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REVIEW ARTICLE

How many lymph nodes should be assessed in patients with gastric cancer? A systematic review

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Abstract
Background Nodal status is one of the most important prognostic factors in gastric adenocarcinoma (GC). As such, it is important to assess an appropriate number of lymph nodes (LNs) in order to accurately stage patients. However, the number of LNs assessed in each GC case varies, and in many cases the number examined per gastric specimen is less than current recommendations.
Purpose We aimed to identify and synthesize findings from all articles evaluating the association of clinicopathological features and long-term outcomes with the number of LNs assessed among GC patients.
Methods Systematic electronic literature searches were conducted using Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1998 to 2009.
Results Twenty-five articles were included in this review. Extensive resection, increased tumor size, and greater TNM staging were all associated with a greater number of LNs assessed. The disease-free survival was longer and recurrence rate was lower in patients with more LNs assessed. Overall survival, as well as survival by TNM and clinical stage, was improved among patients with an increased number of LNs assessed, but much of this appears to be due to stage migration, with the effect more pronounced in more advanced disease.
Conclusion More LNs assessed resulted in less stage migration and possibly better long-term outcomes. Although current guidelines suggest 16 LNs to be assessed, especially in advanced GC, a higher number of LNs should be assessed.

Keywords Gastric cancer · Lymph nodes · Assessment · Survival · Staging

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Introduction

Surgery is the only effective intervention for cure or long-term survival among patients with gastric adenocarcinoma (GC). In areas without screening (i.e., North America and Europe), patients often present late and have a high frequency of nodal involvement [1], with an estimated rate of lymph node (LN) involvement of 3–5 % for T1a; 11–25 % for T1b; 50 % for T2; and 83 % for T3 tumors [2, 3]. Nodal status is one of the most important independent predictors of patient survival [4, 5].

There is international variation in standards for nodal resection in GC. The Japanese Gastric Cancer Association (JGCA) has published detailed guidelines for the pathologic assessment and staging of GC, describing 16 nodal

compartments classified as N1, N2, and N3 groups. While there is strong support in Asia and some European centers for the more extensive D2 LN dissection, which removes both the N1 and N2 nodal groupings, several randomized control trials have failed to demonstrate a survival benefit for this extended surgery, leading to less acceptance of this resection in North America [6, 7]. For example, in the United States, the Intergroup 0116 trial found that only 10 % of patients had the recommended D2 LN dissection; 36 % had a D1 LN dissection; and 54 % had an inadequate D0 LN dissection [8].

An alternative method to determine the extent of LN resection for a given patient is the "Maruyama Index of Unresected Disease" (MI). Researchers at the National Cancer Center Hospital in Tokyo have documented the disease spread in patients treated by D2 or greater lymphadenectomy in a searchable computerized database, referred to as the "Maruyama Program" [9–11]. This program calculates the probability of positive LNs in the 16 stations, determined by seven variables: age, sex, Borrmann type of tumor, greatest dimension of the tumor as measured on the luminal surface, location of the tumor, tumor depth, and histology. The MI is the sum of the probability of nodal involvement for the nodal stations that were not dissected. An MI of 0 can be achieved in all gastric resections [12] if surgical removal of all 'at risk' nodal stations is performed. A strong correlation between a lower MI and an increase in overall survival (OS) has been demonstrated in American, European, and Asian patients [8, 13, 14]. This has led researchers to assert that better local–regional therapy can favorably affect survival in GC, and that the MI may be a better indicator of adequacy of surgery than a particular lymphadenectomy [13, 14]. Additionally, these analyses show that findings from Asian studies have strong implications for patients in the West, despite the assertion that biologic differences explain the improved survival of GC in the East [2]. Regardless of which resection technique is selected, it appears that there is a complex relationship between the LN dissection performed, clinical staging, and ultimate patient outcome.

In 1997 the Union International Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) recommended, in the 5th edition of their staging manual, that a minimum of 15 LNs be assessed per patient [15]. The recommendation was based on the nodal classification system of N1 = 1–6 positive LNs; N2 = 7–15 positive LNs; and N3 = more than 15 positive LNs. The cut-off points were derived from retrospective databases [16]. Subsequent examinations [17, 18] have shown superior predictive ability of LN staging based on number of nodes involved rather than the location of nodal involvement. [19]. Part of this superior predictive ability has been attributed to the category N3 (>15 LNs positive), a group with extremely poor prognosis. The 7th edition of the UICC/AJCC staging manual (2010) revised the nodal classification system such that N1 = 1–2 positive LNs; N2 = 3–6 positive LNs; N3a = 7–15 positive LNs; and N3b = 16 or more positive LNs [20]. As such, the UICC/AJCC now recommends that at least 16 LNs be assessed per patient [20]. The staging changes attempt to minimize the impact of surgical dissection on GC staging, and to improve the prognostic ability of N-staging compared to that in the 5th/6th editions [21]. Unfortunately, despite the changes to simplify staging, the number of LNs assessed in each GC case varies, and in many cases, the number reported per specimen is less than current recommendations [15, 22]. In the United States, a median of only 10 nodes per patient were assessed, and 9 % had no LN assessment at all. Only 29 % of patients had >15 LNs assessed [23–25].

An LN ratio (LNR) has also been proposed and many international groups have examined the utility of an LNR for the prognosis of GC, finding this more predictive than simple analysis of the number of positive LNs [26–28]. However, most studies have excluded patients with fewer than 15 LNs examined, and no uniform cut-off points have been identified to date. Although an LNR does mitigate the effects of stage migration somewhat, its utility in patients in whom fewer than 15 LNs were assessed has not been proven.

Studies have shown that stage migration occurs in patients with a lower number of LNs examined, creating inaccuracies in survival predictions [18, 29–31]. In addition to the importance of nodal status as a prognostic factor in GC, it has been suggested that inadequate LN assessment directly affects patient survival for the worse [32, 33]. Therefore, the purpose of this review was to identify and synthesize findings from all articles evaluating both predictors of nodal harvest and long-term outcomes based on the number of LNs assessed.

Methods

Data sources

Electronic literature searches were conducted using Medline and Embase from January 1, 1998, to December 31, 2010 according to the search algorithm presented in electronic Appendix A. Search terms included: exp Stomach Cancer/or [((gastric or stomach) adj1 cancer$) or ((gastric or stomach) adj1 carcinoma) or ((gastric or stomach) adj1 adenocarcinoma) or ((gastric or stomach) adj1 neoplasm$)).mp.] and [number of lymph nodes or lymph node assessment or lymph node examination or total lymph node count] and [((negative or resection) adj2 margin$).mp. or

exp frozen section/or exp GASTRECTOMY/or ((gastric or stomach) adj2 resect$).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] or omentectom$.mp. or multivisceral resection$.mp.] and [clinical trial/or controlled clinical trial/or exp comparative study/or meta analysis/or multicenter study/or exp practice guideline/or randomized controlled trial/] not [Case Report/or review]. A separate search of the Cochrane Central Register of Controlled Trials (1985–2010) was performed using the search term "gastric cancer". No attempt was made to locate unpublished material.

Study selection and review process

To be eligible, studies had to meet the following criteria: (1) investigated number of LNs examined in newly (not recurrent) diagnosed patients with histopathology-confirmed gastric adenocarcinoma; (2) reported long-term outcomes and clinicopathological factors based on the number of LNs assessed; (3) patients had a pathological examination of the surgical specimens and LNs dissected; (4) involved human patients with a minimum of 30 patients; and (5) published in peer reviewed journals in English. Studies were excluded according to the following criteria: (1) studies that did not provide short- or long-term trial outcomes; (2) involved animals and/or ex vivo samples; (3) involved patients with mixed cancer with no separate analysis of GC subjects; and (4) review articles, meta-analyses, abstracts, conference proceedings, editorials/letters, and case reports. All electronic search titles, selected abstracts, and full-text articles were independently reviewed by a minimum of two reviewers (N.C., R.S., R.C.). Disagreements on study inclusion/exclusion were resolved with a consensus meeting.

