Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients

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Summary

For patients with gastric cancer deemed curable the only treatment option is surgery, but there is disagreement about whether accompanying lymph-node dissection should be limited to the perigastric nodes (D1) or should extend to regional lymph nodes outside the perigastric area (D2). We carried out a multicentre randomised comparison of D1 and D2 dissection.

1078 patients were randomised (539 to each group). 26 allocated D1 and 56 allocated D2 were found not to satisfy eligibility criteria (histologically confirmed adenocarcinoma of the stomach without clinical evidence of distant metastasis). Each of the remainder was attended by one of eleven supervising surgeons who decided whether curative resection was possible and, if so, assisted with the allocated procedure. Among the 711 patients (380 D1, 331 D2) judged to have curable lesions, D2 patients had a higher operative mortality rate than D1 patients (10 *vs* 4%, p=0·004) and experienced more complications (43 *vs* 25%, p<0·001). They also needed longer postoperative hospital stays (median 25 [range 7–277] *vs* 18 [7–143] days, p<0·001). Morbidity and mortality differences persisted in almost all subgroup analyses.

While we await survival results, D2 dissection should not be used as standard treatment for western patients.

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See Commentary page 742

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Introduction

Surgery is the only treatment that offers hope of cure for patients with gastric cancer but there is disagreement about the extent of lymph-node dissection to be done. In western countries, most patients without evidence of metastases are treated with dissection of the perigastric lymph nodes, D1 dissection. In Japan, the conventional treatment for these patients includes dissection of regional lymph nodes outside the perigastric area—D2 dissection or extended lymphadenectomy. The rationale for the extended procedure is based on pathophysiological studies of lymph flow as well as retrospective analysis of mostly Japanese survival data.[1,2] These data suggest a lower recurrence rate and consequently increased survival rate after D2 dissection than after D1 dissection. The practice of D2 dissection in western countries has been hindered for a long time by the lower incidence of gastric cancer and concern about serious complications.[3,4] In an overview of gastric cancer treatment in the USA, the rate of D2 dissections was only 4·7%.[5] However, increasing numbers of reports that extended lymphadenectomy was not associated with an increase in postoperative complications have persuaded western centres to investigate or to use D2 dissection for gastric cancer.[6–8]

In the Netherlands, our prospective randomised trial comparing D2 and D1 dissection began in August, 1989, with entry of patients until July, 1993.[9] The aim was to find out whether extended lymphadenectomy used in a western country would lengthen survival of patients with gastric cancer. We report data on postoperative morbidity and hospital mortality.

Patients and methods

The trial was approved by the medical ethics committee of Leiden University Hospital, and informed consent was obtained from the patients according to the principles of each of the eighty participating hospitals in the Netherlands. Randomisation was stratified by institution, and was done by an independent data centre. Eligible patients had histologically proven adenocarcinoma of the stomach without clinical evidence of distant metastasis, were suitable for both types of operation, had no history of previous malignant disorders or gastrectomy for benign disease, were younger than 85 years, and were undergoing elective resection. Informed consent was obtained from patients according to the principles of each institution. The entry criteria were checked by an independent data centre, where the patient was registered and subsequently randomised.

To ensure standard surgical treatment and pathological assessment, the guidelines of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) were used.[10] According to these guidelines, lymph nodes are grouped into sixteen stations, which are subsequently divided into four levels (N1 to N4) and operations classified according to the level of lymph-node dissection (D1 to D4). To avoid confusion with the TNM R

	D1	D2	Total
Total randomised	539	539	1078
Ineligible*			
No supervising surgeon available	5	30	35
Metastases/second tumour	9	11	20
No adenocarcinoma	8	10	18
Physical condition	4	6	10
Total	26	56	82
Eligible			
Total	513	483	996
Curative resection not possible†	133	152	285
Curative resection possible	380	331	711

*Some patients appear in more than one subgroup.
†Remnant tumour (90 D1, 102 D2), peritoneal metastases (59, 83), lymph-node metastases (36, 37), liver metastases (27,22); some patients had more than one of these features.

