Original Article

Lymph node metastases rate of locoregional and non-locoregional lymph node stations in gastric cancer

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Background: The incidence of lymph node metastases is closely related to the T-stage, and therefore Eastern guidelines advice a D1 lymphadenectomy for early gastric cancer and a D2 lymphadenectomy for advanced gastric cancer. The aim of this study was to compare the lymph node metastases rate in the stations dissected with a D2-lymphadenectomy (stations 8–12) yet spared with a D1-lymphadenectomy, between different T-stages in a Western patient cohort.

Methods: For this retrospective study, patients who underwent a gastrectomy in the Amsterdam University Medical Center (UMC), location Academic Medical Center (AMC), between 2011 and 2016 were identified from a prospectively maintained database. The primary outcome was to compare the rate of lymph node metastases in station 8–12 between different cT-stages.

Results: One hundred twelve patients met our inclusion criteria. There were no positive lymph nodes in the lymph nodes stations 8–12 in cT1 and (y)pT1-stage tumors. The more advanced cT2-4 and (y)pT2-4 stage tumors show a high metastases rate (11.1% to 40.0%) in the lymph node stations 8–12.

Conclusions: The results from this study endorse the Japanese Gastric Cancer Guideline; in early gastric cancer, a D1 lymphadenectomy is sufficient, while in advanced gastric cancer a D2 lymphadenectomy should be performed.

Keywords: Stomach neoplasms; lymph node excision; neoplasm staging; gastrectomy; adenocarcinoma

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Introduction

There is a steady decline in the incidence rates of gastric cancer (1). However, it remains the third most common cause of death of all malignancies worldwide, with an overall 5-year survival rate of only 30% (2). A radical gastrectomy with lymph node dissection is the cornerstone for the curative treatment of gastric cancer. The standard way of lymph node dissection is a modified D2 lymphadenectomy (3). A survival advantage for the more extensive D2 lymphadenectomy in comparison to the less extensive D1 lymphadenectomy has been established (4,5). However, a D2 lymphadenectomy is accompanied with higher morbidity and mortality rates in comparison to the less extensive D1 lymphadenectomy

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(6,7). Studies concerning the overall survival and loco-regional recurrence after D1 versus D2 lymphadenectomies did not distinct between the different T-stages. Yet there is a considerable difference in lymph node metastasis rates between T-stages (T1: 10–40%, T2-4: 45–90%) (8-10). Since the incidence of lymph node metastases in gastric cancer is closely related to the T-stage, patients with early gastric cancer may benefit from a D1 lymphadenectomy while in patients with more advanced gastric cancer a more extensive D2 lymphadenectomy should be performed. The Japanese Guidelines advocates a D1 lymphadenectomy for T1a tumors that do not meet the criteria for endoscopic resection and for cT1bN0 tumors that are 1.5 cm or smaller in diameter and histologically of differentiated type (11). In Western countries this distinction is not made, and sufficient evidence from the West is lacking (12). Studies from the East cannot be directly interpreted for a Western population, since patient characteristics, tumor histology and location, and treatment regimens differ. Eastern studies confirm the sufficiency of a D1 lymphadenectomy in early gastric cancer, Western studies are however, sparse (13).

The Japanese Classification of Gastric Carcinoma from the Japanese Gastric Cancer Association includes a classification of loco-regional lymph node stations. In this classification system, the lymph node stations are defined and numbered. Lymph node stations 1–12 stations and station 14v are regarded as locoregional gastric lymph nodes, other node stations are, generally, considered as distant metastases. For esophageal invading tumors also station 19, 20, 110 and 111 are classified as locoregional. In a total gastrectomy a D1 lymphadenectomy consists of resection of the peri-gastric lymph node stations; station number 1 to 6, and lymph node station 7; a second tier lymph node station. A D2 lymphadenectomy consist of resection of the D1 lymph node stations and the lymph node stations 8a, 9, 10, 11p, 11d and 12a (14,15). In a distal gastrectomy a D1 lymphadenectomy dissects the lymph node stations: 1, 3, 4d, 5, 6 and 7. A D2 lymphadenectomy includes the D1 stations and stations: 8a, 9, 11p and 12a (16).

