Nodal dissection for patients with gastric cancer: a randomised controlled trial

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Summary

Background The survival benefit and morbidity after nodal dissection for gastric cancer remains controversial. We aimed to do a single-institution randomised trial to compare D1 (ie, level 1) lymphadenectomy with that of D3 (ie, levels 1, 2, and 3) dissection for gastric cancer in terms of overall survival and disease-free survival.

Methods From Oct 7, 1993, to Aug 12, 1999, 335 patients were registered. 221 patients were eligible, 110 of whom were randomly assigned D1 surgery and 111 of whom were randomly assigned D3 surgery, both with curative intent. Three participating surgeons had done at least 25 independent D3 dissections before the start of the trial, and every procedure was verified by pathological analyses. The primary endpoints were 5-year overall survival and 5-year disease-free survival. We also analysed risk of recurrence. Main analyses were done by intention to treat. This trial is registered at the US National Institute of Health website http://www.clinicaltrials.gov/ct/show/NCT00260884.

Findings Median follow-up for the 110 (50%) survivors was 94·5 months (range 62·9–135·1). Overall 5-year survival was significantly higher in patients assigned D3 surgery than in those assigned D1 surgery (59·5% [95% CI 50·3–68·7] *vs* 53·6% [44·2–63·0]; difference beteween groups 5·9% [–7·3 to 19·1], log-rank p=0·041). 215 patients who had R0 resection (ie, no microscopic evidence of residual disease) had recurrence at 5 years of 50·6% [41·1–60·2] for D1 surgery and 40·3% [30·9–49·7] for D3 surgery (difference between groups 10·3% [–3·2 to 23·7], log-rank p=0·197).

Interpretation D3 nodal dissection, compared with that of D1, offers a survival benefit for patients with gastric cancer when done by well trained, experienced surgeons.

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Introduction

At present, surgical resection is the treatment of choice for gastric cancer. However, the need for radical lymph-node dissection for curative treatment of gastric cancer continues to be debated. Many surgeons do minimum (ie, D1 or level 1 lymphadenectomy) or no lymph-node dissection. Retrospective studies[1,2] from several centres in Japan, Europe, and USA have reported improved survival for patients who underwent D3 (ie, levels 1, 2, and 3 on first edition of Japanese classification of gastric cancer[3]) lymphadenectomy on gastric resection. Two large randomised trials[4,5] from the Netherlands[4] and the UK[5] have shown no survival benefits, but high morbidity (43–46%) and mortality (10–13%), after D3 (ie, D2 on second edition of Japanese classification of gastric cancer[6]) gastric dissection compared with D1 dissection. These trials[4,5] were multi-institutional, had difficulty in ensuring quality control, and had many participating surgeons with little or no experience in D3 dissection. For a surgical trial to compare meaningfully different operative methods, perhaps participating surgeons should be equally experienced in both techniques.

In Taiwan, gastric cancer is the fifth most common cause of death from cancer. Surgical resection does or does not include wide lymphadenectomy (ie, D2 or D3 resection). We aimed to do a prospective, randomised comparison of D1 and D3 dissection at a single institution, focusing on advanced gastric cancer (ie, invasion beyond the submucosa) because of its high frequency of lymph-node metastasis.[7] Data reported previously[8] from our trial found that: short-term morbidity was higher in patients assigned D3 dissection compared with those assigned D1; there were no deaths in either group within 30 days of surgery; and that D3 dissection was associated with more complications, blood loss, operation time, and a longer hospital stay than was D1 dissection. Here, we report the long-term survival data and the cumulative risk of recurrence for these two surgical groups.