Table 1: **Derivation of study population**

	Number (%) of patients	
	D1 (n=380)	D2 (n=331)
Age group (years)		
<60	115 (30%)	116 (35%)
60–70	137 (36%)	112 (34%)
>70	128 (34%)	103 (31%)
Sex		
Male	216 (57%)	188 (57%)
Female	164 (43%)	143 (43%)
Site of tumour*		
More than two-thirds of stomach	25 (7%)	24 (7%)
Upper third	39 (10%)	34 (10%)
Middle third	108 (28%)	92 (28%)
Distal third	207 (55%)	179 (54%)
Type of resection*		
Total	115 (30%)	126 (38%)
Distal	264 (69%)	203 (61%)
Other surgery*		
Spleen resection	41 (11%)	124 (38%)
Distal pancreatectomy	10 (3%)	98 (30%)

*Data missing for some patients.

Table 2: **Characteristics of 711 randomised patients for whom curative resection was judged possible**

classification (residual tumour load), the original 'R' in the JRSGC termininology has lately been changed to 'D' for dissection.[11] The D1 procedure includes dissection of the perigastric lymph nodes directly attached to the stomach, whereas in D2 procedures lymph nodes in the N2 tier are also dissected. Because this operation had not been done routinely in the Netherlands, participating surgeons were instructed by a Japanese gastric cancer surgeon (MS) during the first 6 months of the trial. After this period, one of eleven specially trained regional supervising surgeons attended all D2 dissections and the coordinator (JJB) attended all D1 operations to observe and advise. They monitored the technique and the extent of lymph-node dissection and retrieved the lymph nodes from the resected specimen in the operation room. Participating surgeons were given a videotape and an instruction booklet, and regular meetings for technical back-up were held with the supervising surgeons, the coordinator, and the instructing surgeon.

Curability assessment was done by the supervising surgeons and the coordinator at laparotomy by standard criteria. A macroscopically complete removable tumour, without peritoneal spread or liver metastasis, and without distant lymph-node metastasis, as established by frozen section examination of a para-aortic lymph-node biopsy sample (station number 16) was regarded as curable. Patients with such tumours underwent the allocated procedure. Distal gastrectomy was allowed irrespective of the randomised procedure, if a safe oral margin of 5 cm could be obtained. All other patients underwent total gastrectomy. The alimentary tract was reconstructed principally by the local surgeon using his preferred method. Resected samples were examined by the local pathologist, and the results were reviewed by a panel of consulting pathologists.

Patients who did not meet the curability criteria had a palliative surgical procedure according to the discretion of the surgeon and irrespective of the allocated dissection.

The postoperative course of all patients was assessed from the trial forms. All complications recorded by the surgeon were registered and those that necessitated reoperation were recorded separately. Hospital mortality was defined as death within 30 days of the operation or during a hospital stay.

To detect a 12% increase in survival (from 20% with D1 to 32% with D2), 5 years after curative surgery, 1062 patients had to be randomised (α=0·05 two sided, power =0·90, with a 60% curability rate). The χ^2 test (with Yates' correction) was used to assess differences in proportions and the Mann-Whitney test to assess the significance of differences in quantitative variables such as age and hospital stay.

Results

1078 patients were enrolled (table 1). The most common reason for exclusion of patients (n=82) was that no supervising surgeon could attend the operation. In 18 patients the diagnosis was found not to be adenocarcinoma at operation (lymphoma 10, dysplasia 4, pancreas carcinoma 2, no proof of adenocarcinoma in resection sample although the biopsy diagnosis was correct at second evaluation 2). In 133 (26%) patients in the D1 group and 152 (31%) in the D2 group curative resection was judged not to be possible and palliative treatment (53% palliative resection, 19% bypass, and 27% exploration only) was given. The remaining patients had the allocated dissection procedure.

The median age was 64·9 (range 31·0–84·0) years in the D1 group and 63·1 (21·0–84·0) years in the D2 group. Both groups contained more men than women (table 2). More than half of the tumours were located in the distal part of the stomach and distal gastrectomy was the commonest type of operation. Splenectomy and pancreatectomy were done more often in the D2 group because of the technical requirements of this operation. The two groups differed by definition in the number of investigated lymph nodes (mean 18·4 [range 0–73] D1 *vs* 31·5 [0–106] D2).