The aim of this study was to compare the lymph node metastases rate in the lymph node stations dissected with a D2-lymphadenectomy yet spared with a D1-lymphadenectomy; lymph node stations 8 to 12, between different T-stages in a Western patient cohort. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-147/rc) (17).

Methods

Design

For this retrospective study, patients with gastric cancer who underwent a gastrectomy in the Amsterdam University Medical Center (UMC), location Academic Medical Center (AMC), between 2011 and 2016 were identified from a prospectively maintained database. This database contained information on baseline characteristics, neoadjuvant treatment, surgery and tumor characteristics. Missing data and specific data on the lymph nodes were obtained from the medical records and completed in the existing database. For this retrospective research, ethical approval for this study is not required under Dutch law. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Patients

Eligible patients were included if they met the following inclusion criteria: (I) primary gastric cancer; (II) radical gastrectomy and lymphadenectomy with curative intent and; (III) the pathological report contained all essential information on the primary tumor and lymph nodes (the metastases rate in lymph node stations 8–12).

Definitions

The 8th edition of the AJCC Cancer Staging Manual was used for c and (y)pTNM classification (18). The Japanese classification of gastric carcinoma was used for the definition of lymph node stations and the Japanese gastric cancer treatment guideline for the definition of a D1- and D2-lymphadenectomy (14).

Outcome

The primary outcome was to compare the rate of lymph node metastases in station 8–12 between different cT-stages. Secondary outcomes were to compare the rate of lymph node metastases in station 1–7 between different cT-stages, to compare the rate of lymph node metastases in station 1–7 and 8–12 between different (y)pT-stages, to investigate the accuracy of cT and cN in patients without neoadjuvant therapy, up- or downstaging in patients following neoadjuvant therapy, and to compare the lymph node metastases pattern; percentage of pathological positive

lymph nodes per lymph node station, between different cT and (y)pT-stages.

Staging and treatment

Patients underwent diagnostic screening with endoscopy with biopsies, CT-scan and on indication endoscopic ultrasound and diagnostic laparoscopy. Diagnostic screening was performed by an experienced radiologist dedicated to gastrointestinal (GI) care and/or an experienced endoscopist dedicated to upper GI cancer care. cT1 tumors were included if not suitable for endoscopic resection. cT2-4 and N+ tumors received perioperative chemotherapy (based on the MAGIC trial) except if surgeon and patient decided otherwise. Patients underwent total or subtotal gastrectomy with a modified D2 lymphadenectomy and complete omentectomy (19). Lymph nodes <5 mm were totally embedded and H&E stained. Larger lymph nodes were embedded in slices of 3–4 mm thick. If micrometastatic disease was suspected, or if extensive response to neoadjuvant therapy was present, additional keratin stains were performed.

Statistical analysis

Statistical analysis was carried out with the use of SPSS (IBM Corp. version 23.0, Armonk, NY, USA). Statistical comparisons were made with the chi-square Pearson test and F-test [analysis of variance (ANOVA)]. A P value of <0.05 (two-sided) was considered significant. Binary and categorical data were presented as a number, accompanied by the percentage of the total. Continuous variables were presented as either a mean value with standard deviation or median with interquartile range. Baseline and demographic characteristics were summarized by standard descriptive summaries.

Results

Patients

From the 168 patients who underwent a gastrectomy between 2011 and 2016 in the Amsterdam UMC-AMC, 112 patients met our inclusion criteria. Reasons for exclusion were: no complete pathological report of the lymph node metastases pattern attainable (n=37), primary esophageal carcinoma (n=8), no carcinoma (n=6), no curative intent (n=5).

