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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Prognostic Value of Lymph Node Yield After Neoadjuvant Chemoradiation for Gastric Cancer

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ABSTRACT

Background. Optimal lymphadenectomy (LAD) for gastric cancer (GC) after neoadjuvant chemoradiation (NACXRT) is not defined. This study assessed the prognostic value of LAD extent after modern preoperative therapy for GC.

Methods. The study analyzed patients who underwent resection after NACXRT for GC at the authors' institution. Survival of the patients was compared between D1 and D2 resections and between lymph node (LN) yields (LNY) of fewer than 15 LNs and 15 or more LNs. The patients with early clinical nodal disease (cN0-1) were separately analyzed. Kaplan-Meier survival analyses were used to assess overall survival (OS) and disease-free survival (DFS).

Results. Resection of GC was performed for 345 patients after NACXRT. Of these patients, 269 (78%) received a D2 resection, and 277 (80%) had an LNY of 15 LNs or more. There were no differences in length of stay (12[10–16] days vs. 12[10–15] days, $p = 0.917$) or in any major complication including leak rates, intraabdominal infections, and bleeding (all $p > 0.05$). There was a significant difference in DFS ($p = 0.050$) and an OS trend ($p = 0.085$) based on D1 versus D2. Those who had 15 LNs removed showed a trend toward improved survival (DFS, $p = 0.082$; OS, $p = 0.096$). Among the patients with early clinical N stage disease (cN0-1), those who underwent D2 resections had better survival (DFS, $p = 0.040$; OS, $p = 0.030$).

Conclusions. Patients with GC who underwent resection after NACXRT showed evidence of improved survival after an extended LAD, particularly those with early N stage disease. Perioperative morbidity did not differ based on extent of LAD. Despite the potential effects of tumor downstaging with preoperative therapy, a thorough locoregional lymphatic resection is recommended.

According to the current National Comprehensive Cancer Network (NCCN) guidelines, regional lymphadenectomy (LAD) for gastric cancer (GC) should include the perigastric (D1) region and the regions along the branches of the celiac axis (D2), with a total lymph node (LN) yield (LNY) of at least 15 LNs.[1–3] However, treatment for resectable GC has undergone a paradigm shift during the past 15 years as randomized studies have shown that various adjuvant therapies improve patient survival,[4–7] and thus multimodal therapy has become the standard for treatment of GC.[8,9]

Most notably, after the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated a survival benefit, the use of preoperative therapy has increased significantly in the United States, with 65% of patients who have T2+ GC undergoing preoperative chemotherapy in recent years compared with

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only 34% in 2006.[10] This shift of GC treatment to preoperative therapy even necessitated a change in the American Joint Committee on Cancer (AJCC) staging manual.[11] In addition to neoadjuvant chemotherapy, survival benefits for neoadjuvant chemoradiotherapy (NACXRT) have been shown, and NACXRT currently is the standard of care for patients with resectable locally advanced gastroesophageal junctional cancer.[12]

In a recent analysis of the National Cancer Database, NACXRT induced primary tumor complete response more frequently than chemotherapy alone for GC.[13] Currently, the international phase 3 Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) is comparing perioperative chemotherapy with perioperative chemotherapy plus NACXRT.[14]

Our institution frequently performs NACXRT before planned curative resection, with high rates of pathologic complete response, R0 resection, and long-term survival.[15] It is important to note that gastric LN stations are preoperatively identified so that the radiotherapy includes not only the primary gastric tumor, but also involved nodes and nodal regions at risk, potentially changing the effects of nodal dissection after preoperative radiotherapy.[16]

Because current guidelines are based on studies of patients who underwent upfront surgery or received neoadjuvant chemotherapy alone,[1–3] the optimal extent of LAD (D1 vs. D2) and total LNY required after NACXRT is not known. Therefore, this study aimed to assess the prognostic value of LAD extent (D1 vs. D2) and total LNY after NACXRT for GC.

METHODS

This study was conducted after the Institutional Review Board approval of the protocol. We reviewed our prospectively maintained database of GC patients treated at MD Anderson from July 1, 1995 to July 1, 2018. The patient selection and variables collected were similar to those in a previous study by our group.[17–19] Patients with primary GC, including Siewert type 3 GE junctional tumors, who underwent potentially curative gastrectomies were included in the study.

