Original article

Quality control of lymph node dissection in the Dutch Gastric Cancer Trial

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Background: **Current guidelines indicate that D2 resection is the standard of care for patients with locally advanced gastric cancer. To assess the impact of quality assurance of lymph node removal, non-compliance and contamination in the D1 and D2 study arms of the Dutch Gastric Cancer Trial were investigated with respect to recurrence and survival.**

Methods: **The location and numbers of lymph nodes detected at pathological investigation in the Dutch Gastric Cancer Trial were compared according to the guidelines of the Japanese Research Society for the study of Gastric Cancer. Non-compliance was defined as inadequate removal of lymph node stations. Contamination was defined as lymph nodes removed outside the intended level of resection. The dissection groups D1 and D2 were divided into non-compliance, compliance and contamination categories. Long-term overall survival was calculated for minor (2 or fewer lymph nodes) and major (more than 2 lymph nodes) non-compliance and contamination in the D1 and D2 group, using Kaplan–Meier plots.**

Results: **Some 1078 patients were included, of whom 711 with potentially curative surgical resections were evaluated. Overall non-compliance was 80·5 per cent in the D1 and 81·6 per cent in the D2 group. Major non-compliance occurred in 15·3 per cent of the D1 and 26·0 per cent of the D2 group. Major contamination hardly occurred. Overall 15-year survival rates in the randomized groups were 21·2 per cent (D1) and 29·0 per cent (D2) ($P = 0·351$). After exclusion of patients with major non-compliance and/or major contamination, survival rates were 23·2 per cent (319 patients) and 32·6 per cent (245) respectively ($P = 0·261$). Where there was major non-compliance, survival rates in the D1 (58 patients) and D2 (86) groups were 10 and 17 per cent respectively ($P = 0·302$). Survival in the D2 compliant + contaminated group (139 patients) was significantly better than that in the D1 group without contamination (282): 35·7 *versus* 19·9 per cent ($P = 0·041$). In the D2 group, there was a significant difference in survival between contaminated (95 patients) and non-contaminated (236) groups: 39 *versus* 25·1 per cent ($P = 0·041$).**

Conclusion: **Non-compliance in the D2 dissection group may have obscured a significant difference in survival between the randomized groups. A D2 dissection with contamination was associated with the best survival, suggesting that extended D2 lymph node dissections improve survival.**

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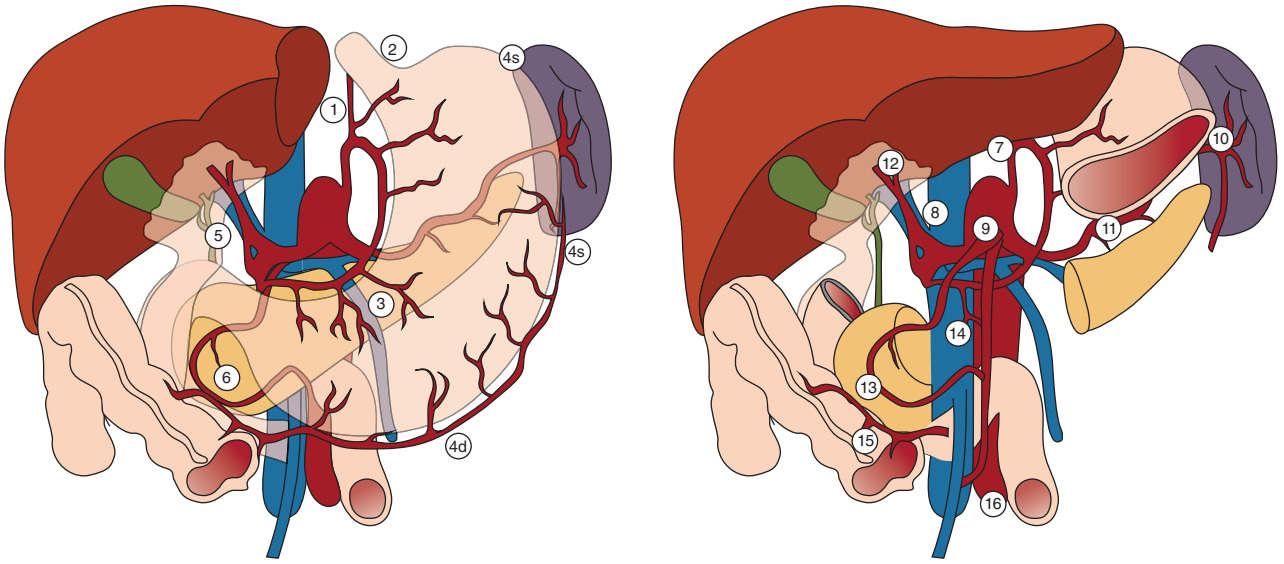
Introduction