Patient characteristics

Detailed patient information is shown in *Table 1*. From the 112 included patients: 79 were men (70.5%), 33 women (29.5%), median age was 66. Eight patients (7.1%) were diagnosed with a cT1 gastric tumor, 18 patients (16.1%) with a cT2 tumor, 57 patients (50.9%) with a cT3 tumor and 5 patients (4.5%) with a cT4 tumor. Clinical T-stage was not recorded in 24 patients (21.4%); 46 patients (41.1%) underwent endoscopic ultrasonography (EUS) screening and 21 patients (18.8%) underwent a diagnostic laparoscopy previous to treatment; 34 patients (30.4%) were operated minimally invasively and 78 (69.6%) open. A total gastrectomy was performed in 54 patients (48.2%) and a subtotal gastrectomy in 58 patients (51.8%), with a Roux-Y or Billroth-II reconstruction. Median lymph node yield was 25 (range, 4–72). Patients with less than 15 lymph nodes in the resection specimen (9 patients) were patients that had previous gastric surgery or acute/semi-acute surgery. Correct clinical staging could only be investigated in the small group of patients without neoadjuvant therapy (Tables S1,S2). The results show in the six patients with cT1: four pT1, one pT2 and one pT3 tumors. In the three patients with cT2: one pT1, one pT2 and one pT4 tumor. In the 17 patients with cT3: three pT2, seven pT3 and seven pT4 tumors. In the one patient with cT4: one patient with pT4 tumor. Finally, in the seven patients with cTx: one pT1, one Pt2, four pT3 and one pT4 tumor. In Tables S1,S2 results are depicted for cN compared to pN and cT and cN compared to ypT and ypN. There was no significant difference among the different clinical T-stages for age, sex, administration of neo-adjuvant chemotherapy, surgical approach, type of resection, tumor location, tumor size, differentiation type and Lauren classification (*Table 1*). Pathological T-stage (P=0.01), cN status (P≤0.01) and pN status (P=0.03) differed between the four groups, with generally more lymph node metastases in the higher cT stage groups. cT1-stage correlated in 4/8 patients with the pT1-stage (50%), cT2-stage correlated in 4/18 patients with the pT2-stage (22.22%), cT3-stage correlated in 21/57 patients with the pT3-stage (36.8%), cT4-stage correlated in 3/5 with the pT4-stage (60%).

Lymph node metastases pattern

The primary outcome: the rate of lymph node metastases in station 8–12 between different cT-stages, is shown in *Table 2*.