The patient and tumor characteristics collected were age, sex, race/ethnicity, primary tumor location, cT category, cN status, final yp stage according to the 8th edition of the AJCC staging manual, and histologic grade. The cN status was determined via endoscopic ultrasound (EUS). The treatment variables included use of NACXRT, type of resection, extent of LAD, and total LNY.

Extent of LAD (D1 vs. D2 dissection) was determined according to nodal stations as defined by Japanese gastric cancer treatment guidelines.[20] Notably, station 7 is defined as part of a D1 LAD according to Japanese guidelines but as part of a D2 LAD in current NCCN guidelines. As previously reported, we defined D2 LAD as removal of stations 8, 9, and 10, and our D1 LAD included removal of station 7 as part of the regional nodes.[21,22]

Preoperative chemotherapy and chemoradiation techniques at our institution also have been described previously.[17–19] For radiotherapy, the clinical treatment volume (CTV) included the primary gastric tumor, at least a 4-cm mucosal margin, involved nodes, and nodal regions at risk.

Radiation oncologists preoperatively identify gastric LN stations to aid in definition of the elective CTV for three-dimensional conformal techniques (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc radiotherapy (VMAT). In our study, the standard regimen of NACXRT used for the patients with GC was a radiation dose of 45 Gy administered concurrently with 5-fluorouracil (5-FU), most commonly after induction chemotherapy with a 5-FU-based regimen.[16] Similar neoadjuvant therapy was provided to patients with distal tumors because our phase 2 trials showed benefit of NACXRT included patients with distal tumors.[15]

About 6 to 8 weeks after the completion of NACXRT, the patients underwent restaging with CT, positron emission tomography (PET)/CT imaging, EUS, and resection. The patients who did not undergo surgery due to progression of disease or comorbidities were not included in the study.

Our standard surveillance practice is to perform follow-up assessment of 4–6 months with imaging. Due to infrequent locoregional relapse rates after curative resection, with low yield and high costs associated with rigorous surveillance, we do not perform routine endoscopic evaluation during surveillance.[23]

Data are reported as mean ± standard deviation if normally distributed or as median (interquartile range) if not. Differences were compared with Student's *t* test for parametric data and with the Mann-Whitney *U* test for nonparametric data. Categorical data were compared with Pearson chi-square. If cell counts were lower than 5, Fisher's exact test was used. Kaplan-Meier survival analyses were used to examine effects on overall survival (OS) and disease-free survival (DFS). Survival of the patients was compared between D1 and D2 resections and between lymph node (LN) yields (LNY) of fewer than 15 LNs and 15 or more LNs. The patients with early clinical nodal disease (cN0-1) were separately analyzed.

A multivariate Cox regression analysis was performed to confirm any survival associations identified via univariate analysis. Propensity scores were assigned based on a logistic regression model for predicting whether a patient would undergo an extended LAD using patient and tumor

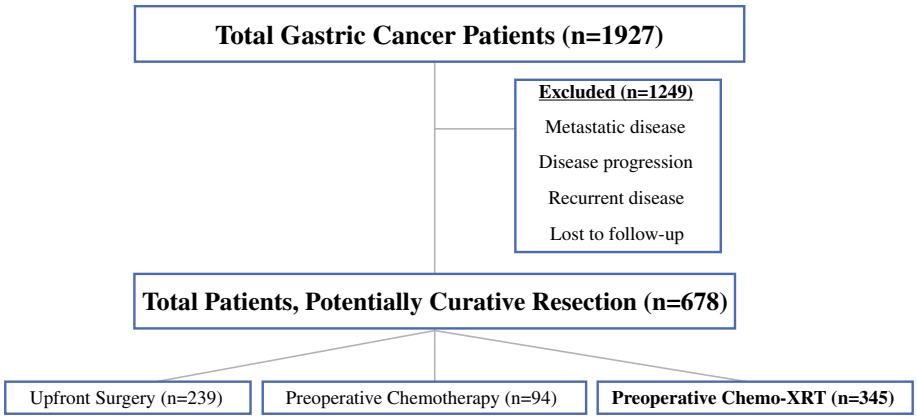

FIG. 1 All patients treated for gastric cancer (n = 1927), treatment algorithm

characteristics (e.g., age, sex, race, tumor histology). A 1:1 fixed-ratio nearest-neighbor matching was performed to minimize bias without sacrificing power.[24] Only the patients who underwent an R0 resection were matched. Comparisons between propensity-matched cohorts were performed.