Data extraction and analysis

A systematic approach to data extraction was used to produce a descriptive summary of participants, interventions, and study findings. Data abstracted included the study type, number of patients, patient characteristics, resection margin status, number of LNs removed, number of positive LNs, and follow-up time. Data on associations with clinicopathological factors (resection type, tumor location, tumor size, TNM stage, and clinical stage) and the number of assessed LNs were extracted. Disease-free survival, recurrence rate, overall survival, and survival by subgroups (TNM and clinical stage) relating to the number of LNs assessed were extracted. The first reviewer (A.B.) independently extracted the data and a second reviewer (R.S.) checked the data extraction. No attempt was made to contact authors for additional information.

Results

Literature search

A total of 3,608 titles/abstracts were identified from the electronic searches and reference lists for preliminary review. After the removal of duplicates and screening for relevant titles and abstracts, a total of 52 articles were identified as pertaining to the examination of LN number and long-term outcomes, and these were submitted for a full-text review. A total of 25 retrospective articles [5, 18, 23–25, 29–31, 34–50] involving 74,228 patients were included in this review (Fig. 1). The descriptive characteristics of each included study are presented in Table 1.

Clinicopathological factors and the number of LNs assessed

Details on the various clinicopathological factors associated with the number of LNs assessed are presented in electronic Appendices B–D. Five studies [5, 24, 31, 35, 38] reported significant associations between increased surgical resection (extended dissection or total gastrectomy) and an increased number of LNs assessed (Table 2). Three studies found an association between tumor location (distal tumors in two studies, and middle or upper-third tumors in one study) and an increased number of assessed LNs [35, 38, 43], whereas four studies did not [5, 31, 44, 48] (Table 2). Increased tumor size was significantly associated with a greater number of assessed LNs in 3 studies [35, 38, 48], while one study reported no significant relationship [31]. Four studies found a significant relationship between advanced T stage and increased number of LNs assessed

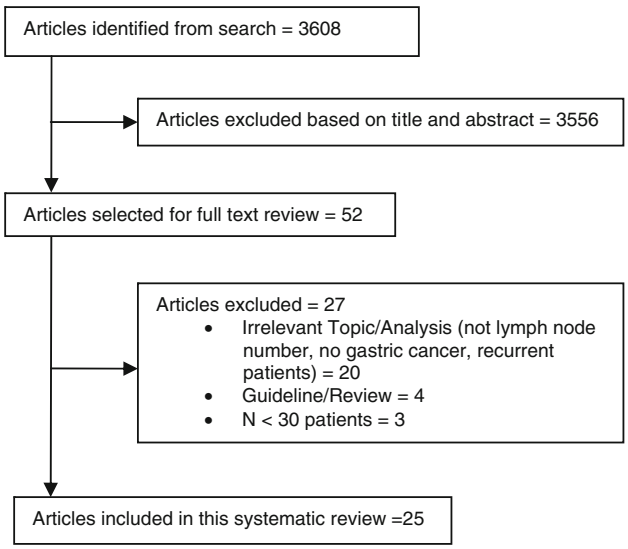

Fig. 1 Article selection flow

Table 1 Characteristics of studies evaluating the number of lymph nodes assessed

Study	Country	Study type	Patients (*N*)	Patient characteristics	Resection margin	No. of LNs removed	No. of positive LNs	Follow up
Barbour [31]	USA	R (1985–2003)	366	M: 287 (78 %) W: 79 (22 %) Age: 66 (25–90) years	R0: 366 (100 %)	≤D1: Md = 14 ≥D2: Md = 21	<15 LNs: Md = 2, Mn = 4 ≥15 LNs: Md = 1, Mn = 2	Md; 2.5 years
Borie [34]	France	R (1979–1988)	332	M: 208 (62.7 %) W: 124 (37.3 %) Age: 64 ± 13 years	NR	NR	NR	Mn: 6.7 (0–16.4) years
Bouvier [35]	France	R (1976–1996)	749	M: 489 (65 %) W: 260 (35 %) Age: 68.2 ± 13 years	R0: 664 pts (88.6 %)	Mn: 8.4	NR	NR
Bruno [36]	Italy	R (1986–1998)	367	M: 238 (64.9 %) W: 129 (35.1 %) Age: 67 (32–88) years	NR	Mn: 17.4 ± 12.3 (1–84), Md: 15	NR	Md: 4.1 years
Coburn [24]	USA	R (1988–2002)	10,807	M: 6,916 (64 %) W: 3,891 (36 %) Age: 70 (18–102) years	R0: 10,807 (100 %)	Md: 9 (0–90)	NR	Mn: 5 years
Deng [37]	China	R (1997–2000)	196	M: 148 (76 %) W: 48 (24 %) Age: 69.5 (65–77) years	R0: 196 (100 %)	<15 LNs: Mn = 8.4 ± 3.4 (3–14) ≥15 LNs: Mn = 23 ± 5 (15–44)	NR	Mn: 7 (0.5–12) years
Giuliani [38]	Italy	R (1992–1998)	154	M: 99 (64.3 %) W: 55 (35.7 %) Age: 65 (mn)	R0: 154 (100 %)	Mn: 22.6	Mn: 8.1 per specimen	Mn: 5 years
Huang [39]	China	R (1996–2002)	236	M: 197 (83.5 %) W: 39 (16.5 %) Age: 58.8 (30–79) years	R0; 236 (100 %)	Md: 23 (7–74) Mn: 23.8 ± 8.8	NR	Md: 3.7 (0.08–11.3) years
Huang [40]	China	R (1995–2004)	211	M: 164 (78 %) W: 47 (22 %) Age: 57.4 (29–84) years	R0: 211 (100 %)	Md: 22 (6–48) Mn: 22.7 ± 7.0	0 % (all N0)	Total 5 years

Table 1 continued

Study	Country	Study type	Patients (*N*)	Patient characteristics	Resection margin	No. of LNs removed	No. of positive LNs	Follow up
Hundahl [41]	USA	R (1985–1996)	33,085	M: 21,174 (64.0 %) W: 11,911 (36.0 %) Age: NR	NR	NR	NR	NR
Ichikura [30]	Japan	R (1982–1995)	925	Sex: NR Age: 57 ± 20 years	R0: 925 (100 %)	Md: 30 Mn: 32 ± 17 N0: 29 ± 15 N1: 33 ± 16 N2: 38 ± 18 N3: 49 ± 15	NR	Total 5 years
Karpeh [18]	USA	R (1985–1999)	1,038	M: 689 (66 %) W: 349 (34 %) Age: 65 (21–94) years	R0: 1,038 (100 %)	Md: 21 Mn: 23.9	Md: 4 Mn: 6.87	Md: 1.9 (0.02–13.7) years
Le [42]	USA	R (1983–2002)	7,809	NR	NR	NR	NR	Total 1 year
Lee [29]	Korea	R (1986–1995)	4,789	M: 3,209 (66.7 %) W: 1,580 (33.3 %) Age: 54 (19–88) years	R0: 4,789 (100 %)	Mn: 31.9 ± 15.2 Md: 30 (1–119)	Mn: 8.9 ± 9.2	Mn: 4.25 (0.08–11.75) years
Liu [44]	USA	R (1992–2001)	147	M: 93 (63.3 %) W: 54 (36.7 %) Age: 64.7 years (Mn)	R0: 147 (100 %)	≤15 LNs: 7.6 ± 4.2 >15 LNs: 22.3 ± 7.8	Stage III pts only: ≤15 LNs = 6.6 ± 8.2; >15 LNs = 8.2 ± 4.5	Md: 2.5 years
Liu [43]	China	R (1980–2005)	392	M: 299 (76.3 %) W: 93 (23.7 %) Age: 58 (19–86) years	R0: 392 (100 %)	Mn: 15.8 (1–78)	NR	Md: 5.6 (0.5–26) years
Marchet [45]	Italy	R (1988–2001)	1,853	M: 257 (60 %) W: 175 (40 %) Age: NR	R0: 1,853 (100 %)	NR	NR	Md: 3.79 (0.33–15.2) years
Marubini [46]	Italy	P (1982–1993)	615	NR	R0: 615 (100 %)	Md: 21 (15–29)	NR	NR
Scartozzi [47]	Italy	R (years NR)	418	M: 249 (59.6 %) W: 169 (40.4. %) Age: 68 (30–92) years	R0: 418 (100 %)	NR	NR	Md: 2.08 (0.08–10.8) years