Table 1 Patients characteristics

Characteristics	Total (N=112)	cT1 (N=8)	cT2 (N=18)	cT3 (N=57)	cT4 (N=5)	cTx (N=24)	P value**
Age at time of surgery, year							0.45
Median	66	74	62	66	63	67	
Range	32–86	33–83	39–78	41–86	55–73	32–82	
Sex, n (%)							0.08
Male	79 (70.5)	4 (50.0)	10 (55.6)	46 (80.7)	2 (40.0)	17 (70.8)	
Female	33 (29.5)	4 (50.0)	8 (44.4)	11 (19.3)	3 (60.0)	7 (29.2)	
Additional diagnostic screening, n (%)							
EUS	46 (41.1)	5 (62.5)	4 (22.2)	24 (42.1)	3 (60.0)	10 (41.7)	0.30
Diagnostic laparoscopy	21 (18.8)	1 (12.5)	2 (11.1)	13 (22.8)	3 (60.0)	2 (8.3)	0.07
Neo-adjuvant therapy, n (%)							0.24
Chemotherapy	78 (69.6)	2 (25.0)	15 (83.3)	40 (70.2)	4 (80.0)	17 (70.8)	
None	34 (30.4)	6 (75.0)	3 (16.7)	17 (29.8)	1 (20.0)	7 (29.2)	
Surgical approach, n (%)							0.53
Minimal invasive	34 (30.4)	3 (37.5)	5 (27.8)	14 (24.6)	3 (60.0)	9 (37.5)	
Open	78 (69.6)	5 (62.5)	13 (72.2)	43 (75.4)	2 (40.0)	15 (62.5)	
Resection, n (%)							0.19
Total gastrectomy	54 (48.2)	5 (62.5)	5 (27.8)	27 (47.4)	5 (100.0)	12 (50.0)	
Subtotal gastrectomy	58 (51.8)	3 (37.5)	13 (72.2)	30 (52.6)	0	12 (50.0)	
Tumor location, n (%)							0.37
Fundus	11 (9.8)	0	1 (5.6)	7 (12.3)	1 (20.0)	2 (8.3)	
Corpus	24 (21.4)	4 (50.0)	3 (16.7)	11 (19.3)	2 (40.0)	4 (16.7)	
Antrum	34 (30.4)	3 (37.5)	10 (55.6)	13 (22.8)	0	8 (33.3)	
Pylorus	15 (13.4)	0	1 (5.6)	11 (19.3)	0	3 (12.5)	
Whole rumen	11 (9.8)	1 (12.5)	1 (5.6)	4 (7.2)	1 (20.0)	4 (16.7)	
Oesophagus and gaster	9 (8.0)	0	2 (11.1)	5 (8.8)	1 (20.0)	1 (4.2)	
Unknown	8 (7.1)	0	0	6 (10.5)	0	2 (8.3)	
Tumor size, cm							0.25
Median	4	2	4	4	5	4	
Range	0–15.0	0–5.0	0.2–6.5	0–15.0	3.5–7.0	1.0–8.0	
Differentiation, n (%)							0.744
Well to moderate differentiated	23 (20.5)	2 (25.0)	2 (11.1)	13 (22.8)	2 (40.0)	4 (16.7)	
Poorly to undifferentiated	59 (52.7)	4 (50.0)	11 (61.1)	31 (54.4)	2 (40.0)	11 (45.8)	
Unknown	30 (26.8)	2 (25.0)	5 (8.3)	13 (22.8)	1 (20.0)	9 (37.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (N=112)	cT1 (N=8)	cT2 (N=18)	cT3 (N=57)	cT4 (N=5)	cTx (N=24)	P value**
Lauren classification, n (%)							0.746
Intestinal type	39 (34.8)	2 (25.0)	8 (44.4)	20 (35.1)	2 (40.0)	7 (29.2)	
Diffuse type	36 (32.1)	3 (37.5)	5 (27.8)	15 (26.3)	1 (20.0)	12 (50.0)	
Mixed	6 (5.4)	0	1 (5.6)	3 (5.3)	1 (20.0)	1 (4.2)	
Unknown	31 (27.7)	3 (37.5)	4 (16.7)	19 (33.3)	1 (20.0)	4 (16.7)	
Pathological T-stage, n (%)							0.01*
(y)pT1	23 (20.5)	4 (50.0)	8 (44.4)	6 (10.5)	1 (20.0)	4 (16.7)	
(y)pT2	22 (19.6)	1 (12.5)	4 (22.2)	10 (17.5)	0	7 (29.2)	
(y)pT3	33 (29.5)	1 (12.5)	2 (11.1)	21 (36.8)	1 (20.0)	8 (33.3)	
(y)pT4	27 (24.1)	0	4 (44.4)	15 (26.3)	3 (60.0)	5 (20.8)	
(y)pT0***	7 (6.3)	2 (25.0)	0	5 (8.8)	0	0	
Clinical node status, n (%)							<0.01*
Positive	45 (40.2)	1 (12.5)	6 (33.3)	32 (56.1)	3 (60.0)	3 (12.5)	
Negative	56 (50.0)	7 (87.5)	9 (50.0)	22 (38.6)	1 (20.0)	17 (70.8)	
Unknown	11 (9.8)	0	3 (16.7)	3 (5.3)	1 (20.0)	4 (16.7)	
Pathological node status, n (%)							0.03*
Positive	60 (53.6)	2 (25.0)	11 (61.1)	33 (57.9)	5 (100.0)	9 (37.5)	
Negative	52 (46.4)	6 (75.0)	7 (38.9)	24 (42.1)	0	15 (62.5)	
No. of lymph nodes dissected							0.21
Median	25	21	25	27	27	22	
Range	4–72	4–32	6–47	4–72	23–39	8–45	
No. of positive lymph nodes							0.15
Median	1	0	1	2	5	0	
Range	0–40	0–1	0–40	0–17	1–12	0–10	

*, P value <0.05 is defined as significant; **, determined with the Chi-Square Pearson test and F-test (ANOVA); between cT1-cT4; ***, no vital tumor rest detectable. EUS, endoscopic ultrasonography; ANOVA, analysis of variance.