Although perioperative chemotherapy and chemoradiotherapy improve survival rates for advanced gastric cancer, surgery is still the cornerstone of treatment[1,2]. Since the introduction of the Japanese guidelines for the standardization of surgical treatment and pathological evaluation of gastric cancer in 1981, the extent of lymph node dissection has been a point of debate. In Western countries a limited D1 lymphadenectomy (dissection of perigastric nodes) has been standard of care for many years, whereas in Asia an extended D2 lymphadenectomy (inclusion of nodes along the major arteries of supply to the stomach) has been performed routinely[3].

Several randomized clinical trials have been undertaken in Western countries comparing limited D1 with the more



N1 Lymph nodes (perigastric)
1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along lesser curvature
4 Nodes along greater curvature
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)
7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around coeliac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes
12 Nodes at hepatoduodenal ligament
13 Retropancreatic (perioduodenal) nodes
14 Nodes at root of mesentery

N4 Lymph nodes
15 Nodes along middle colic vein
16 Para-aortic nodes

Fig. 1 Lymph node locations and numbering according to the Japanese Research Society for the study of Gastric Cancer. D1 resection comprises removal of N1 lymph nodes, and D2 resection removal of N1 and N2 lymph nodes

extended D2 lymph node dissection. In the UK Medical Research Council (MRC) trial[4] and the Dutch Gastric Cancer Trial (DGCT)[5,6], 400 and 711 patients respectively undergoing total or subtotal gastrectomy were randomized to D1 or D2 lymphadenectomy. In both trials, extended D2 lymph node dissection did not improve survival, and was associated with higher morbidity and mortality rates. The high rate of pancreatic resection and splenectomy, which was part of the D2 resection for proximal tumours in these two trials, is often cited as one of the explanations for the high postoperative mortality and the absence of survival benefit[7]. In later Italian[8,9] and Taiwanese[10] studies, where pancreaticosplenectomy was not performed routinely, the postoperative mortality rate after D2 dissection was much lower than in the MRC trial and DGCT. A Japanese study[11] comparing standard D2 dissection with D2 dissection and removal of the para-aortic nodes also did not show a survival benefit for the more extended para-aortic resection. Based on these studies, there has been little enthusiasm for adoption of D2 dissection in the West. An early report[12] from the DGCT, however, showed that many patients who were randomized to D1 lymphadenectomy had more nodes removed than described in the study protocol (contamination), and that some of the patients randomized to the D2 arm had fewer nodes removed than described in the protocol (non-compliance). The purpose of the present study was to investigate the effect of non-compliance and contamination on long-term survival in the DGCT.

Methods

From September 1989 to June 1993, patients with gastric cancer were included in a multicentre randomized clinical trial in the Netherlands that compared D1 and D2 lymph node dissection. The dissection technique was taught by a Japanese surgeon, by means of video instruction and a booklet with step-by-step photographic instruction.