Significance was determined by a p value lower than 0.05. Statistical analyses were performed using SPSS version 24 (IBM Corporation; Armonk, NY, USA).

RESULTS

The patient selection for the study is demonstrated in Fig. 1. Of 1927 patients in our institutional GC database, 678 underwent potentially curative gastrectomies, and a total of 345 underwent resection after NACXRT. The age of the patients was 61 ± 13 years. Of the 345 patients, 217 (63%) were male, 188 (55%) were white, and 203 (59%) underwent total gastrectomy.

The variability of radiation delivery to the patients in this cohort was low. Only 13 patients received less than 40 Gy of the planned 45 Gy due to toxicities and/or logistical reasons. Of the 345 patients, 269 (78%) received a D2 resection and 277 (80%) had ≥15 total LNY.

Comparison of the D1 and D2 cohorts showed differences between sex and race but no significant differences based on histology or preoperative T or N stage (Table 1). As expected, the patients who underwent a D2 resection more often had more than the recommended 15 nodes resected (84% vs. 67%; p = 0.002). Although differences in perioperative complication rates between patients undergoing D1 and D2 have been assessed in various trials, our analysis showed no differences in length of stay (12[10–16] days vs. 12[10–15] days, p = 0.917) and no other major complications including leak rates, intraabdominal infections, and bleeding (all $p > 0.05$). The final AJCC disease stage did not differ between the groups based on D1/D2 or total LNY (all $p > 0.05$). The rates of complete pathologic response (ypT0, ypN0) were similar (nearly 20%) between those who underwent D1 and those who had D2, as well as similar overall final pathological T and N stage (Table 1).

The Kaplan-Meier survival analysis showed a significant difference in DFS and in an OS trend between the cohorts based on D1 versus D2 LAD (Table 1; Fig. 2a and b). When the population was assessed based on the number of LNs resected, a survival trend was observed among those who had the recommended 15 LNs removed during gastrectomy (Fig. 2c and d). Among the patients with early clinical N stage (cN0-1), those who had D2 resections showed improved 5-year OS and DFS (Fig. 2e and f). A multivariate Cox regression analysis confirmed the survival association of D2 in early N stage patients (p = 0.034; Fig. S1).

Although our D1 and D2 populations were relatively similar, to control for differences in baseline characteristics, propensity scores were assigned, and patients were matched using the aforementioned methods. As depicted in Table 2, the cohorts were effectively similar in terms of age, sex, race, histology, and preoperative stage after propensity score matching. Still, we identified a survival trend in those who had a D2-extended LAD (Fig. 3a and b).

In our index cohort, 128 tumors (37.1%) were isolated to the distal stomach. The rates of D2 LAD were similar between proximal and distal gastric tumors (79.3% vs. 75.8%; p = 0.502). The patients exhibited similar numbers of LNs examined (25 ± 12 vs. 23 ± 11; p = 0.148) and similar positive LN ratios (0.8 ± 0.18 vs. 0.6 ± 0.15; p = 0.308) when proximal and distal tumors were compared. Both populations of patients with proximal and distal tumors showed a survival trend for D2 LAD (Fig. S2).

TABLE 1 Patients who underwent resection for gastric cancer after neoadjuvant chemoradiation (n = 345), with comparison of subgroups based on extent of lymphadenectomy