The secondary outcomes; the rate of lymph node metastases in station 1–7 between different cT-stages and the rate of lymph node metastases in station 1–7 and 8–12 between different (y)pT-stages are shown in *Table 2*. The secondary outcome; the lymph node metastases pattern; percentage of pathological positive lymph nodes per lymph node station, between different cT and (y)pT-stages is shown in *Table 3*.

cT1-stage gastric cancer

The lymph node metastases rate in the lymph node stations 1–7 is 25.0% (2/8). There were no positive lymph nodes in the stations 8–12.

cT2-stage gastric cancer

The lymph node metastases rate in the lymph node stations 1–7 is 61.1% (11/28). The lymph node metastases rate in the stations 8–12 is 11.1% (2/18).

cT3-stage gastric cancer

The lymph node metastases rate in the lymph node stations 1–7 is 52.6% (30/57). The lymph node metastases rate in the stations 8–12 is 16.7% (10/57).

Table 2 Lymph node metastasis rate in the locoregional and non-locoregional lymph node stations

Tumor stage	LN stations	
	Locoregional, station 1–7	Non-locoregional, station 8–12
Clinical T-stage		
cT1	2/8 (25.0%)	0/8
cT2	11/18 (61.1%)	2/18 (11.1%)
cT3	30/57 (52.6%)	10/57 (16.7%)
cT4	5/5 (100%)	2/5 (40.0%)
cTx*	9/24 (37.5%)	3/24 (12.5%)
Total	57/112 (50.9%)	17/112 (15.2%)
Pathological T-stage		
pT1	10/23 (43.5%)	0/23
pT2	9/23 (39.1%)	3/23 (13.0%)
pT3	18/33 (54.5%)	6/33 (18.2%)
pT4	20/27 (74.1 %)	8/27 (29.6%)
pT0**	0/7	0/7
Total	57/112 (50.9%)	17/112 (15.2%)

*, no consensus based on CT scan; **, no vital tumor-rest detected. LN, lymph node; CT, computed topography.

cT4-stage gastric cancer

The lymph node metastases rate in the lymph node stations 1–7 is 100% (5/5). The lymph node metastases rate in the stations 8–12 is 40.0% (2/5).

Discussion

As a primary outcome, this retrospective study investigated the rate of lymph node metastases in station 8–12 for each cT-stage in gastric cancer, in a Western patient cohort. There were no metastases found in the lymph node stations 8–12 for in the cT1-stage tumors. The more advanced cT2-4 stage tumors showed a high metastases rate in the lymph node stations 8–12. Additionally, this study investigated the rate of lymph node metastases in station 1–7 between different cT-stages, the rate of lymph node metastases in station 1–7 and 8–12 between different (y)pT-stages and the lymph node metastases pattern between different cT and (y)pT-stages. The metastases rate was overall high in the lymph node station 1–7, with the more advanced tumors showing a higher metastases rate. There were no metastases found in the lymph node stations 8–12 for the (y)pT1-stage tumors. The more advanced (y)pT2-4 tumors showed a high metastases rate in the lymph node stations 8–12. No relation was observed between the lymph node metastases pattern and the different gastric T-stages

This retrospective analysis is consistent with previous literature from the East, regarding the rate of metastases in different echelons of lymph node stations differentiated per tumor stage; the lymph node metastases rate increases with increasing tumor depth and T1-stage tumors are accompanied with lower metastases rates in any of the lymph node stations 8–12 (0.0–1.6%) in comparison to the more advanced T4-stage tumors (10.5–29.3%) (20-22). Studies from the West are sparse, and cannot be directly compared with studies from the East. Differences between patients with gastric cancer in the East and West are related to the baseline patient characteristics (*Helicobacter pylori* status, body mass index) and environmental and dietary differences (23). Additionally, the differences in tumor histology and the heterogeneity in neoadjuvant and adjuvant treatment regimens between the East and West further explain the difficulties in the interpretation of the results of Eastern studies in a Western population (24). This study, conducted with a Western patient cohort emphasises these differences; since this study shows significantly more advanced tumors and the majority of patients in this cohort received neo-adjuvant chemotherapy. It distinguishes itself by reporting the rate of metastases in different lymph node stations differentiated per tumor stage as a primary outcome, in a Western patient cohort.