Methods

Registration and randomisation

This trial was open for accrual from Oct 7, 1993, to Aug 12, 1999. The institutional review board of Taipei Veterans General Hospital approved the study, and all patients gave written informed consent. The design and methods of the trial have been reported previously.[8] Briefly, eligible patients had histologically proven, potentially curable gastric adenocarcinoma, and had physical fitness suitable for elective operation of either type of lymphadenectomy. Exclusion criteria were as follows: age older than 75 years; previous or concomitant other cancer; previous or concomitant gastrectomy for benign disease; previous chemotherapy or radiotherapy; clinical evidence of early gastric cancer on laparotomy; oesophageal involvement; macroscopically enlarged lymph nodes around the hepatoduodenal ligament or para-aortic regions; and distant metastatic disease.

The data centre of National Health Research Institutes (Taipei, Taiwan) was responsible for trial registration and randomisation. All registered patients underwent staging laparotomy at Taipei Veterans General Hospital, Taiwan. On completion of the final assessment of eligibility, patients were enrolled randomly in permuted blocks of four, six, or eight that were chosen randomly by a computer algorithm generated by the protocol statistician (CAH) and the research assistant (HTY), and assigned to either a D1 resection or D3 resection. Randomisation was done by CAH and HTY. The data manager YLH notified surgeons of which procedure had been assigned to a particular patient. The trial was not masked.

After randomisation, peritoneal fluid was obtained for cytological analyses by a pathologist (Chiung-Ru Lai); positive cytology was regarded as presence of distant metastasis.

Treatment groups

Surgery was done at the Taipei Veterans General Hospital. Surgical procedures and pathological assessment were standardised in accordance with the Japanese classification of gastric cancer.[3] Lymph nodes were classified into stations ranging from one to 16. D1 surgery dissects perigastric lymph nodes in close proximity to the primary tumour along the lesser and greater curvatures; D3 surgery additionally dissects lymph nodes around the blood vessels supplying the stomach that arise from the coeliac axis (ie, left gastric, common hepatic, and splenic arteries), lymph nodes in the hepatoduodenal ligament and retropancreatic region, and lymph nodes surrounding the superior mesenteric vein.

A total or distal subtotal gastrectomy was selected on the basis of distance between cardia and tumour. A margin of 3 cm is needed for superficial and well defined tumours; a margin of 5 cm is needed for those that are poorly defined. Thus, a subtotal gastrectomy is the standard procedure for distal gastric cancer, whereas a total gastrectomy is the common procedure for proximal gastric cancer. For D3 resection, combined-organ (ie, en-bloc) resection involving hemipancreaticosplenectomy, total gastrectomy, or both, might be done to facilitate node dissection in patients with lymph-node metastases along the splenic artery (ie, at station 11) or at the right paracardia region (ie, at station one), confirmed by frozen section.[8,9]

Quality control

A participating surgeon (CWW) learned the operative technique from several different medical centres in Japan, and set-up our standard procedure. Two other surgeons (SSL and MCH) gained experience of this standard procedure by serving as assistants and operators under the training of CWW. Before the trial, all participating surgeons had done at least 25 independent D3 resections. Every surgeon had equal probability of doing D1 and D3 resections.[8] After surgery, the pathologist (AFL) assessed samples of primary tumour and lymph nodes according to Japanese and Lauren's histological classification to verify the depth of cancer invasion, number of lymph nodes removed, and number of positive nodes. The pathologist held regular meetings for participating surgeons to check patient details, in particular surgical procedures including the number and location of lymph nodes identified at pathological analysis. Any clinicopathological discrepancy, such as depth of cancer invasion, was discussed in monthly gastric-cancer conferences at Taipei Veterans General Hospital, which were attended by gastroenterologists, radiologists, pathologists, and surgeons.

Endpoints and follow-up

The primary endpoints were 5-year overall survival and 5-year disease-free survival. We also analysed 5-year disease-specific survival. Overall survival was calculated from the time of randomisation until death or the last follow-up contact (ie, censoring). Patients who had complete (ie, R0) resection were used to assess cumulative risk of recurrence—the event used to assess disease-free survival. Data for a patient were censored at last follow-up when they were alive with no evidence of disease, or when they had died of causes other than gastric cancer without evidence of recurrence.[10] Recurrence was defined as clinical and radiological signs of disease, or presence of an abnormal lesion on endoscopy. Disease-specific survival was defined as the proportion of patients who had not died from gastric cancer. Main analyses were done by intention to treat.