Table 1 continued

Study	Country	Study type	Patients (*N*)	Patient characteristics	Resection margin	No. of LNs removed	No. of positive LNs	Follow up
Schwartz [25]	USA	R (1973–2000)	1,377	M: 891 (65 %) W: 486 (35 %) Age: 68 (20–97) years	R0: 1,377 (100 %)	Md: 17 (7–94)	Md: 11 (7–68)	Md: 3.8 (0.08–11.67) years
Shen [48]	China	R (1987–2000)	1,895	M: 1,262 (66.6 %) W: 633 (33.4 %) Age: 55 years (Mn)	R0: 1,895 (100 %)	Md: 43 Mn: 24 (≤30 LNs) Mn: 46 (>30 LNs)	NR	Md (95 % CI): 5.09 (4.44–5.75) years
Siewert [5]	Germany	P (1986–1989)	1,654	M: 1,048 (63.4 %) W: 606 (36.6 %) Age: NR	R0: 1,182 (71.5 %)	Mn: 35.3 ± 20.4 Md: 33	NR	Md: 8.4 years
Smith [23]	USA	R (1973–1999)	3,793	M: 2,352 (62 %) W: 1,441 (38 %) Age: 71 (18–100) years	R0: 3,793 (100 %)	Md: 8 (1–89)	NR	Md: 4.83 (0.08–11.92) years
Volpe [49]	USA	R (years NR)	114	M: 99 (87 %) W: 15 (13 %) Age: 62 (26–85) years	R0: 114 (100 %)	<15 LNs: Md = 8; ≥15 LNs: Md = 24	<15 LNs: Md = 2; ≥15 LNs: Md = 3	Md: 2.33 (1.08–21.33) years
Xu [50]	China	R (1990–2002)	906	M: 485 (66 %) W: 244 (33 %) Age: 60 (16–88) years	R0: 906 (100 %)	≤15 LNs: Md = 6, Mn = 6.7 (1–15); >15 LNs: Md = 20, Mn = 22.4 (16–53)	≤15 LNs: Md = 5 (1–12); >15 LNs: Md = 3, Mn = 5.9 (0–34)	Md: 3.83 years Mn: 3.91 (0.33–16.16) years

LN lymph node, *M* men, *W* women, *Mn* mean, *Md* median, *NR* not reported, *R* retrospective, *P* prospective

[24, 29, 35, 44]; six studies found a significant association between advanced N stage and increased number of assessed LNs [5, 23, 31, 43, 44, 48]; and two studies found a significant association between advanced clinical stage and increased number of LNs assessed [31, 44].

Recurrence and disease-free survival and the number of lymph nodes assessed

Disease-free survival (DFS) and/or recurrence rate was reported in 3 studies [37, 40, 47] (Table 3). In two studies, DFS was significantly longer in patients with a greater number of assessed LNs [37, 47], regardless of whether the patient was node-negative or node-positive [47]. Local recurrence was significantly lower in patients with a higher number of LNs assessed [47]. The recurrence rate was also lower among patients with more LNs assessed according to T stage [40]. If recurrence was observed, median overall survival (OS) with recurrence was significantly longer in patients with at least 15 LNs assessed [37]. In patients with positive nodes, DFS was still significantly longer when more than 25 LNs were assessed [47].

Overall survival and the number of LNs assessed

OS was reported in 18 studies [5, 24, 25, 31, 34, 36–40, 42–47, 49, 50] (Tables 4, 5, 6). Improved OS was significantly associated with an increased number of LNs assessed in just over half of the studies (10 of 18) [24, 25, 34, 36, 37, 39, 40, 42, 46, 47]. Studies investigating OS in only N0 (Table 3) or N+ (Table 6) cohorts are shown in separate Tables, as stage migration is a factor in these cohorts. Four studies [31, 39, 40, 50] reported OS by T stage for number of LNs assessed (Table 7). One study found a significant relationship with improved OS for all T stages with an increased number of assessed LNs [40], while other studies only found significant associations for T2 patients [31], or T4 patients [39]. One study found no significant association between the number of LNs assessed and survival rates according to T stage [50].

Eleven studies [18, 24, 30, 31, 38, 39, 43, 45, 47, 48, 50] reported survival rates by N stage (Table 8), and found a significant relationship with improved survival among N0 patients [24, 30, 31, 38, 45, 50], N1 patients [18, 31, 39, 45, 50], and N2 patients [18, 31, 39, 45, 48, 50], with an

Table 2 Clinicopathological factors associated with the number of LNs assessed

Study	Number of LNs assessed	Resection type	Tumor location	Tumor size	T stage	N stage	Clinical stage
Barbour [31]	<15 LNs: 116 pts (32 %) vs. ≥15 LNs: 250 (68 %)	Y[a]	N	N	N	Y	Y
Bouvier [35]	0 LNs: 87 pts (11.6 %) vs. 1–9 LNs: 359 pts (47.9 %) vs. 10–14 LNs: 171 pts (22.8 %) vs. ≥15 LNs: 132 pts (17.6 %)	Y[b]	Y	Y	Y	–	–
Coburn [24]	<15 LNs: 7,673 pts (71 %) vs. ≥15 LNs: 3,134 pts (29 %)	Y[b]	–	–	Y	–	–
Giuliani [38]	15–26 LNs: 115 pts (74.7 %) vs. >26 LNs: 39 pts (25.3 %)	Y[b]	Y	Y	N	–	–
Huang [39]	<15 LNs: 36 pts (15.3 %) vs. 15–19 LNs: 43 pts (18.2 %) vs. 20–24 LNs: 62 pts (26.3 %) vs. 25–29 LNs: 40 pts (16.9 %) vs. ≥30 LNs: 55 pts (23.3 %)	–	–	–	N	–	–
Lee [29]	<15 LNs: 424 pts (9.9 %) vs. 15–29 LNs: 1,826 (42.8 %) vs. ≥30 LNs: 2,020 pts (47.3 %)	–	–	–	Y	–	–
Liu [44]	≤15 LNs: 124 pts (84.4 %) vs. >15 LNs: 23 pts (15.6 %)	–	N	–	Y	Y	Y
Liu [43]	<15 LNs: 208 pts (53.1 %) vs. 15–25 LNs: 125 pts (31.9 %) vs. >25 LNs: 59 pts (15.1 %)	–	Y	–	–	Y	–
Shen [48]	≤30 LNs: 432 (22.8 %) vs. >30 LNs: 1,463 (77.2 %)	–	N	Y	–	Y	–
Siewert [5]	≤25 LNs: 558 pts (33.7 %) vs. >25 LNs: 1,096 pts (66.3 %)	Y[a]	N	–	N	Y	N
Smith [23]	1–9 LNs: 2,143 pts (56.5 %) vs. 10–19 LNs: 1,153 pts (30.4 %) vs. 20–29 LNs: 215 pts (5.7 %) vs. 30–39 LNs: 215 pts (5.7 %) vs. >40 LNs: 67 pts (1.8 %)	–	–	–	Y[c]		–

Please see electronic Appendix C for details

Y yes, *N* no, – not reported, *pts* patients

[a] <D2 versus ≥D2

[b] Subtotal gastrectomy vs total gastrectomy

[c] T stage and N stage combined

Table 3 Disease Free Survival and Recurrence Rate associated with the number of LN assessed