There is a known discrepancy between the pathological and clinical T-stage. There is no single gold standard modality for gastric cancer staging; no consensus exists on which imaging modality, the multidetector computed topography (MDCT), EUS or magnetic resonance imaging (MRI), most accurately determines the gastric cT-stage (3,25). EUS is often used as the standard modality for preoperative staging of tumor depth in esophageal cancer and considered as an accurate diagnostic imaging modality for the loco-regional staging. In gastric cancer, EUS is not usually part of initially staffing, although, a large Cochrane database systematic review reported a sensitivity of 0.86 and a specificity of 0.90 for discriminating between cT1 to cT2 versus cT3 to cT4 gastric carcinomas and a sensitivity of 0.87 and a specificity of 0.75 for discriminating between cT1 and cT2 gastric carcinomas. This systematic review reported a sensitivity and specificity of 0.83 and 0.67 respectively for discriminating between cN– (no lymph

Table 3 Lymph node metastasis pattern of the non-locoregional lymph node stations

Tumor stage	LN station				
	8	9	10	11	12
Clinical T-stage					
cT1	0/8	0/8	0/5	0/8	0/8
cT2	2/18 (11.1%)	1/18 (5.6%)	0/5	0/18	2/18 (11.1%)
cT3	6/57 (10.5%)	5/57 (8.8%)	0/22	2/57 (3.5%)	4/57 (7.0%)
cT4	0/5	1/5 (20.0%)	0/4	1/5 (20.0%)	0/5
cTx*	1/24 (4.2%)	2/24 (8.3%)	0/14	0/24	0/24
Total	9/112 (8.0%)	9/112 (8.0%)	0/50	3/112 (2.7%)	6/112 (5.4%)
Pathological T-stage					
pT1	0/23	0/23	0/13	0/23	0/23
pT2	1/22 (4.5%)	2/22 (9.1%)	0/6	0/22	2/22 (9.1%)
pT3	3/33 (9.1%)	2/33 (6.1%)	0/17	1/33 (3.0%)	1/33 (3.0%)
pT4	5/27 (18.5%)	5/27 (18.5%)	0/14	2/27 (7.4%)	3/27 (11.1%)
pT0**	0/7	0/7	0	0/7	0/7
Total	9/112 (8.0%)	9/112 (8.0%)	0/50	3/112 (2.7%)	6/112 (5.4%)

*, no consensus based on EUS and CT scan; **, no vital tumor-rest detected. LN, lymph node; EUS, endoscopic ultrasonography; CT, computed topography.

node metastases) and cN+ (clinically suspected lymph node metastases) for EUS (26). A systematic review of Kwee *et al.* reported a diagnostic accuracy of 77.1% to 88.9% for determining the cT-stage for MDCT, 65% to 92.1% for EUS and 71.4% to 82.6% for MRI. This wide range may be due to lack of standard imaging criteria (27). This deviation between pathological and clinical gastric T-stage and N-stage needs to be considered with regard to the applicability of the imaging modalities.

Peri-operative chemotherapy is the standard for curative gastric cancer. The majority of patients included in this study received pre-operative chemotherapy (69.6%). Chemotherapy potentially downstages the T-stage and N-stage. This results in an increase in the discrepancy between the cT-stage, determined before administration of chemotherapy, and the ypT-stage, determined after administration of chemotherapy. This study demonstrates this discrepancy as there is a notable difference in the distribution of the different T-stages between the cT-stage and (y)pT-stage. The downstaging of the T-stage can be explained by chemotherapy treatment, however, the upstaging seen in this study cannot. This is possible the result of disease progression or the low accuracy of the imaging modalities used for clinical staging. Possible downstaging was also shown for the N-stage, as cN was generally higher than ypN stage in neoadjuvantly treated patients. However, clinical lymph node staging is known to be even more unreliable than clinical tumor staging.