		D1 (n = 76)	D2 (n = 269)	p Value
Age (years)		62 ± 10	61 ± 12	0.356
Male		75.0%	59.5%	0.015
Race	White	60.5%	52.8%	0.019
	Hispanic	11.8%	15.2%	
	Black	7.9%	6.3%	
	Other	19.8%	25.6%	
Histology	Well-differentiated adenocarcinoma	1.3%	0.0%	0.152
	Moderately differentiated adenocarcinoma	30.7%	21.6%	
	Poorly differentiated adenocarcinoma	61.3%	70.6%	
	Other	6.7%	7.8%	
Signet ring cells		40.8%	51.5%	0.119
Linitis plastica		5.4%	6.1%	1.000
EUS T stage	cT0/cTis	0.0%	0.4%	0.948
	cT1	0.0%	0.4%	
	cT2	11.8%	13.4%	
	cT3	75.0%	70.7%	
	cT4	11.8%	13.4%	
	cTx	1.5%	1.3%	
EUS N stage	cN0	41.2%	43.5%	0.415
	cN1	50.0%	40.6%	
	cN2	2.9%	9.2%	
	cN3	1.5%	2.1%	
	cNx	4.4%	4.6%	
Procedure performed	Total gastrectomy	52.6%	60.6%	0.283
	Subtotal/distal gastrectomy	40.8%	36.1%	
	Proximal gastrectomy	6.6%	3.3%	
Lymphadenectomy (15 or more LNs)		67.1%	84.0%	0.002
Mean LNs removed		22 ± 13	25 ± 11	0.570
Mean LN ratio		0.10 ± 0.21	0.07 ± 0.16	0.259
Median length of stays (days)		12 (10–16)	12 (10–15)	0.917
Complication	Wound	27.6%	21.2%	0.277
	Intraabdominal infection	13.2%	10.8%	0.543
	Leak	6.6%	6.7%	1.000
	Respiratory	14.5%	13.0%	0.706
	Renal	2.6%	1.5%	0.617
	Cardiac	5.3%	5.6%	1.000
	Anemia	5.3%	1.9%	0.112
	Other	7.9%	9.7%	0.823
ypT stage	ypT0/Tis	19.7%	18.2%	0.705
	ypT1	21.0%	13.4%	
	ypT2	14.5%	20.4%	
	ypT3	31.6%	38.7%	
	ypT4	11.8%	8.6%	
ypN Stage	ypN0	60.5%	63.2%	0.529
	ypN1	21.1%	21.6%	
	ypN2	11.8%	8.6%	
	ypN3	6.6%	6.7%	
DFS	Median DFS: months	30 (20–40)	94 (54–132)	0.050
	5-Year DFS	32.6%	54.6%	
OS	Median OS: months	40 (25–55)	95 (58–131)	0.085
	5-Year OS	35.1%	58.8%	

EUS endoscopic ultrasound, *LN* lymph node, *DFS* disease-free survival, *OS* overall survival