Study	N	DFS	RecR	Survival with Recurrence	RecR by T stage	DFS or RecR by N stage	Significance (*P*)
Deng [37][A]	< 15 LNs: 49 pts (25 %)	Md: 0.9 y[a]	OA: 85.7 %	Md: 0.25 y[b]	NR	NR	0.038[a]
	≥ 15 LNs: 147 pts (75 %)	Md: 1.6 y[a]	OA: 68.0 %	Md: 0.33 y[b]			0.023[b]
Huang [40][B]	< 15 LNs: 18 pts (8.5 %)		NR		RecR T1–2: 62.5 %[c]	NR	0.001[c]
					RecR T3–4: 80 %[d]		<0.0001[d]
	15-19 LNs: 49 pts (23.2 %)				RecR T1–2: 33.3 %[c]		
					RecR T3–4: 56.2 %[d]		
	20-24 LNs: 63 pts (29.9 %)				RecR T1–2: 20 %[c]		
					RecR T3-4: 34.8 %[d]		
	25-29 LNs: 44 pts (20.9 %)				RecR T1–2: 17.8 %[c]		
					RecR T3–4: 25 %[d]		
	≥ 30 LNs: 37 pts (17.5 %)				RecR T1–2: 5.6 %[c]		
					RecR T3–4: 15.8 %[d]		
Scartozzi [47][c]	≤ 25 LNs: 306 (73.2 %)	5-y: 37.5 %[e]	Local: 23 %[g]		NR	DFS in N+ pts: 1.87 y[i]	
		Md: 2.4 y[f]	Distant:37 %[h]			DFS in N-pts:	
						0–6 LNs: 1.92 y[j]	0.0027[e,f]
						7–15 LNs: 2.5 y[j]	0.0001[g]
						16–22 LNs : DFS not reached[f]	NS[h]
						> 22 LNs: DFS not reached[j]	0.0036[i]
	> 25 LNs: 112 (26.7 %)	5-y: 55 %[e]	Local: 4.7 %[g]			DFS in N+pts: 4.72 y[i]	0.0067[j]
		Md: 4.9 y[f]	Distant: 24.8 %[h]				

DFS disease free survival, *LN* lymph node, *Md* median, *NR* not reported, *NS* not significant, *OA* overall, *RecR* recurrence rate

[A] N+ cohort

[B] N0 cohort

[C] mixed N cohort

Table 4 Overall survival rates associated with the number LN assessed for mixed N-stage cohorts

Study	N	Overall Survival (Univariate)	Overall Survival (Multivariate)	Significance (*P*)
Barbour [31][A]	< 15 LNs: 116 pts (32 %)	Siewert II: Md = 2.33 y[a] Siewert III: Md = 1.75 y[b]	NR	NS[a,b]
	≥ 15 LNs: 250 (68 %)	Siewert II: Md = 2.75 y[a] Siewert III: Md = 3.17 y[b]		
Borie [34][A]	< 10 LNs: 210 pts (63.3 %)	5-y: 90.5 %[c]; 7-y: 84.5 %[d]	OR (95 % CI): 3.7 (1.5–8.8)[e]	0.001[c,d]
	≥ 10 LNs: 122 pts (36.7 %)	5-y: 95.5 %[c]; 7-y: 94.0 %[d]	OR (95 % CI): 1[e]	0.003[e]
Coburn [27][A]	<15 LNs: 7673 pts (71 %)	5-y: 30.5 %	HR (95 % CI): 1[f]	<0.05[f]
	≥15 LNs: 3134 pts (29 %)		HR (95 % CI) = 0.635 (0.597–0.676)[f]	
Giuliani [38][A]	15–26 LNs: 115 pts (74.7 %)	NR	OR (±SE): 1[g]	NS[g]
	> 26 LNs: 39 pts (25.3 %)		OR (±SE): -0.134[g]	
Le [42][A]	< 15 LNs: 5826 pts (74.6 %)	1-y LD: 82.5 % 1-y RD: 60 % 1-y DD: 19.6 %	HR (95 % CI): 1[h]	<0.001[h]
	≥ 15 LNs: 1983 pts (25.4 %)	1-y LD: 100 % 1-y RD: 80 % 1-y DD: 36 %	HR (95 % CI): 0.81 (0.76–0.87)[h]	
Liu [44][A]	≤ 15 LNs: 124 pts (84.4 %)	5-y: 31 %[i]; Md: 1.9 y[j]	NR	NS[i,j]
	> 15 LNs: 23 pts (15.6 %)	5-y: 27 %[i]; Md: 2.65 y[j]		
Liu [43][A]	< 15 LNs: 208 pts (53.1 %)	5-y: 41.8 %[k]	HR (95 % CI): 1.125 (0.942–1.344) for total retrieved LNs[k]	NS[k]
	15–25 LNs: 125 pts (31.9 %)	5-y: 38.4 %[k]		
	> 25 LNs: 59 pts (15.1 %)	5-y: 32.8 %[k]		
Marchet [45][A]	≤ 15 LNs: 432 (23.3 %)	5-y: 59.0 %[l]	NR	NS[l]
	> 15 LNs: 1421 (76.7 %)	5-y: 59.2 %[l]		
Marubini [46][A]	≤ 15 LNs: 165 (26.8 %)	NR	HR (95 % CI):	0.02[m]
	16– 20 LNs: 131 (21.3 %)			NS[n]
	21- 25 LNs: 91 (14.8 %)		20 vs 15 LNs: 0.85 (0.76–0.95)[m]	
	26–30 LNs: 93 (15.1 %)		25 vs 15 LNs: 0.76 (0.61–0.95)[m]	
	31–45 LNs: 102 (16.6 %)		30 vs 25 LNs: 0.93 (0.81–1.06)[n]	
	> 45 LNs: 33 (5.4 %)		40 vs 25 LNs: 0.88 (0.69–1.13)[n]	
Scartozzi [47][A]	≤ 25 LNs: 306 (73.2 %)	5-yr: 50 %[o]; Md: 4.9 y[p]	HR (95 % CI): 1[q]	0.0371[o,p]
	> 25 LNs: 112 (26.7 %)	5-yr: 85 %[o]; Md: 7.07 y[p]	HR (95 % CI): 0.59 (0.39–0.89) for number of resected LNs[q]	0.012[q]
Siewert [5][A]	≤ 25 LNs: 558 pts (33.7 %)	5-y RO: 50 %[r] 5-y RO: 45 %[r]	NR	NS[r]
	> 25 LNs: 1096 pts (66.3 %)			
Volpe [49][A]	< 15 LNs: 52 pts (46 %)	5-y: 25 %[s]; Md: 2.16 y[s]	NR	NS[s]
	≥ 15 LNs: 62 pts (54 %)	extended dissection: 5-y: 21 %[t]; Md: 2.17 y[t] 5-y: 29 %[s]; Md: 2.16 y[s] extended dissection: 5-y: 36 %[t]; Md: 3.5 y[t]		0.06[t]
Xu [50][A]	≤ 15 LNs: 729 pts (80.5 %)	5-y: 49.9 %	NR	NS[u]
	> 15 LNs: 177 pts (19.5 %)	(95 % CI, 46.3- 53.5)[u] 5-y: 53.1 % (95 % CI, 45.8- 60.5)[u]		

CI confidence interval, *HR* hazard ratio, *Md* median, *NR* not reported, *NS* not significant, *OD* odds ratio, *LD* local disease, *RD* regional disease, *DD* distant disease

[A] mixed N cohort

Table 5 Overall survival rates associated with the number LN assessed for N0 cohorts

Study	N	Overall Survival	Overall Survival (Multivariate)	Significance (*P*)
Bruno [36][A]	≤ 15 LNs: 301 pts (82 %)	5-y: 59 %[a]	NR	< 0.001[a]
	> 15 LNs: 66 pts (18 %)	5-y: 82 %[a]		
Huang [39][A]	< 15 LNs: 36 pts (15.3 %)	5-y: 19.4 %[b]	RR (95 % CI): 0.959 (0.941–0.977) for number of total LNs[c]	0.0009[b]
	15–19 LNs: 43 pts (18.2 %)	5-y: 25.0 %[b]		< 0.05[c]
	20–24 LNs: 62 pts (26.3 %)	5-y: 37.4 %[b]		
	25–29 LNs: 40 pts (16.9 %)	5-y: 45.0 %[b]		
	≥30 LNs: 55 pts (23.3 %)	5-y: 38.2 %[b]		
Huang [40][A]	< 15 LNs: 18 pts (8.5 %)	5-y: 43.2 %[d]	RR (95 % CI): 0.527 (0.399–0.695) for number of resected LNs[e]	< 0.0001[d]
	15–19 LNs: 49 pts (23.2 %)	5-y: 76.8 %[d]		< 0.05[e]
	20–24 LNs: 63 pts (29.9 %)	5-y: 84.5 %[d]		
	25–29 LNs: 44 pts (20.9 %)	5-y: 90.6 %[d]		
	≥ 30 LNs: 37 pts (17.5 %)	5-y: 94.5 %[d]		

RR relative risk

[A] N0 cohort

increased number of LNs assessed. Only one study found this relationship to be significant among N3 patients [39]. Scartozzi et al. [47] found this relationship significant for all node-positive patients, whereas Liu et al. [43] did not find any significant associations between number of LNs assessed and survival according to N stage.