Table 3 summarises complications in the eligible group and in patients for whom curative resection was judged possible. Among all eligible patients the hospital mortality rate was higher in the D2 group than the D1 group but the difference did not achieve significance (10 *vs* 6%, p=0·06). There were significant differences in favour of

	Eligible patients (n=996)				Curative resection patients (n=711)			
	D1 (n=513)	D2 (n=483)	95% CI*	p	D1 (n=380)	D2 (n=331)	95% CI*	p
Postoperative deaths	33 (6%)	48 (10%)	0–7%	0·06	15 (4%)	32 (10%)	2–9%	0·004
Complications	128 (25%)	183 (38%)	7–19%	<0·001	94 (25%)	142 (43%)	11–25%	<0·001
Reoperation	39 (8%)	76 (16%)	4–12%	<0·001	30 (8%)	59 (18%)	5–15%	<0·001
Mean (range) hospital stay (days)†	18 (3–154)	22 (6–277)	2–7	<0·001	18 (7–143)	25 (7–277)	4–10	<0·001

*95% CI for difference between D2 and D1. †Postoperative deaths excluded.

Table 3: **Postoperative complications**

	D1 (n=380)	D2 (n=331)
Surgical		
Haemorrhage	8 (2%)	15 (5%)
Wound infection /dehiscence	15 (4%)	30 (9%)
Anastomotic leakage	16 (4%)	30 (9%)
Intra-abdominal infection	30 (8%)	55 (17%)
Pancreatic leakage	3 (1%)	10 (3%)
Non-surgical		
Cardiac	14 (4%)	17 (5%)
Pulmonary	23 (6%)	49 (15%)
Urinary tract	6 (2%)	5 (2%)
Thromboembolic	2 (1%)	7 (2%)
Other	11 (3%)	12 (4%)

Table 4: **Types of complications in patients who underwent curative resection**

the D1 group in the frequency of complications and of reoperation and in mean postoperative hospital stay (table 3).

Among patients actually treated with D1 or D2 dissection (curative group), hospital mortality was significantly higher after D2 than after D1 dissection (10 *vs* 4%, p=0·004). Again, the frequencies of complications and reoperation and the hospital stay were all greater in the D2 group. All complications occurred more commonly in the D2 group than in the D1 group but anastomotic leakages and intra-abdominal infections showed the most pronounced difference (table 4).

To examine further the effect of type of dissection on complications and hospital mortality, we defined various subgroups based on age, sex, type of resection, whether spleen or pancreatic resection was done, the number of randomised patients at a centre, and whether blood transfusion was given. In all subgroups, the number of postoperative deaths and the number of patients with complications were higher after D2 than after D1 dissection (table 5), except for distal pancreatectomy, for which numbers were too small for evaluation.

	Number of patients		% of subgroup					
			Hospital deaths		Complications		Reoperation	
	D1	D2	D1	D2	D1	D2	D1	D2
Age (years)								
<60	115	116	1	3	16	33	7	10
60–70	137	112	4	9	28	52	7	20
>70	128	103	7	18	30	45	10	25
Sex								
Male	216	188	4	14	27	48	7	21
Female	164	143	4	4	21	36	9	10
Resection type								
Total	115	126	5	14	33	53	12	25
Distal	264	203	3	7	21	37	6	14
Spleen resection								
Yes	41	124	5	15	39	55	17	26
No	338	204	4	6	23	36	7	13
Distal pancreatectomy								
Yes	10	98	20	11	80	53	40	24
No	369	230	4	9	23	39	7	16
Patients randomised at centre								
<5	14	13	7	8	14	54	7	15
5–14	115	100	3	11	21	45	6	19
≥15	251	218	4	9	27	41	9	18
Blood transfusion								
Yes	113	170	2	14	29	54	11	24
No	229	126	5	5	20	32	5	10

Table 5: **Subgroup analysis of patients who underwent curative resection**

Discussion

D2 dissection is increasingly being advocated for curative treatment of gastric cancer. Japanese studies have documented a beneficial survival effect,[2] but this effect was not confirmed in the only previous randomised trial of D1 and D2 dissection.[4] The small size of that trial means that its results must be interpreted cautiously, but D2 was associated with excessive morbidity. Reports of non-randomised studies from specialised centres contradict this conclusion.[6–8] Improvements in perioperative care have enabled surgeons to carry out bigger operations with less hospital mortality, but this factor should not justify radical surgery for gastric cancer until there is proven benefit in terms of long-term survival or quality of life. In our trial we paid special attention to morbidity. An interim analysis of hospital morbidity and mortality showed that the two dissection procedures had similar complication rates.[9] At subsequent times, however, increasing differences in favour of D1 dissection became clear and the final data for all eligible patients led us to reassess our original conclusion.