We did biopsy samping to confirm evidence of recurrent disease or distant metastases; biopsy was not done for new, multiple pulmonary lesions or for lesions characteristic of osseous metastases on CT or whole-body bone scans. Surgeons transferred patients with disease recurrence or distant metastases to the medical-oncology unit for chemotherapy and close follow-up of progression until death. For patients that died while not being treated at our hospital, we attempted to obtain medical charts.

Follow-up assessments were done every 3 months for the first 5 years after surgery, and then every 6 months until the patient's death. Follow-up procedures were: medical history, physical examination, routine blood tests, liver-function tests, analyses of tumour markers carcinoembryonic antigen and cancer antigen 199, chest radiograph, and other imaging work-up. All routine procedures were done by surgeons; upper endoscopy was done by gastroenterologists; and upper gastrointestinal series, abdominal sonography, and CT was done by radiologists. All follow-up was done at Taipei Veterans General Hospital.

Patients who had recurrence of gastric cancer after surgery could receive chemotherapy with 20 mg/m^2 cisplatin, 450 mg/m^2 fluorouracil, and 90 mg/m^2 leucovorin, given in 0·5 L normal saline and infused intravenously and simultaneously over 96 h every 21 days.

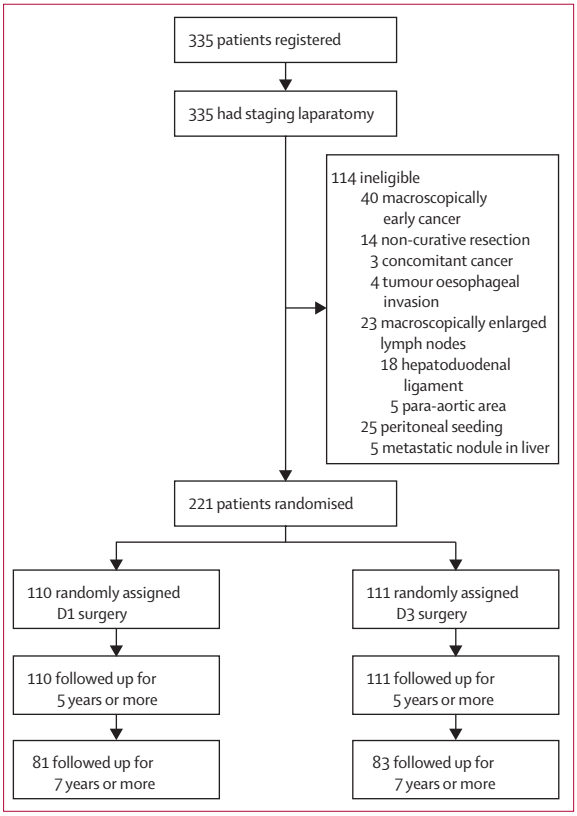

Figure 1: **Trial profile**

This treatment could be delayed or modified according to the protocol if the patient had onset of toxic effects.

Statistical analyses

The sample size was calculated on the basis of an expected 5-year survival of 20% for patients allocated D1 surgery and 40% for those allocated D3 surgery. By use of a significance level of 0·05 (two sided) and power of 0·80, a minimum of 150 evaluable patients were needed. The protocol did not stipulate an interim analysis.

Treatment comparisons were made by use of the log-rank test. Potential prognostic factors were entered into a Cox's regression model. These factors were: age (≤65 years *vs* >65 years); sex; site of tumour in stomach (whole *vs* lower *vs* middle *vs* upper); gross appearance (superficial *vs* Bormann types I and II *vs* Bormann types III and IV); tumour stage (T1 *vs* T2 *vs* T3 *vs* T4); nodal stage (N0 *vs* N1 *vs* N2 *vs* N3); removal of spleen or pancreas (neither *vs* spleen or both); gastrectomy (subtotal *vs* total) blood transfusion; and Lauren's histological type (diffuse *vs* intestinal). For univariate analyses, we put the prognostic factor of interest and treatment group as covariates in the Cox regression model.