Among the three studies [5, 23, 25] investigating OS according to combined T and N stage (Table 9), two found a significant relationship between improved OS and increased number of LNs assessed irrespective of T and N stage [23, 25], whereas one study found this association significant only at specific stages (T2N1, T3N0, T2N2, and T4N0) [5]. OS by clinical stage was reported in 10 studies [5, 18, 24, 29, 30, 35, 39, 41, 44, 49] (electronic Appendix E). Two studies found a significant relationship with improved OS among patients with stage I GC and increased number of LNs assessed [24, 30]; four studies found this association significant among stage II patients [5, 24, 39, 49]; seven studies found this relationship significant among stage III patients [5, 18, 24, 29, 30, 39, 44]; and three studies found this association significant among stage IV patients [18, 24, 39]. An increased relative risk of death was reported among patients with fewer LNs assessed in a combined analysis of stage I and II patients [35]. Although one study did not report *P* values, a visible trend was found for improved OS among patients with increased numbers of assessed LNs among all 4 stages [41].

Discussion

Nodal status is one of the most important prognostic factors in GC [5]. To ensure that patients are accurately staged and provided the optimal treatment, it is important to assess an adequate number of LNs. Currently the UICC/AJCC recommends that at least 16 LNs be assessed per patient [22]. However, the number of LNs assessed in each GC case varies; in the United States, the median number assessed is 10 [24, 51], while in Asia, it is generally three to four times higher [29, 39, 40, 48]. This significant variation may affect both staging accuracy and patient survival. A significant problem with the current staging system, as well as with the 5th and 6th UICC/AJCC editions, is stage migration [15, 21, 22]. If an inadequate number of LNs are assessed, a patient may be inappropriately considered "node-negative" or designated a lower N stage and therefore classified as a lower overall stage; however, these patients have a worse survival than patients who were classified appropriately through a thorough LN assessment. Additionally, a classification of N3 (using the 5th or 6th UICC/AJCC staging editions [15, 22]) could not be given unless 16 LNs were positive. In the current 7th UICC/AJCC staging edition [20], the minimum recommendation has now been increased to 16, which addresses the above issue and also allows for the classification of the new N3b category (16 or more positive LNs) [20]. However, the likelihood of a patient being staged as N3b, if only the minimum number of 16 LNs are assessed, is obviously lower than that if more than 16 LNs are assessed. Studies of surgical dissections have shown that a mean of 26 LNs (range 8–55) were removed with a D1 LN dissection, whereas 37.4 LNs (15–72) were included in a D2 LN dissection [52]. Roukos et al. [52] also reported that the number of nodes found at each station had high variation in nodal yields, and many stations contained no LNs despite adequate resection and thorough pathological examination. Thus, it is difficult to define an ideal number of LNs in a surgical specimen, and the type of LN dissection may significantly affect the number of LNs assessed.

Table 6 Overall survival rates associated with the number LN assessed for N+ cohorts

Study	N	Overall Survival	Overall Survival (Multivariate)	Significance (*P*)
Deng [37][A]	< 15 LNs: 49 pts (25 %)	5-y Median: 1.6 y[a]	NR	[a] < 0.001
	≥ 15 LNs: 147 pts (75 %)	5-y Median: 4.08 y[a]		
Schwarz [28][A]	7–9 LNs: # of pts NR	< 15 LNs vs ≥ 15 LNs: 3-y	RR (95 % CI): 0.968 (0.960–0.976) for number of LNs examined[f]	0.0005[b]
	10–15 LNs: # of pts NR	= 15% vs 20%[b]		0.0020[c]
	16–19 LNs: # of pts NR	< 25 LNs vs ≥ 25 LNs: 3-y		0.0062[d]
	20-24 LNs: # of pts NR	= 10% vs 21 %[c]		NS[e]
	25-29 LNs: # of pts NR	< 30 LNs vs ≥ 30 LNs: 3-y		< 0.0001[f]
	30–39 LNs: # of pts NR	= 12 % vs 21 %[d],		
	≥ 40 LNs: # of pts NR	< 40 LNs vs ≥ 40 LNs: 3-y		
		= 15 % vs 15 %[e]		

NR not reported, *RR* relative risk

[A] N+ cohort

Stage migration confounds comparisons of survival across centers and countries in the evaluation of surgical techniques, adjuvant treatments, and the conduct of trials. However, over and above stage migration, authors suggest there may be an actual survival benefit from an extensive lymphadenectomy [5, 44, 47, 49]. Thus, we performed a systematic review to examine clinicopathological factors associated with the assessment of higher numbers of LNs, as well as the outcomes of these assessments based on the number of LNs assessed. While other overviews have been published, to our knowledge, this is the first systematic review to address this issue.

Clinicopathological factors associated with number of LNs assessed

The results of the present systematic review show that patients with a larger tumor size, more advanced disease, or those who had a more extensive lymphadenectomy were likely to have more LNs assessed (Table 1, Appendix C–E). This can either be attributed to the surgeon performing a more extensive primary resection which would include more LNs, or a more thorough examination of the specimen by the pathology team for more advanced cancers. Additionally, with more advanced cancers, LNs may be grossly positive, and thus more easily identified during specimen processing than microscopically involved or uninvolved LNs. For example, as only 43 % of pathologists in a recent survey reported using fat-clearing solutions, such as acetic acid, LNs that are not grossly involved and thus smaller may be missed [53]. Although some studies found an association with tumor location and the number of LNs assessed, this relationship was unclear, as two articles reported that patients with tumors in the distal stomach were likely to have more LNs assessed [38, 43], while another article reported that tumors in the middle or upper-third of the stomach allowed for a greater number of LNs to be assessed [35]. Heterogeneity in surgical techniques among these studies may confound these results. Furthermore, these findings contradict studies showing more LNs are assessed in patients having a more extensive surgical resection (total vs subtotal gastrectomy) [5, 24, 31, 35, 38].

Recurrence and disease-free survival and the number of lymph nodes assessed

The three articles reporting DFS in the context of LN assessment [37, 40, 47] showed longer times to recurrence when more LNs were assessed. Scartozzi et al. [47] reported a remarkable decrease in local recurrence, from 23 % in patients with ≤25 LNs assessed compared with 4.7 % in patients with >25 LNs assessed. It has been hypothesized that the removal of additional LNs results in better locoregional control. For example, in the 15-year analysis of the Dutch D1/D2 randomized controlled trial (RCT), local recurrence was 22 % in the D1 group, compared with 12 % in the D2 group; while regional recurrence was 19 % in the D1 group, and 13 % in the D2 group ($P = 0.015$) [54]. However, because Huang et al. [40] explored node- negative patients only, and Scartozzi et al. [47] explored T2–3 N1–3 and T3N0 patients only, it is likely that the main effect they measured was that of stage migration.