All patients underwent laparotomy and curability was determined. In the event of metastasis (peritoneum, liver, distant lymph nodes or local unresectability) the patient was classified as having non-curative disease, and a palliative resection or no resection was performed. The remaining patients underwent D1 or D2 resection. The surgeon or pathologist dissected the specimen to ensure that the removed lymph nodes were placed correctly in numbered containers corresponding to the numerical system for lymph node identification described by the Japanese Research Society for the study of Gastric Cancer[13].

Table 1 Protocol deviations

Lymph node yield per station	Indication for dissection of station	
	Yes	No
0	Non-compliance	No contamination
≥ 1	Compliance	Contamination

Table 2 Patient characteristics

	D1 dissection ($n = 380$)	D2 dissection ($n = 331$)
Median age (years)	67	65
Sex ratio (M : F)	215 : 165	187 : 144
Gastrectomy		
Total	115 (30·3)	126 (38·1)
Partial	265 (69·7)	205 (61·9)
Resection of spleen	41 (10·8)	124 (37·5)
Resection of pancreatic tail	10 (2·6)	98 (29·6)
Tumour stage		
T1	98 (25·8)	85 (25·7)
T2	181 (47·6)	152 (45·9)
T3	94 (24·7)	82 (24·8)
T4	3 (0·8)	9 (2·7)
Tx	4 (1·1)	3 (0·9)
Lymph node involvement	205 (53·9)	185 (55·9)

Values in parentheses are percentages.

Table 3 Extent of compliance (711 patients)

	D1 dissection ($n = 380$)	D2 dissection ($n = 331$)
Compliance	74 (19·5)	61 (18·4)
Non-compliance	306 (80·5)	270 (81·6)
Minor non-compliance*	248 (65·3)	184 (55·6)
1	169	101
2	79	83
Major non-compliance*	58 (15·3)	86 (26·0)
3	37	44
≥ 4	21	42

Values in parentheses are percentages. *Number of nodes not removed.

Trained pathologists processed the resection specimens and reported the number of lymph nodes retrieved per station and the number of tumour-containing lymph nodes.

A correct D1 dissection was defined as the removal of lymph stations 3–6 during partial gastrectomy and lymph node stations 1–6 in total gastrectomy (*Fig. 1*). For D2 dissection and partial gastrectomy, stations 1, 3 and 7–9 had to be removed, whereas stations 1–11 had to be removed in total gastrectomy. Resection of the spleen and tail of the pancreas was performed in D2 dissections to remove stations 10 and 11. Non-compliance was defined as no yield of lymph nodes from the indicated stations[14]. Contamination was defined as removal of one or more lymph nodes in stations outside the intended extent of resection (*Table 1*).

Table 4 Extent of contamination (711 procedures)

	D1 dissection ($n = 380$)	D2 dissection ($n = 331$)
No contamination	282 (74·2)	236 (71·3)
Contamination	98 (25·8)	95 (28·7)
Minor contamination*	95 (25·0)	95 (28·7)
1	76	72
2	19	23
Major contamination*	3 (0·8)	0 (0)
3	1	0
4	2	0

Values in parentheses are percentages. *Number of lymph node stations too many removed.

Nodal yields were calculated to determine the validity of the assumption that all stations contained at least one lymph node. Information on the number and distribution of lymph nodes was obtained from the trial forms.

For the present analysis, both the D1 and D2 groups were divided into major non-compliance (more than 2 intended lymph node stations not removed), minor non-compliance (1 or 2 intended lymph node stations not removed), compliance, major contamination (more than 2 intended lymph node stations too many removed), minor contamination (1 or 2 intended lymph node stations too many removed) and non-contamination categories. In this way, it was possible for a patient to be in a non-compliance subgroup as well as a contamination subgroup.

Overall survival was defined as time from surgery to death or last follow-up (censoring). Probabilities of overall survival were estimated using the Kaplan–Meier method. Differences in overall survival between groups with or without non-compliance or contamination were assessed using the log rank test.