Role of the funding source

The sponsor of this study had no role in the trial design; in the analysis and interpretation of the data; or in the writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

	D1 surgery (n=110)	D3 surgery (n=111)
Clinicopathological features		
Age (years)		
Median (95% CI)	63·0 (60·9–65·1)	65·2 (63·2–67·2)
Sex		
Men	84 (76%)	86 (77%)
Women	26 (24%)	25 (23%)
Number of lymph nodes removed		
Mean (95% CI)	19·4 (17·0–21·9)	37·2 (34·7–39·7)
Number of involved lymph nodes		
Mean (95% CI)	3·4 (2·5–4·3)	3·9 (2·9–4·9)
Status after resection		
Site of tumour		
Upper stomach	15 (14%)	13 (12%)
Middle stomach	34 (31%)	26 (23%)
Lower stomach	58 (53%)	70 (63%)
Whole stomach	3 (3%)	2 (2%)
Pathological tumour stage		
T1	23 (21%)	29 (26%)
T2	26 (24%)	20 (18%)
T3	56 (51%)	59 (53%)
T4	5 (5%)	3 (3%)
Pathological nodal stage*		
N0	39 (35%)	44 (40%)
N1	54 (49%)	43 (39%)
N2	14 (13%)	18 (16%)
N3	3 (3%)	6 (5%)
Operative procedures		
Type of gastrectomy		
Total	30 (27%)	23 (21%)
Subtotal	80 (73%)	88 (79%)
Distal pancreatosplenectomy	1 (1%)	13 (12%)
Splenectomy	3 (3%)	1 (1%)
R0 resection	107 (97%)	108 (97%)
Status at last follow-up		
Alive	46 (42%)	64 (58%)
Alive without recurrence	44 (40%)	59 (53%)
Alive with recurrence	2 (2%)	5 (5%)
Locoregional	2 (2%)	2 (2%)
Distant	0	3 (3%)
Died	64 (58%)	47 (42%)
Died without recurrence	10 (9%)	7 (6%)
Died with recurrence	54 (49%)	40 (36%)
Locoregional	13 (12%)	8 (7%)
Locoregional and distant	20 (18%)	13 (12%)
Distant	21 (19%)	19 (17%)

Data are number (%), unless otherwise stated. Percentages might not add to 100% because of rounding. *N1=1–6 involved nodes; N2=7–15 involved nodes; N3, >15 involved nodes.