Stage migration

Studies in which survival is stratified based upon the determination of N stage will suffer from stage migration as more LNs are assessed (Tables 7, 8, 9). Additionally, if a study has limited the cohort under examination to node-negative or node-positive patients only, stage migration

Table 7 T-stage survival rates associated with the number LN assessed

Study	N	T1	T2	T3	T4	Significance (*P*)
Barbour [31][B]	< 15 LNs: 116 pts (32 %)	Md-T1: 9.5 y 5-y T1N-any: 73 %[a]	Md-T2: 1.92 y[b]	Md-T3: 1.58 y[c]	Md-T4: 1.42 y[d]	NS[a,c,d]
	≥ 15 LNs: 250 (68 %)	Md-T1: NR 5-y T1N-any: 77 %[a]	Md-T2: 3.25 y[b]	Md-T3: 1.83 y[c]	Md-T4: 0.25 y[d]	0.02[b]
Huang [39][A]	< 15 LNs: 36 pts (15.3 %)	NR	5-y T2: 25 %[e]	5-y T3: 13.8 %[f]	5-y T4: 4.6 %[g]	NS[e,f]
	15–19 LNs: 43 pts (18.2 %)		5-y T2: 50 %[e]	5-y T3: 22.6 %[f]	5-y T4: 7.5 %[g]	0.0015[g]
	20-24 LNs: 62 pts (26.3 %)		5-y T2: 55.6 %[e]	5-y T3: 45.1 %[f]	5-y T4: 13.5 %[g]	
	25–29 LNs: 40 pts (16.9 %)		5-y T2: 33.3 %[e]	5-y T3: 37 %[f]	5-y T4: 23.1 %[g]	
	≥ 30 LNs: 55 pts (23.3 %)		5-y T2: 0 %[e]	5-y T3: 48.5 %[f]	5-y T4: 37.5 %[g]	
Huang [40][A]	< 15 LNs: 18 pts (8.5 %)	5-y T1: 37.5 %[h]	5-y T2: 25 %[i]	5-y T3: 57.1 %[j]	5-y T4: 33.3 %[k]	0.003[h]
	15–19 LNs: 49 pts (23.2 %)	5-y T1: 83.9 %[h]	5-y T2: 70.1 %[i]	5-y T3: 72.7 %[j]	5-y T4: 75 %[k]	0.005[i]
	20–24 LNs: 63 pts (29.9 %)	5-y T1: 88.9 %[h]	5-y T2: 89.4 %[i]	5-y T3: 83.5 %[j]	5-y T4: 50 %[k]	0.022[j]
	25–29 LNs: 44 pts (20.9 %)	5-y T1: 100 %[h]	5-y T2: 90.9 %[i]	5-y T3: 88.9 %[j]	5-y T4: 66.7 %[k]	0.045[k]
	≥ 30 LNs: 37 pts (17.5 %)	5-y T1: 100 %[h]	5-y T2: 100 %[i]	5-y T3: 92.3 %[j]	5-y T4: 80 %[k]	
Xu [50][B]	≤ 15 LNs: 729 pts (80.5 %)	5-y T1: 86.0 %[l]	5-y T2: 66.3 %[l]	5-y T3: 43.9 %[l]	5-y T4: 17.7 %[l]	NS[l]
	> 15 LNs: 177 pts (19.5 %)	5-y T1: 93.3 %[l]	5-y T2: 74.3 %[l]	5-y T3: 47.1 %[l]	5-y T4: 21.4 %[l]	

Md median, *NS* not significant, *NR* not reported

[A] N0 cohort

[B] mixed N cohort

Table 8 N-stage survival rates associated with the number LN assessed

Study	N	N0	N1	N2	N3	Significance (*P*)
Barbour [31]	< 15 LNs: 116 pts (32 %)	Md-N0: 4.08 y[a]	Md-N1: 1.5 y[c]	Md-N2: 0.92 y[e]	Md-N3: NR	NS[a]
		5-y ≥ T2N0: 31 %[b]	5-y ≥ T2N1: 15 %[d]	5-y ≥ T2N2: 0 %[f]		0.03[b,d]
	≥ 15 LNs: 250 (68 %)	Md-N0: 12.5 y[a]	Md-N1: 2.25 y[c]	Md-N2: 1.5 y[e]	Md-N3: 0.75 y	0.02[c]
		5-y ≥ T2N0: 54 %[b]	5-y ≥ T2N1: 27 %[d]	5-y ≥ T2N2: 10 %[f]		0.05[e,f]
Coburn [24]	<15 LNs: 7673 pts (71 %)	12.5-y T1N0: 31 %[g,h]		NR		NS[g]
	≥ 15 LNs: 3134 pts (29 %)	12.5-y T1N0: 50 %[h]	12.5-y T1N1: 37 %[g,h]		NR	< 0.027[h]
Giuliani [38]	15-26 LNs: 115 pts (74.7 %)	< 23 LNs assessed:		NR		0.0001[i]
		5-y N0: 28 %[i]				
	>26 LNs: 39 pts (25.3 %)	> 23 LNs assessed:		NR		
		5-y N0: 60 %[i]				
Huang [39]	< 15 LNs: 36 pts (15.3 %)	5-y N0: 15 %[j]	5-y N1: 8.7 %[k]	5-y N2: 7.7 %[l]	NR	
	15–19 LNs: 43 pts (18.2 %)	5-y N0: 41.7 %[j]	5-y N1: 13.3 %[k]	5-y N2: 8.3 %[l]	5-y N3: 0 %[m]	NS[j]
	20–24 LNs: 62 pts (26.3 %)	5-y N0: 60 %[j]	5-y N1: 37.8 %[k]	5-y N2: 12.5 %[l]	5-y N3: 0 %[m]	0.0005[k]
						0.0034[l]
	25–29 LNs: 40 pts (16.9 %)	5-y N0: 62.5 %[j]	5-y N1: 52.9 %[k]	5-y N2: 25 %[l]	5-y N3: 0 %[m]	0.0016[m]
	≥30 LNs: 55 pts (23.3 %)	5-y N0: 40 %[j]	5-y N1: 40.7 %[k]	5-y N2: 30 %[l]	5-y N3: 7.6 %[m]	
Ichikura [30]	1–4 LNs: 8 pts (0.86 %)	N0: 3-y = 75 %[n,o];		NR		
		5-y = 75 %[n,o]				
	5–9 LNs: 45 pts (4.9 %)	N0: 3-y = 87 %[p,q];	N1: 3-y = 60 %[r];		NR	0.007[n]
		5-y = 82 %[p,q]	5-y = 60 %[r]			0.0003°
						0.02[p]
						0.001[q]
	10–14 LNs: 58 pts (6.3 %)	N0: 3-y = 95 %[n,p];	N1: 3-y =73 %;		NR	
		5-y = 92 %[n,p]	5-y = 73 %			
	15-19 LNs: 102 pts (11.0 %)	N0: 3-y = 91 %°[,q];	N1: 3-y = 81 %;	N2: 3-y = 29 %;	NR	0.07[r]
		5-y = 87 %[oq]	5-y = 71 %	5-y = 29 %		
	20–29 LNs: 244 pts (26.4 %)	N0: 3-y = 95 %[o,q];	N1: 3-y = 76 %;	N2: 3-y = 61 %;	NR	
		5-y = 91 %[o,q]	5-y = 72 %	5-y = 30 %		
	> 30 LNs: 468 pts (50.6 %)	N0: 3-y = 97 %[o,q];	N1: 3-y = 86 %[r];	N2: 3-y = 45 %;	NR	
		5-y = 95 %[o,q]	5-y = 80 %[r]	5-y = 39 %		
Karpeh [18]	< 15 LNs: 286 pts (27.6 %)	NR	Md-N1 = 1.92 y[s]	Md-N2 = 1.02 y[t]	NR	< 0.01[s,t]
	≥ 15 LNs: 752 pts (72.4 %)	NR	Md-N1 = 3.85 y[s]	Md-N2 = 1.87 y[t]	Md-N3 = 1.05 y	
Liu [43]	< 15 LNs: 208 pts (53.1 %)	5-y N0: 50.6%[u]	5-y N1: 36.9 %[v]		NR	NS[u,v]
	15–25 LNs: 125 pts (31.9 %)	5-y N0: 58.1 %[u]	5-y N1: 36.9 %[v]		NR	
	> 25 LNs: 59 pts (15.1 %)	5-y N0: 64.3 %[u]	5-y N1: 36.9 %[v]		NR	