Results

Of the 1078 patients included in the DGCT, 711 were randomized, with 380 allocated to D1 and 331 to D2 lymphadenectomy. Surgery took place in 80 hospitals and 55 pathologists assessed the lymph nodes. Patient characteristics are shown in *Table 2*. Most characteristics were comparable between the randomized groups. More than half of the tumours were located in the distal part of the stomach and distal gastrectomy was the most common type of operation (69·7 per cent in D1, 61·9 per cent in D2). Splenectomy and pancreatectomy were performed more often in the D2 group because of the technical requirements of this operation. As expected, there was a difference in the number of lymph nodes removed between the two groups: a

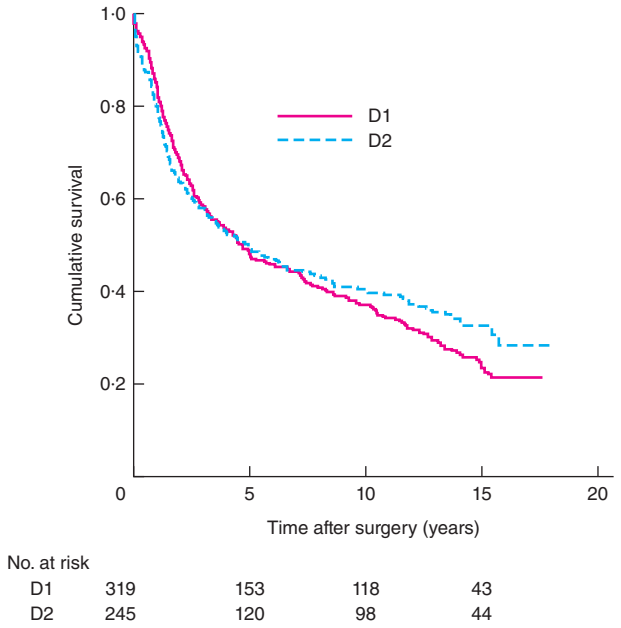


Fig. 2 Survival curves for D1 (319 patients) and D2 (245) subgroups without major non-compliance or major contamination. $P = 0{\cdot}261$ (log rank test)

mean of 18·4 (range 0–73) lymph nodes was investigated in D1 and 31·5 (0–105) in D2.

Rates of compliance and non-compliance are shown in *Table 3*. Complete compliance occurred in 74 (19·5 per cent) of 380 patients in the D1 group and 61 (18·4 per cent) of 331 patients in the D2 group. Minor non-compliance occurred in 65·3 per cent of the D1 dissection group and 55·6 per cent of the D2 group, whereas major non-compliance was present in 15·3 and 26·0 per cent respectively. Non-compliance occurred most often for lymph node station number 5 in both dissection groups.

Contamination occurred in 98 (25·8 per cent) of 380 patients of the D1 group and in 95 (28·7 per cent) of 331 in the D2 group (*Table 4*). Minor contamination (1–2 intended lymph node stations too many) was equally distributed over the D1 and D2 treatment arms. Major contamination occurred sporadically in the D1 group and did not occur in the D2 group. Contamination occurred most often for lymph node station 7 (37 of 380) in the D1 group (in both partial and total gastrectomies) and for station 11 (42 of 174) in partial gastrectomies in the D2 dissection group.

Overall 15-year survival rates in the randomized groups were 21·2 per cent for D1 and 29·0 per cent for D2 dissection ($P = 0{\cdot}351$). After exclusion of patients with major contamination and/or major non-compliance, rates were 23·2 and 32·6 per cent for the D1 (319 patients) and D2 (245) groups respectively ($P = 0{\cdot}261$) (*Fig. 2*). Overall survival at 15 years after procedures with major non-compliance in the D1 (58) and D2 (86) groups was 10 and 17 per cent respectively ($P = 0{\cdot}302$). The 15-year overall survival rate in the compliant D1 group (74 patients) was 17 per cent *versus* 38 per cent in the D2 group (61) ($P = 0{\cdot}126$). Other subgroups showed no significant differences between D1 and D2 dissections (*Table 5*).