Table 1: **Characteristics of intention-to-treat population (n=221)**

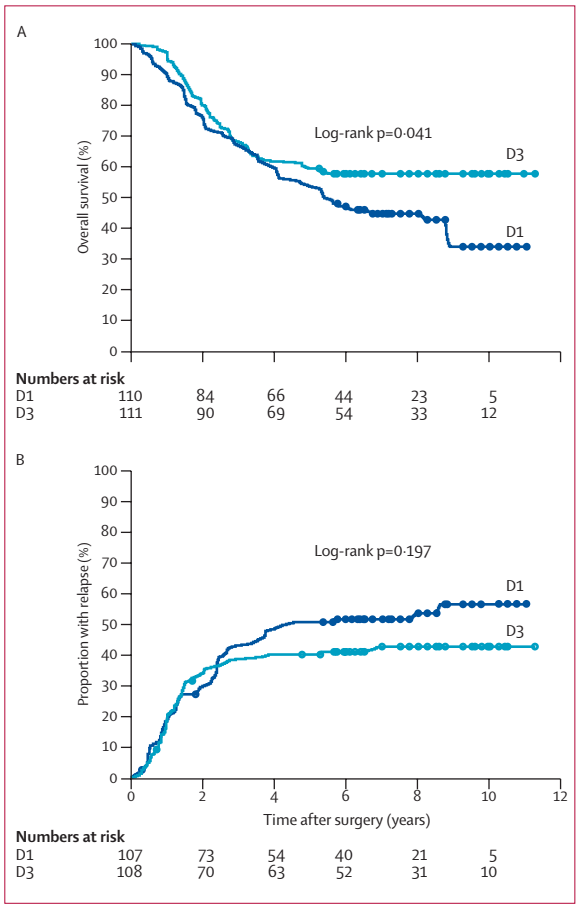

Figure 2: **(A) Overall survival in intention-to-treat population (n=221). (B) Proportion of patients who relapsed during follow-up for patients with R0 resection (n=215)**

Results

335 patients (median age 64·1 years [95% CI 62·6–65·6]) were registered at the National Health Research Institutes. At laparotomy, 114 patients were regarded ineligible and were thus not randomised (figure 1). 221 patients were randomised: 110 were allocated to D1 surgery and 111 to D3 surgery (figure 1). All patients were followed up for at least 5 years (ie, until July 18, 2005), and were thus available for analyses by intention to treat. Table 1 shows the characteristics of these patients. In the D3 group, 27 patients with pathological nodal stage (Japanese classification)[3] N2 and four with stage N3 had positive lymph nodes removed from the nodal basin. Median follow-up for the 110 (50%) survivors was 94·5 months (range 62·9–135·1). Of the 111 (50%) deaths, 94 (85%) were due to tumour recurrence, two (2%) to other malignant disease, and 15 (13%) to other diseases or accidents.

No patients received preoperative or postoperative adjuvant radiotherapy or chemotherapy. 215 patients had an R0 resection; six patients had an incomplete resection (three had positive microscopic margins, one had simultaneous liver metastasis, one had positive cytology, and one had omentum seeding).

64 patients did not fit the protocol histologically (ie, had early cancer, oesophageal invasion, or positive resection margin on pathological analyses): 52 had early cancer (ie, confined to submucosa or mucosa); five had invasion to the oesophagus; three had positive microscopic margins; two had a second tumour (hepatocellular carcinoma) or simultaneous metastasis; one had positive peritoneal cytology; and one had omentum cancer seeding. One patient had technical violation of the protocol by having a more-extensive lymph-node dissection than was intended. The remaining 156 patients were treated per protocol (76 in the D3 group and 80 in the D1 group).

In the intention-to-treat population (n=221), 5-year overall survival was 59·5% (95% CI 50·3–68·7) for the D3 group and 53·6% (44·2–63·0) for the D1 group (difference between groups 5·9% [–7·3 to 19·1], log-rank p=0·041; figure 2A). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed that patients assigned D3 surgery were less likely to die than were those assigned D1 surgery (hazard ratio [HR] 0·49 [0·32–0·77], p=0·002; table 2, multivariable analyses).

Per-protocol analysis showed that 5-year overall survival was 51·3% (40·1–62·5) for the 76 patients in this analysis who had D3 surgery and 45·0% (34·0–56·0) for the 80 patients in this analysis who had D1 surgery (difference between groups 6·3% [–6·4 to 22·0], log-rank p=0·056). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed a HR of 0·42 (0·26–0·69), p=0·0006.

Intention-to-treat analysis showed that 5-year disease-specific survival was 63.1% (54·0–72·2) for patients allocated D3 surgery and 57·8% (48·4–67·2) for those assigned D1 surgery (difference between groups 5·3% [–7·8 to 18·4], log-rank p=0·068). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed a HR of 0·72 [0·57–0·91], p=0·006.

Per-protocol analysis showed that 5-year disease-specific survival was 54·3% (43·0–65·7) for the 76 patients who had D3 surgery and 49·5% (38·4–60·7%) for the 80 patients who had D1 surgery (difference between groups 4·8% [–11·1 to 20·7], log-rank p=0·151). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed a HR of 0·70 [0·53–0·90], p=0·006).