Table 8 continued

Study	N	N0	N1	N2	N3	Significance (*P*)
Marchet [45]	≤ 15 LNs: 432 (23.3 %)	5-y N0: 74.3 %[w]	5-y N1: 44.3 %[x]	5-y N2: 14.7 %[y]	NR	0.002[w]
	> 15 LNs: 1421 (76.7 %	5-y N0: 83.4 %[w]	5-y N1: 54.3 %[x]	5-y N2: 32.7 %[y]	NR	0.01[x]
						0.004[y]
Scartozzi [47]	≤ 25 LNs: 306 (73.2 %)	N+ pts: 4.27 y[z]				
		N - pts: 0–6 LNs assessed: 2 y[aa]; 7–15 LNs assessed: 6.3 y[aa]; 16–22 LNs assessed: not reached[aa]; >22 LNs assessed: not reached[aa]				0.0316[Z]
						0.0032[aa]
	> 25 LNs: 112 (26.7 %)	N+ pts: 7. 03 y[z]				
Shen [48]	≤ 30 LNs: 432 (22.8 %)	10-y T3N0: 55.4 %[bb]	10-y T3N1: 53.7 %[cc]	5-y T3N2: 29.9 %[dd]	NR	NS[bb,cc]
	> 30 LNs: 1463 (77.2 %)	10-y T3N0: 65.8 %[bb]	10-y T3N1: 53.3 %[cc]	5-y T3N2: 38.8 %[dd]	NR	0.027[dd]
Xu [50]	≤ 15 LNs: 729 pts (80.5 %)	5-y N0: 75.4 %[ee]	5-y N1: 36 %[ff]	5-y N2: 17.5 %[gg]	NR	0.02[ee]
						0.027[ff]
	> 15 LNs: 177 pts (19.5 %)	5-y N0: 84.3 %[ee]	5-y N1: 50 %[ff]	5-y N2: 33.3 %[gg]	5-y N3: 14.3 %	0.036[gg]

LN lymph node, *Md* median, *NS* not significant, *NR* not reported

will occur [25, 36, 37, 39, 40]. With the exception of the article by Liu et al. [43], which examined T2b cancers only, all of the studies which examined survival by N stage found a significant difference when more LNs were assessed, likely the effect of stage migration [18, 24, 30, 31, 38, 39, 45, 47, 48, 50].

The effect of stage migration is most striking when fewer than 10 LNs are assessed [23, 35], but continues with even greater numbers of LNs examined [23, 55]. For example, 45 % of nodes were found to be positive when only 10 or fewer were examined compared with 17 % positive if more than 40 LNs were examined [55]. Bouvier et al. [55] estimate that the risk of misclassification is 47.1 % when fewer than 10 LNs are examined, while Bando et al. report that 45 % of patients with LN involvement would have been understaged if a D1 LN dissection had been performed [56].

A linear regression analysis by Smith et al. [23] showed a statistically significant observation in which one positive node was found for each additional five nodes that were examined. Furthermore, using a model-predicted 5-year survival with only one LN examined as a baseline, Smith et al. [23] found that for every 10 extra LNs dissected, the calculated overall survival improved by 7.6 % for T1/2N0 patients, 5.7 % for T1/2N1 patients, 11 % for T3N0 patients, and 7 % for T3N1 patients. Schwarz et al. [25] performed a similar analysis using a model-predicted 3-year survival with a baseline of 0 LNs examined, and found that for every 10 extra LNs assessed, the calculated overall survival (OS) increased by 5.7 % for T2b–3N2 patients, 4.6 % for T2b–3N3 patients, and 5.9 % for the entire cohort, with differences found for up to 40 LNs assessed. However, as the analysis was performed based upon the N stage of the patients, stage migration may explain much of these findings.

It is not surprising that many studies found no statistically significant survival effects for N3 cancers (Table 7), as dissection of more LNs will not put the patient into a higher staging category, and, in order to achieve an N3 stage (by the 5th/6th edition of the UICC/AJCC staging manual), a minimum of 16 LNs were assessed. Some authors have postulated that improved survival for N3 patients should not occur through stage migration, as there is no worse stage from which the patients can migrate. Huang et al. [39] found an apparent survival benefit from more LNs dissected and assessed, and attributed this to the removal of additional cancer burden. However, a patient found to be N3b by virtue of having 16 positive nodes of 16 LNs assessed may have many more positive nodes and thus poorer prognosis than a patient with 16 positive nodes out of 50 nodes assessed. Therefore, the stage migration effect is possible even within this group of poor prognosis patients.

Table 9 Combined TN stage survival rates associated with the number of LNs assessed

Study	N	Survival by combined TN stage		Significance
Schwarz [25]	7–9 LNs:	3-years T2bN2: 10 % 3-years T2bN3: – 3-years T3N2: 4 % 3-years T3N3: –	3-years T2b–3N2: 8 % 3-years T2b–3N3: – 3-y T2b–3N2–3: 8 %	For T2b–3N2: <15 LNs vs. ≥15 LNs: 3-years = 10 vs. 25 %, $P < 0.0001$; <20 LNs vs. ≥20 LNs: 3-years = 10 vs. 22 %, $P < 0.0001$; <25 LNs vs. ≥25 LNs: 3-years = 15 vs. 30 %, $P < 0.0001$; <30 LNs vs. ≥30 LNs: 3-years = 15 vs. 30 %, $P = 0.0014$; for T2b–3N3: <30 LNs vs. ≥30 LNs: 3-years = 5 vs. 15 %, $P = 0.0066$; <40 LNs vs. ≥40 LNs: 3-years = 7 vs. 10 %, $P = 0.0339$
	10–15 LNs:	3-years T2bN2: 14 % 3-years T2bN3: – 3-years T3N2: 9 % 3-years T3N3: –	3-years T2b–3N2: 12 % 3-years T2b–3N3: – 3-years T2b–3N2–3: 12 %	
	16–19 LNs:	3-years T2bN2 21 % 3-years T2bN3 4 % 3-years T3N2: 18 % 3-years T3N3: 8 %	3-years T2b-3N2: 20 % 3-y T2b-3N3: 5 % 3-years T2b-3N2–3: 18 %	
	20–24 LNs:	3-years T2bN2: 23 % 3-years T2bN3: 11 % 3-years T3N2: 18 % 3-years T3N3: 0 %	3-years T2b-3N2: 21 % 3-years T2b-3N3: 6 % 3-years T2b-3N2–3: 15 %	
	25–29 LNs:	3-years T2bN2: 41 % 3-years T2bN3: 4 % 3-years T3N2: 11 % 3-years T3N3: 8 %;	3-years T2b–3N2: 31 % 3-years T2b–3N3: 6 % 3-years T2b-3N2–3: 18 %	
	30–39 LNs:	3-years T2bN2: 23 % 3-years T2bN3: 9 % 3-years T3N2: 52 % 3-years T3N3: 18 %;	3-years T2b-3N2: 37 % 3-years T2b-3N3: 13 % 3-years T2b–3N2–3: 24 %	
	≥ 40 LNs:	3-years T2bN2: 27 % 3-y T2bN3: 13 % 3-years T3N2: 27 % 3-years T3N3: 13 %	3-years T2b–3N2: 22 % 3-years T2b–3N3: 12 % 3-years T2b-3N2–3: 17 %	
Siewert [5]	≤25 LNs: 558 pts (33.7 %)	T1N0: 5-years = 81.4 %[b]; 10-years = 73.9 %[b] T2N0: 5-years = 68.1 %[d]; 10-years = 48.0 %[d] T2N1: 5-years = 27.9 %[f]; 10-years = 17.6 %[f] T2N2: 5-years = 25.4 %[h]; 10-years = 21.1 %[h] T4N0: 5-years = 0 %[j]; 10-years = 0 %[j] T2N2: 5-years = 20.7 %[l]; 10-years = 12.4 %[l]	T1N1: 5-years = 75.0 %[c]; 10-years = 75.0 %[c] T1N2: 5-years = 66.7 %[e]; 10-years = 0 %[e] T3N0: 5-years = 26.3 %[g]; 10-years = 26.3 %[g] T3N1: 5-years = 24.6 %[i]; 10-years = 13.1 %[i] T4N1: 5-years = 0 %[k]; 10-y = 0 %[k]	P = NS[b,c,d,e,i,k,l] $P = 0.0037$[f] $P = 0.005$[g] $P = 0.032$[h] $P = 0.0006$[j]
	>25 LNs: 1,096 pts (66.3 %)	T1N0: 5-years = 84.3 %[b]; 10-years = 70.1 %[b] T2N0: 5-years = 66.5 %[d]; 10-years = 54.8 %[d] T2N1: 5-years = 51.1 %[f]; 10-years = 44.9 %[f] T2N2: 5-years = 36.2 %[h]; 10-years = 21.3 %[h] T4N0: 5-years = 42.9 %[j]; 10-years = 28.6 %[j] T2N2: 5-years = 13.5 %[l]; 10-years = 9.8 %[l]	T1N1: 5-years = 83.3 %[c]; 10-years = 83.3 %[c] T1N2: 5-years = 82.9 %[e]; 10-years = 82.9 %[e] T3N0: 5-years = 53.1 %[g]; 10-years = 44.1 %[g] T3N1: 5-years = 21.2 %[i]; 10-years = 14.5 %[i] T4N1: 5-years = 12.5 %[k]; 10-years = 12.5 %[k]	