Overall survival at 15 years in the contaminated D2 dissection group (95 patients) was 39 per cent, and 25·1 per cent in the non-contaminated D2 dissection group (236) ($P = 0{\cdot}041$).

There was no significant difference in 15-year survival between the D1 compliant + contaminated group (160 patients) and the remaining patients who underwent D1 dissection (220): 21·9 *versus* 20·7 per cent respectively ($P = 0{\cdot}980$). In the D2 compliant + contaminated group (139 patients), 15-year survival was significantly different from that in the remaining patients who underwent D2 dissection (192): 35·7 *versus* 24·0 per cent ($P = 0{\cdot}046$).

The D2 compliant + contaminated group (139 patients) also showed a significant survival benefit over the D1 group without contamination (282): 35·7 *versus* 19·9 per cent 15-year survival rate ($P = 0{\cdot}041$) (*Fig. 3*). The 15-year survival rate in this D2 compliant + contaminated group was also better than that in the overall D1 dissection group: 35·7 *versus* 21·2 per cent ($P = 0{\cdot}043$).

In the D2 contaminated group (95 patients), 57 per cent of the tumours were located in the antrum and 38 per cent in the middle of the stomach. Lymph node stations 2, 10 and 11 were the most frequent stations to cause contamination in which metastatic disease was present.

In the D2 group, antral tumour location was associated with the most compliant resections (25 per cent) but this

Table 5 Overall survival

	15-year survival (%)			15-year survival (%)		
	Compliance	Non-compliance	*P**	Contamination	Non-contamination	*P*†
D1	17 ($n = 74$)	22·5 ($n = 306$)	0·862	27 ($n = 98$)	19·9 ($n = 282$)	0·919
D2	38 ($n = 61$)	26·9 ($n = 270$)	0·126	39 ($n = 95$)	25·1 ($n = 236$)	0·041

*Compliance *versus* non-compliance; †contamination *versus* no contamination (log rank test).

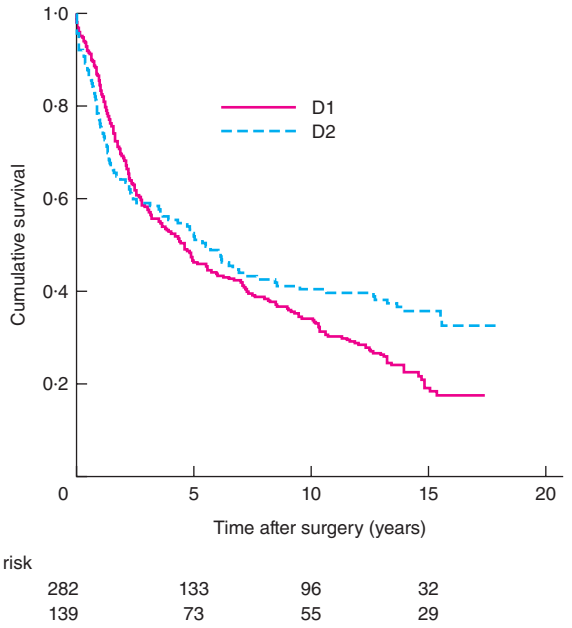


Fig. 3 Survival curves for D2 compliant + contaminated (139 patients) and D1 without contamination (282) subgroups. $P = 0{\cdot}041$ (log rank test)

did not lead to better survival. When the tumour was located in the body of the stomach, a compliant resection led to better survival than a non-compliant resection: 60 *versus* 13 per cent ($P = 0{\cdot}050$). In the D2 group, contamination occurred in 15 per cent of patients when the tumour was located diffusely (antrum, middle and corpus) in the stomach, and led to a better survival rate of 40 per cent compared with 3·7 per cent in the non-contaminated group ($P = 0{\cdot}005$). In the D1 group, neither compliant nor contaminated resections led to better survival in relation to tumour location.