56 (52%) of 107 patients in the D1 group who had R0 resection had disease recurrence compared with 45 (42%) of 108 patients in the D3 group who had R0 resection (p=0·117, χ^2 test). Patients who had R0 resection in the D3 group had significantly higher 5-year overall survival than did those who had R0 resection in the D1 group (61·1% [51·9–70·3] *vs* 54·2% [44·8–63·6]; difference between groups 6·9% [–6·3 to 20·7], log-rank p=0·026).

Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed an HR of 0·46 (0·30–0·72), p=0·0007. 5-year disease-specific survival was 64·9% (55·8–74·0) for patients in the D3 group who had R0 resection and 58·5% (49·0–68·0) for those in the D1 group who had R0 resection (difference between groups 6·4% [–7·0 to 19·7], log-rank p=0·044). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed an HR of 0·69 (0·54–0·88), p=0.002. Recurrence at 5 years was 50·6% (41·1–60·2) for the D1 group and 40·3% (30·9–49·7) for the D3 group (difference between groups 10·3% [–3·2 to 23·7], log-rank p=0·197; figure 2B). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed a HR of 0·65 (0·41–1·02), p=0·063.

For the 203 patients who did not need splenectomy or pancreatectomy (106 of whom were assigned D1 surgery and 97 of whom were assigned D3 surgery), those in the D1 group had lower 5-year overall survival than did those in the D3 group (53·8% [44·3–63·3] *vs* 60·8% [51·1–70·5]; difference between groups 7·1% [–6·5 to 20·6], log-rank p=0·024). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed an HR of 0·47 (0·30–0·76), p=0·002. Furthermore, those in the D3 group who did not need splenectomy or pancreatectomy had higher 5-year disease-specific survival than did those in the D1 group who did not need splenectomy or pancreatectomy (63·6% [53·9–73·2] *vs* 57·4% [47·9–67·0]; difference between groups 6·2% [–7·5 to 19·7], log-rank p=0·039). Cox proportional-hazard analysis, which controlled for the effect of prognostic factors defined in the methods, showed an HR 0·68 (0·53–0·88), p=0·003.

The skill of an individual surgeon did not affect survival (p=0·616, log-rank test). The HR for the surgeons SSL and MCH relative to surgeon CWW were 1·19 (0·79–1·79, p=0·188, univariate Cox regression analysis) and 1·24 (0·71–2·15, p=0·450, univariate Cox regression analysis), respectively. In univariable analyses, HR for death differed for seven prognostic factors for overall survival: tumour site; gross appearance; tumour stage; nodal stage; type of gastrectomy; blood transfusion; and treatment (table 2). Multivariate analyses showed that nodal disease, a tumour in the whole stomach, Borrmann type III and IV appearance, and allocation to D1 surgery were associated with poor survival (table 2).