Table 9 continued

Study	N	Survival by combined TN stage		Significance
Smith [23]	1–9 LNs: 2,143 pts (56.5 %)	5-years T1/2N0: 61 % (95 % CI 57–66)	5-years T3N0: 33 % (95 % CI 29–37)	For <10 LNs vs. ≥10 LNs: T1/2N0: $P = 0.002$
		5-years T1/2N1: 33 % (95 % CI 25–40)	5-years T3N1: 14 % (95 % CI 12–17)	T1/2N1: $P < 0.0001$
				T3N0: $P < 0.0001$
				T3N1: $P < 0.0001$
	10–19 LNs: 1,153 pts (30.4 %)	5-years T1/2N0: 67 % (95 % CI 61–74)	5-years T3N0: 50 % (95 % CI 43–57)	For <15 LNs vs. ≥15 LNs: T1/2N0: $P = 0.0048$
		5-years T1/2N1: 51 % (95 % CI 41–61)	5-years T3N1: 25 % (95 % CI 20–29)	T1/2N1: $P = 0.001$
				T3N0: $P < 0.001$
	20–29 LNs: 215 pts (5.7 %)	5-years T1/2N0: 71 % (95 % CI 60–83)	5-years T3N0: 56 % (95 % CI 43–68)	T3N1: $P < 0.001$
		5-years T1/2N1: 65 % (95 % CI 50–80)	5-years T3N1: 33 % (95 % CI: 24–42)	
	30–39 LNs: 215 pts (5.7 %)	5-years T1/2N0: 87 % (95 % CI: 74–100)	5-years T3N0: 58 % (95 % CI 37–79)	
		5-years T1/2N1: 25 % (95 % CI 0–67)	5-years T3N1: 42 % (95 % CI 26–57)	
	>40 LNs: 67 pts (1.8 %)	5-years T1/2N0: 93 % (95 % CI 79–100)	5-years T3N0: 83 % (95 % CI 62–100)	
		5-years T1/2N1: 70 % (95 % CI 41–99)	5-years T3N1: 50 % (95 % CI 30–70)	

CI confidence interval, *LN* lymph node, *NS* not significant

Survival

Many studies show a difference in OS based upon the number of LNs examined. In univariate analysis, six of eleven cohorts found no survival difference according to the number of LNs assessed [5, 31, 43–45, 50]; while others showed that there was a significantly improved survival when >10 [34], >15 [49], or >25 LNs [47] were assessed (Table 3). Volpe et al. [47, 49]and Scartozzi et al. [47, 49] attributed the survival benefit to the close association of more LNs assessed with a D2 LN dissection [47, 49]. However, these studies also found that the survival benefit was highly stage-specific (stage 2 [5, 49]; stage 3 [44]); thus, the effect of stage migration cannot be ignored. If there is a true survival effect based upon the removal of additional LNs, this could be explained by the additional removal of disease. It is therefore reasonable that no significant survival difference was found in the T1 cancers, as these cancers have a significantly lower chance of LN involvement than higher T-stage cancers [31, 50].

In order to account for the effect of stage migration and to determine whether the assessment of more LNs yields a survival benefit, many authors have utilized multivariate survival modeling, incorporating both N stage and number of LNs assessed. In most of these models, survival is associated with both variables (Table 3). An increased number of LNs assessed was found to have a hazard ratio (HR) of death of 0.635 (95 % confidence interval [CI] 0.597–0.676) [24], 0.81 (95 % CI 0.76–0.87) [42], 0.76 (95 % CI 0.61–0.95) [46], and 0.59 (95 % CI 0.39–0.89) [47], and an odds ratio (OR) of survival of 3.7 (95 % CI 1.5–8.8) [34]. However, Giuliani et al. [38, 43] and Liu et al. [38, 43] found no difference in survival outcomes by number of LNs assessed. These conflicting findings fuel the debate of whether there is a true, independent positive effect of greater number of LNs removed versus the possibility that a confounding factor exists, such as extended LN dissection, that is associated with both the increased number of LNs removed and improved survival outcomes. An additional challenge for these analyses is making the assumption that the variables N stage and number of LNs assessed are fully independent, while in reality there may be significant interactions between these two variables, which may not be fully accounted for. Of note, none of the multivariable models to date reported testing for an interaction between the number of LNs assessed and N stage. While these studies do show a statistically significant association between survival and more LNs assessed, they cannot confirm causation.

The appropriate number of LNs to assess

While many studies found a significant difference in survival when >15 LNs were assessed, most only analyzed the data utilizing the cut-off point of 15 LNs based upon the 5th/6th edition of the UICC/AJCC staging manual. Many groups have suggested that the number of LNs assessed

should vary according to stage and should be fewer than 15 LNs for early gastric cancer (EGC), and greater than 15 for more advanced cancers [30, 34, 50]. Lee et al. [29] found no significant stage migration for the stage Ia patients in their cohort based upon the number of LNs assessed. In comparison, in their analysis of EGC, Borie et al. [34] found that patients with <10 LNs assessed had significantly lower 5- and 7-year OS rates compared with patients with ≥10 LNs assessed (Table 3). Siewert et al. [5] and Volpe et al. [49] found stage migration to be most prominent in stage II patients, while Karpeh et al. [18] and Liu et al. [44] found migration in stage III patients (Table 9), suggesting that a higher cut-off point of LNs assessed should be used for accurate staging in more advanced disease in an effort to avoid stage migration.

Smith et al. [23] and Schwarz et al. [25] have stated that the AJCC/UICC minimum goal of 15 LNs appears insufficient in the context of advanced-stage cancers [23, 25]. They recommend that the minimum goal should be set to at least ten LNs above the number of positive nodes, which would require at least 25 LNs for patients with advanced nodal staging. Although other groups have suggested numbers as high as 40 LNs assessed, a goal of 25 seems reasonable, even in the context of surgery performed in North America. Paradoxically, in Western countries it may be necessary to set the recommended number of LNs for dissection and assessment higher than 15 due to the advanced presentation of disease.

Limitations

There are many limitations to the data included in this review. All of these studies were retrospective; thus, there was no standard surgical or pathology protocol. There may be inherent differences in the patients receiving an extensive versus a limited LN dissection that are also associated with survival (i.e., co-morbid status, palliative resections, positive margins, institutional factors), and therefore the potential for unreported confounders continues to exist. The evaluation of the specimen for LNs, the histological evaluation of the node and methods to detect disease are also unaccounted for and introduce further potential bias to the studies being evaluated. Finally, a bias for publication of positive results may exist, decreasing the number of statistically non-significant results reported in the literature.

Conclusion

The extent of nodal involvement continues to be one of the most important prognostic factors for GC survival. Thus, an adequate number of LNs must be assessed to ensure patients are accurately staged and optimal treatment is prescribed. Population-based studies have indicated that the number of LNs assessed in each GC case varies, and in many cases is sub-optimal. From our systematic literature review of the data, we found that increased resection, tumor location, tumor size, and TNM staging information were all associated with a greater number of LNs assessed. With respect to long-term outcomes, patients with an increased number of assessed LNs have a better prognosis; however, much of this appears to be the effect of stage migration. Although current guidelines support a minimum number of 16 LNs to be assessed for patients with GC, it is apparent that extensive dissections, nodal harvest, and pathological identification of more LNs limit the effects of stage migration. Therefore, a goal of more than 16 LNs appears to be an appropriate target for surgery and pathological analysis.

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