Discussion

Despite intense preparation and control for quality assurance, major non-compliance in this study occurred in 15·3 per cent in the D1 and 26·0 per cent in the D2 dissection group. This non-compliance in the D2 dissection group seems likely to have offset a real difference in survival after 15 years of follow-up between the randomized groups.

In the MRC trial[4], non-compliance and contamination were acknowledged but not quantified. In the Asian randomized trials by Wu and colleaues[10] and Sasako *et al.*[11] this issue was not mentioned. In the most recent Western randomized trial[8,9], despite a strict quality control protocol for surgery and pathology, a substantial number of patients did not undergo the allocated treatment. Major contamination occurred in 18 per cent of patients undergoing D1 and major non-compliance in 33·6 per cent allocated to D2 dissection. This overlap between the two dissection groups may make it more difficult to identify any true difference in survival.

The early conclusion (1995) of the DGCT was that D2 resection should not be used as standard treatment for Western patients[5]. In 1999 the 5-year survival rates did not differ, although there had been significant differences in surgical mortality in favour of D1 dissection[15]. After 11 years of follow-up, there was still no long-term survival benefit between the randomized groups but, for patients staged with N2 disease using the TNM system at that time, an extended resection seemed to offer some survival benefit. It was concluded that a D2 resection may be of benefit if morbidity and mortality could be avoided[7]. After 15 years' follow-up, the cancer-related death rate was significantly lower in the D2 dissection group[6], so that nowadays a D2 dissection is advised, with the proviso that pancreaticosplenectomy should be performed only where there is direct tumour invasion into these organs. This is supported by a subgroup analysis of the DGCT that showed a significant survival benefit for the D2 dissection group when pancreaticosplenectomy was avoided (11-year survival rate 33 *versus* 47 per cent; $P = 0{\cdot}018$)[16].

The present analysis was undertaken to compare the groups that had a resection more or less according to protocol, excluding those who did not. After exclusion of patients who had a major protocol deviation, there was a survival difference of 9·4 per cent (23·2 per cent *versus* 32·6 per cent) in favour of the D2 dissection group; this was not statistically significant ($P = 0{\cdot}261$). When the D1 dissection group without contamination was compared with the D2 dissection group without non-compliance to exclude overlap between the groups, there was a significant difference in survival at 15 years (35·7 per cent after D2 *versus* 19·9 per cent following D1 dissection; $P = 0{\cdot}041$). It seems likely that non-compliance in the D2 dissection group probably offset the difference in survival after 15 years of follow-up between the randomized groups.

Lymph node station 5 was the most frequent station of non-compliance in both the D1 and the D2 group. Resection according to protocol was most often achieved for tumours in the antrum of the stomach, with more protocol deviations for tumours elsewhere. It is not understood why the removal of station 5 was so often violated. Resection of this station is not technically difficult. There may have been incorrect numbering of these nodes when they were separated after the resection.

The risk of leaving behind potentially involved lymph nodes as calculated by the Maruyama Index has been

shown to influence survival[17,18]. The best survival in the present study was seen in the contaminated D2 dissection group and this was significantly better than in the non-contaminated D2 group (39 *versus* 25·1 per cent; $P = 0{\cdot}041$). Any *post hoc* analysis carries bias. The effects of contamination and non-compliance between the randomized study arms in the present study and another Western trial[4] mean that significant differences in overall survival cannot be shown, and the data seem to support those who advocate D1 dissection. Subgroup analysis in the DGCT[6] and the Italian[8] trials have, however, shown that there is a significant disease-specific survival benefit for D2 dissection. The present analysis adds weight to the view that a properly performed D2 dissection is superior to D1 dissection in terms of long-term survival if postoperative morbidity and mortality can be avoided.

Disclosure

The authors declare no conflict of interest.

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