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	p*	HR (95% CI)	p†
Treatment				
D1 surgery	1 (Ref)	..	1 (Ref)	..
D3 surgery	0·68 (0·46–0·99)	0·042	0·49 (0·32–0·77)	0·002
Age (years)				
≤65	1 (Ref)	..	1 (Ref)	..
>65	1·30 (0·88–1·92)	0·188	1·25 (0·80–1·97)	0·326
Sex				
Men	1 (Ref)	..	1 (Ref)	..
Women	0·88 (0·55–1·39)	0·580	1·32 (0·79–2·23)	0·292
Tumour site				
Whole stomach	1 (Ref)	..	1 (Ref)	..
Lower stomach	0·25 (0·09–0·68)	0·007	0·29 (0·09–0·89)	0·030
Middle stomach	0·21 (0·08–0·53)	0·001	0·20 (0·07–0·58)	0·003
Upper stomach	0·22 (0·09–0·55)	0·001	0·23 (0·08–0·67)	0·007
Gross appearance				
Superficial	1 (Ref)	..	1 (Ref)	..
Borrmann types I and II	3·57 (1·56–8·17)	0·003	1·41 (0·53–3·72)	0·492
Borrmann types III and IV	6·60 (3·31–13·13)	<0·0001	2·49 (1·11–5·62)	0·028
Tumour stage				
T1	1 (Ref)	..	1 (Ref)	..
T2	2·64 (1·08–6·48)	0·034	0·74 (0·25–2·21)	0·586
T3	9·04 (4·17–19·60)	<0·0001	1·96 (0·71–5·39)	0·192
T4	8·71 (2·91–26·14)	0·0001	1·42 (0·34–5·88)	0·626
Lymph-node stage				
N0	1 (Ref)	..	1 (Ref)	..
N1	5·82 (3·19–10·60)	<0·0001	3·75 (1·90–7·41)	<0·0001
N2	13·53 (6·88–26·61)	<0·0001	6·44 (2·90–14·30)	<0·0001
N3	20·48 (8·59–48·86)	<0·0001	11·53 (4·02–33·09)	<0·0001
Spleen or pancreas removed				
Neither removed	1 (Ref)	..	1 (Ref)	..
Spleen or both removed	1·65 (0·88–3·11)	0·120	1·05 (0·49–2·26)	0·895
Gastrectomy				
Total	1 (Ref)	..	1 (Ref)	..
Subtotal	0·55 (0·37–0·83)	0·004	0·78 (0·43–1·43)	0·429
Blood transfusion				
No	1 (Ref)	..	1 (Ref)	..
Yes	1·88 (1·28–2·78)	0·002	1·14 (0·75–1·75)	0·541
Lauren's histological type				
Intestinal	1 (Ref)	..	1 (Ref)	..
Diffuse	1·44 (0·99–2·10)	0·058	1·20 (0·80–1·80)	0·371

Ref=reference category. *Derived from tests of HR for prognostic factors (see methods) in univariate model adjusted for treatment group in Cox proportional-hazards model. †Cox-regression analysis, controlling for prognostic factors listed in table.

Table 2: **HR for death in intention-to-treat population (n=221)—univariable and multivariable analyses**

Discussion

We have shown that D3 lymphadenectomy has a significant long-term survival benefit over that of D1 lymphadenectomy. Even a well conceived surgical technique might lead to substantial morbidity because of its complexity. We have shown previously[8] that D3 surgery has definite but acceptable morbidity. Here, we have shown that D3 resection for gastric cancer is associated with a survival benefit, but we think the procedure should be done by well trained, experienced surgeons who work in hospitals that treat many patients with gastric cancer to achieve results with minimum morbidity.

By contrast with trials done in Hong Kong,[11] the UK,[5] and by Dutch researchers,[10] we found that patients assigned D3 surgery had a survival benefit compared with those assigned D1 surgery. D3 surgery for gastric cancer in the lower third of the stomach does not need

total gastrectomy and distal pancreatosplenectomy—the techniques used in the Hong Kong trial.[11] Both the Dutch[10] and UK[5] trials included learning periods and low hospital volume of D2 and D3 surgery for every participating surgeon. Moreover, some variation in the trials[5,10,11]—eg, too many participating surgeons—might have led to wide variations in operating skill and postoperative care. Furthermore, the preparation and analysis of resected stomach samples and lymph nodes and histological assessment varied with different pathologists in these trials,[5,10] whereas in our study we had only one pathologist during the entire trial.

We noted that four patients allocated D3 surgery had recurrence after 3 years (figure 2). These data are consistent with our previous report[12] that about 90% of recurrences occur within 3 years of D3 surgery. Although most of the D1 group had recurrence before 3 years, some continued to recur after 3 years—a finding recorded by the Dutch[10] and UK[5] trialists. These data suggest that cancerous tissue can proliferate and grow from a few residual cells or one cell in lymph nodes that are not excised surgically.