To prevent variations among surgeons in this trial, we used a quality control system that achieved a high degree of standardisation.[12] D2 dissection was introduced by a Japanese surgeon experienced in the treatment of gastric cancer, and the technique of lymph-node dissection was checked by specially trained supervising surgeons, who attended all D2 dissections in their assigned regions of the Netherlands. Although variations have been shown in lymph-node retrieval by different pathologists, the intended level of lymph-node dissection was maintained and even improved in the course of the trial.[13,14]

In our study protocol, total gastrectomy with D2 lymph-node dissection required distal pancreatectomy and splenectomy, whereas in D1 dissection, these procedures were needed only for cases of tumour involvement of these organs. Additional organ resection is associated with a higher risk of postoperative complications. A pancreas-preserving technique has been proposed by Maruyama to decrease the morbidity associated with distal pancreatectomy that occurs even in Japanese series. However, as shown by our subgroup analysis, this factor is not the full explanation for the difference in outcome with the two procedures. 10 D1 and 98 D2 patients had distal pancreatectomy, but there was no association with excessive morbidity and mortality in these patients. On the other hand, the differences in postoperative morbidity and mortality between D1 and D2 were apparent in patients who had not had distal pancreatectomy.

We do not believe that inexperience of Dutch surgeons with D2 dissection is the reason for the higher complication rates, because of our extensive quality control system. Each supervising surgeon did an average of 90 D2 dissections during the trial (range 61–151). We assessed complication rates throughout the trial and could detect not a learning curve for any surgeon. Furthermore, the postoperative course was similar in patients operated on by the Japanese instructing surgeon and in those operated on by the regional supervising surgeons, although the numbers in this comparison were low.[9] In the UK, it has been suggested that complication rates and hospital mortality are lower in patients treated by surgeons who do more than 15 stomach operations per year,[15] but we found no such effect. Not all patients with gastric cancer treated in the participating hospitals were

admitted or accepted for the trial and those enrolled might not be representative of the hospital's whole patient populations. The quality control system, with experienced surgeons available for all operations should have stabilised the complication rates also.

The rate of anastomotic leakage was higher after D2 than D1 dissection, but since anastomoses were made by the local surgeon after resection in nearly all cases, the difference reflects an effect of D2 dissection rather than the experience of the surgeon. A comparison with leakage rates in Japan is hampered by different indications for D1 and D2 dissection, but the overall leakage rates are similar to those observed in the National Cancer Center Hospital in Tokyo: among 1133 patients undergoing resection between 1987 and 1991, 5% had anastomotic leakage, compared with 6·5% in our series (data provided by MS). However, mortality after anastomotic leakage is about 10% in Japan, compared with 30% in our trial. The difference may be due to the higher average age of western gastric cancer patients, the frequent occurrence of cardiopulmonary complications, and the different ways of treating leakage. Moreover, additional abdominal complications are encountered less frequently in Japanese patients, because the physical characteristics (shallow abdominal cavity) and the lower amounts of intra-abdominal fatty tissue in Asian people mean that the anatomical view is better and access to the abdomen easier, with lower operative blood loss. These explanations are speculative, and further analysis to assess the impact of age, physical characteristics, and cardiopulmonary complications on morbidity after D2 surgery is necessary.

The discrepancy between the conclusions of this large randomised trial and those of non-randomised series reflects the influence of variability between surgeons associated with retrospective studies.

Should any treatment with a postoperative mortality rate twice that of the standard technique be accepted as general practice, if no long-term survival benefit has yet been demonstrated? While we await the final results of our trial, D2 dissection should not be regarded as standard treatment for gastric cancer for western patients.

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