In addition, for analysis of accuracy of cT-stage and cN-stage in patients without neoadjuvant therapy, sample size was limited. The results show poor accuracy, however, these analyses should be repeated in larger studies with prospective data.

In current literature there is still controversy concerning the extent of lymphadenectomy; it demonstrates an advantage in survival for D2 lymphadenectomy. However, possibly a D2 lymphadenectomy is accompanied with higher morbidity and mortality (6,7). Considering, the overall low lymph node metastases rate in T1 stage gastric tumors it is uncertain if a D2 lymphadenectomy is the most beneficial lymph node dissection extent for all gastric tumors (3). Two large Randomized Controlled Trials failed to demonstrate the superiority of a D2 lymphadenectomy over a D1 lymphadenectomy. One of these trials: Bonenkamp

et al. showed a higher morbidity (43% versus 25%) and mortality (10% versus 4%) after D2 lymphadenectomy (28). Five-year follow-up showed no significant difference in overall survival (D2: 47% versus D1: 45%). Fifteen-year follow-up showed a significant difference in loco-regional recurrence after D1 lymphadenectomy (D2: 21.8% versus D1: 40.7%) (5). In addition, there was a high cross-over in this study: 52% of patients in the D1 group underwent a more extended lymphadenectomy than D1, while in the D2 group, 84% underwent a more limited dissection than D2 (29). Another trial, Cuschieri *et al.* also showed higher morbidity and mortality (13% versus 6.5%) after D2 lymphadenectomy. It did not demonstrate a benefit for D2 lymphadenectomy over D1 lymphadenectomy in terms of overall survival (D2: 33% versus D1: 35%) (30). It is important to take into account that these studies are 25 years old. Since then, surgical procedures have become more minimal invasive. A study from Degiuli *et al.* showed a lower overall morbidity rate (D2: 17.9% versus D1: 12.0%) in comparison to the previous studies, nonetheless in favor of a D1 lymphadenectomy (6,28,30). With regard to the overall survival there was no significant difference found (D2: 64.2% versus D1: 66.5%). Aforementioned studies did not distinguish between T-stage in the primary analysis. Degiuli *et al.* did however performed a subgroup analysis where they compared the survival between D1 and D2 lymphadenectomy between different T-stages and different N-stages. Subgroup analysis showed a higher 5-year survival in the pT1 group after D1 lymphadenectomy (D2: 83% versus D1: 98%) (31). It showed no significant difference between D1 and D2 lymphadenectomy in overall 5-year survival for node negative status and node positive status. However, a trend towards improved survival for D1 lymphadenectomy is seen for node negative tumors (D2: 90% versus D1: 97%) and a trend towards improved survival for D2 lymphadenectomy is seen for node positive tumors (D2: 61% versus D1: 46%). This trend towards improved survival for D2 lymphadenectomy is specifically seen for more advanced pT2-4 gastric tumors with positive lymph nodes (D2: 59% versus D1: 38%). This controversy in current literature between the superiority of either, D1 or D2 lymphadenectomy, and a trend toward improved survival for D1 or D2 depending on T-stage and N-stage suggest the necessity for a more tailored approach. In addition, based on the data of the current study, in combination with unreliable staging, a D2 lymphadenectomy for cT1 may not be omitted, and further, larger and prospective studies are needed to confirm these study results.

It is of importance to consider the role of surgery for T1 gastric tumors. T1 gastric tumors are the minority of tumors seen in Western countries; in contrast to Asian countries, there is no routine screening for gastric cancer. From the 112 included patients in this study, only eight patients (7.1%) were diagnosed with a cT1 gastric tumors. In most cT1-stage tumors, an endoscopic resection can be performed. Curative endoscopic resection can be considered for intramucosal differentiated-type adenocarcinoma, without ulceration and ≤2 cm. Extended endoscopic resection can be considered for intramucosal differentiated-type adenocarcinoma, without ulceration >2 cm; intramucosal differentiated-type adenocarcinoma, with ulceration ≤3 cm; intramucosal undifferentiated-type adenocarcinoma ≤2 cm; and differentiated-type adenocarcinoma with superficial submucosal invasion (sm1, ≤500 μm), and ≤3 cm (32). Patients with tumors that do not meet these criteria require surgery with lymph node dissection.