We recorded higher recurrence of gastric cancer after D1 surgery compared with after D3 surgery, although the difference between groups was not significant. Because gastric cancer mainly recurs within 2–3 years,[12] factors other than the extent of resection, such as locoregional recurrence, might increase late recurrences and death in the D1 group (locoregional recurrence 63% for D1 *vs* 51% for D3). Furthermore, the risk of recurrence was based on a small number of events, and because the two curves for recurrence in each group cross, we caution that the Cox proportional-hazard model might not be reliable. Long-term follow-up or a larger sample size are needed.

Macdonald and colleagues[13] have reported improved overall survival with chemoradiotherapy and surgery (54 had D2 dissection, 199 had D1, and 299 had D0) compared with surgery alone for adenocarcinoma of the stomach or gastro-oesophageal junction. Similar to the D1 patients in our study, both treatment groups in the study by Macdonald and colleagues[13] continued to recur 3 years after surgery. Furthermore, Cunningham and co-workers[14] recorded that perioperative chemotherapy improved resectability and survival compared with surgery alone. Most patients had surgery (ie, D0 or D1) without sufficient locoregional control (ie, D3). Comparisons of adjuvant chemoradiotherapy and perioperative chemotherapy with D3 gastric resection alone might be useful in the future.

Unlike the allocation of a drug to a patient in a trial, the conduct of a surgical trial varies greatly with the participating surgeons' operative skill and experience. Uniformity of treatment is important, and is an advantage of single-centre trials. However, disadvantages of single-institution trials include difficulties in recruitment of a large sample size in a short period and extrapolation of the results to other centres. The participating surgeons in this trial gained experience in D1 and D3 surgery through a tutoring system, and obtained experience in good postoperative care (eg, in the prevention and control of postoperative abdominal abscesses).[15] Such preparation before the trial kept variations in the surgeon's operating technique to a minimum. Furthermore, surgeons did an equal number of D1 and D3 resections during the trial,[8] thus balancing comparisons between the two groups, with no confounding bias to individual surgeons' skill.

We have reported previously[16] that D3 surgery leads to more accurate staging: nine (8%) of 108 R0 patients had a change in nodal status after surgery. Such stage migration subsequently affected stage-specific survival.[16] These data are consistent with the findings of Bunt and colleagues.[17] Therefore, stage migration might partly explain the high stage-specific survival in D3 surgery compared with that of D1.

Although this study focused mainly on advanced cancer, exclusion before surgery of patients with early cancer was impossible by CT scan. Endoscopic sonography might aid identification of early cancer, but was not available at our hospital at the time of the trial. Therefore, we excluded 40 patients with macroscopic early cancer at laparotomy, five of whom were stage T2 (ie, invasion to the muscle layer). By contrast, 52 patients regarded macroscopically as stage T2 (ie, had suspicious serosa invasion) had early cancer on histological analysis after randomisation and thus did not fit the protocol requirements histologically. Because surgical morbidity is high in the D3 group, as in the Dutch[18] and UK[19] trials, endoscopic sonography before surgery might help identify patients who should receive a limited nodal dissection.

Nodal dissection has been reported to increase morbidity;[20] however, low, short-term morbidity (17%) and no mortality for patients who underwent D3 resection has also been reported.[8] These findings differ from those recorded in the Hong Kong (47%),[11] Dutch (43%),[18] and UK trials (46%),[19] but are consistent with findings from Japan.[21] Experience as a result of sustained caseload, surgical skill, and case selection are important.[5,9,22] Throughout these studies, it has been noted repeatedly that D3 surgery should be done by well trained and experienced surgeons.

Contributors

C W Wu and W Y Lui had the original idea and designed the study. C W Wu, S S Lo, and M C Hsieh were participating surgeons, and, together with J H Chen, reviewed the operation reports and contributed follow-up data. C A Hsiung was the statistician, and designed the study, analysed data, and reviewed the paper. A F Li was the pathologist, and contributed all pathological data. J Whang-Peng supervised the trial progress and reviewed the paper.

Conflicts of interest

We declare no conflicts of interest.

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