon, Royal Gwent Hospital; and Mr. Keith D. Vellacott, DM, FRCS, Consultant Surgeon, Royal Gwent Hospital.

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