There is no large study comparing D1 and D2 lymphadenectomy with the primary outcome distinguishing between the different T-stages. This retrospective analysis showed that a D2 lymphadenectomy can be considered for T2-4 tumors. The lymph node metastases rate in the stations 8–12 is overall high in these more advanced tumors. As no metastases in the stations 8–12 for the T1 gastric tumors are seen, this study showed that possibly, a D1 lymphadenectomy could be sufficient for T1 gastric tumors. This is however, strongly dependent on the imaging modalities for gastric cancer. As staging for these tumors is still not optimal. Further research focussing on the imaging modalities, and subsequently on tailoring the treatment for different T-stages is recommended. If accurate T1 prediction can be made, a D1 lymphadenectomy can be considered for T1 stage tumors that are not eligible for endoscopic resection. A D2 lymphadenectomy should always be considered if consensus cannot be reached on imaging.

This study has several limitations. Firstly, the sample size is small: only eight patients with a cT1-stage could be included. In the Netherlands, gastric cancer is a quite rare disease with only approximately 1,100 new patients per year, and only 600 gastrectomies (33,34). Therefore, there is no screening for gastric cancer, and most patients present with advanced and even incurable disease. We realize that this study is very much limited by the small sample size but this is only a first step in investigating the distribution of lymph node metastases in a Western gastric cancer population. This preliminary work will

need to be followed up with prospective and multicenter studies. Especially whether a limited D1 dissection is justified in patients with cT1 disease needs to be further investigated, also considering the accuracy of both clinical T and N staging. With this in mind, studies investigating the value of sentinel node navigation surgery seem very promising (35). Furthermore, there were 9 patients with <15 lymph nodes examined, these patients were probably understaged, which may have influenced results. These patients however, were not excluded from analyses to prevent selection bias. This underlines the difficulties in accurate staging and the possible influence of chemotherapy. Furthermore, the retrospective nature of this study has its potential sources of bias and confounding. Seeing, however, the limited research regarding a more tailored approach in the treatment of gastric cancer, this study provides promising results and demonstrates the necessity for more research concerning accurate staging.

Conclusions

No lymph node metastases in the stations 8–12 were observed in cT1 and (y)pT1 gastric cancer in a Western patient cohort, whereas in all other stages lymph node metastases were detected. The results from this study endorse the Japanese Gastric Cancer Guideline and these guidelines can be extrapolated to the West; in early gastric cancer, a D1 lymphadenectomy seems sufficient, while in advanced gastric cancer a D2 lymphadenectomy should be considered.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. For this retrospective research, ethical approval for this study is not required under Dutch law. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 cT-stage compared to (y)pT-stage

	cT1 (n=8)	cT2 (n=18)	cT3 (n=57)	cT4 (n=5)	cTx (n=24)
pT1	4	1	-	-	1
pT2	1	1	3	-	1
pT3	1	-	7	-	4
pT4	-	1	7	1	1
ypT1	-	7	6	1	3
ypT2	-	3	7	-	6
ypT3	-	2	14	1	4
ypT4	-	3	8	2	4
ypT0	2	-	5	-	-

Table S2 cN-stage compared to (y)pN-stage

	cN0 (n=56)	cN1 (n=29)	cN2 (n=14)	cN3 (n=2)	cNx (n=11)
pN0	16	2	-	-	-
pN1	6	5	-	-	1
pN2	2	3	-	-	1
pN3	6	1	3	-	1
ypN0	11	11	6	1	5
ypN1	8	3	2	-	2
ypN2	2	1	1	-	1
ypN3	5	3	2	1	-

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