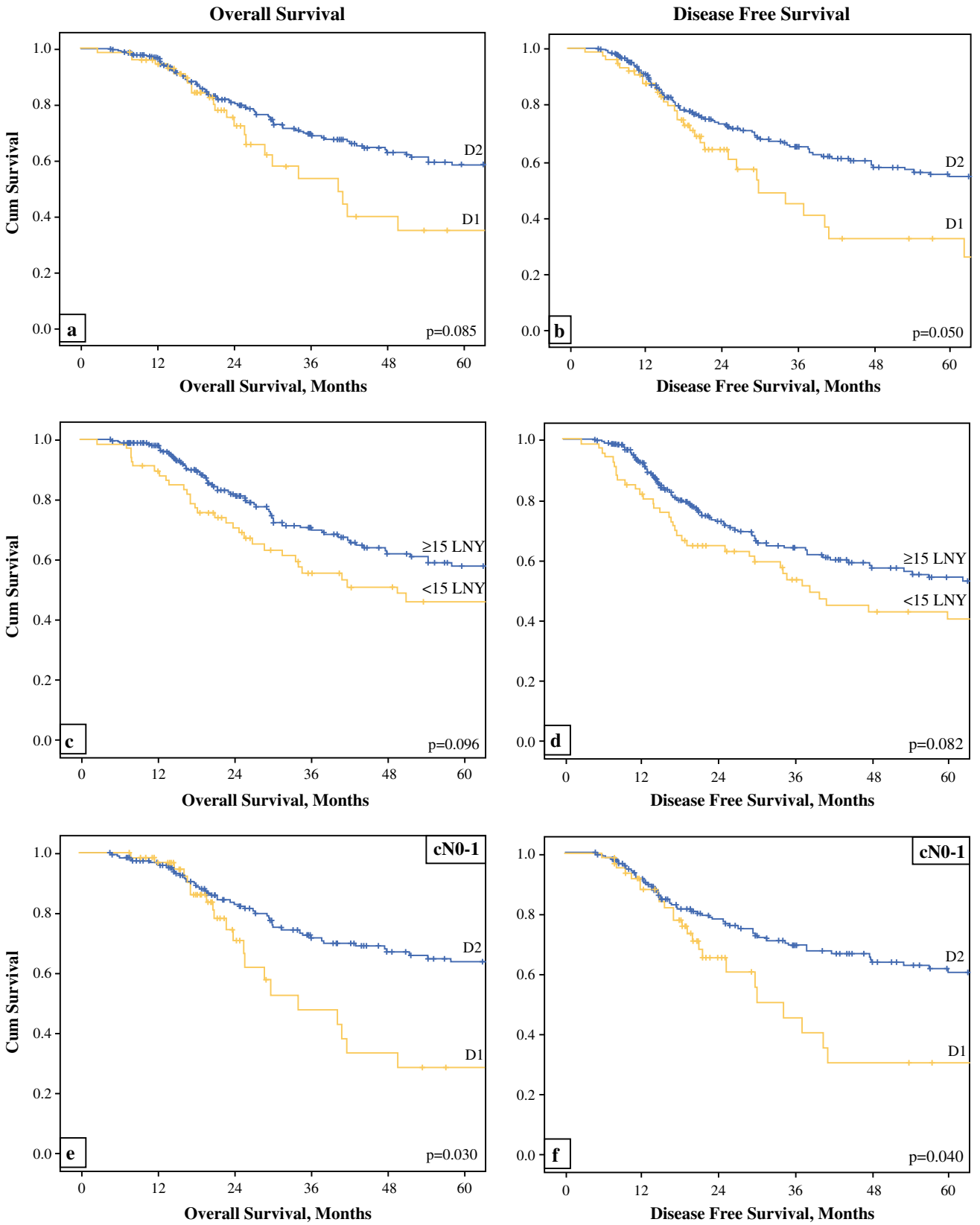

FIG. 2 Kaplan–Maier survival analyses ($n = 345$). **a** Overall survival: D1 versus D2. **b** Disease-free survival: D1 versus D2. **c** Overall survival: LNY $<$ 15 versus $\geq$ 15. **d** Disease-free survival: LNY $<$ 15 versus $\geq$ 15. **e** Overall survival: D1 versus D2, cN0-1. **f** Disease-free survival: D1 versus D2, cN0-1. *LNY* lymph node yield

TABLE 2 Patients who underwent resection for gastric cancer after neoadjuvant chemoradiation (n = 102), with comparison of propensity score-matched subgroups

		D1 (n = 51)	D2 (n = 51)	p Value
Age (years)		62 ± 10	63 ± 12	0.514
Male		72.5%	72.5%	1.000
Race	White	60.8%	64.7%	0.908
	Hispanic	9.8%	7.8%	
	Black	3.9%	2.0%	
	Other	25.4%	25.4%	
Histology	Well differentiated	2.0%	0.0%	0.666
	Moderately differentiated	27.5%	23.5%	
	Poorly differentiated	62.7%	64.7%	
	Other	7.8%	11.8%	
Signet ring cells		41.2%	51.0%	0.427
Linitis plastica		6.0%	6.1%	1.000
EUS T stage	cT0/cTis	0.0%	2.1%	0.583
	cT1	0.0%	2.1%	
	cT2	9.1%	12.8%	
	cT3	79.5%	78.7%	
	cT4	9.0%	2.1%	
	cTx	2.3%	2.1%	
EUS N stage	cN0	34.1%	36.2%	0.335
	cN1	59.1%	44.7%	
	cN2	2.3%	8.5%	
	cN3	0.0%	4.3%	
	cNx	4.5%	6.4%	
Mean LNs removed		17±12	21±8	0.116
Mean LN ratio		0.13 ± 0.25	0.08 ± 0.19	0.286
Median length of stays (days)		12 (10–19)	13 (10–18)	0.543
ypT stage	ypT0/Tis	23.5%	15.7%	0.406
	ypT1	21.6%	15.7%	
	ypT2	11.8%	21.6%	
	ypT3	25.5%	35.3%	
	ypT4	15.7%	9.8%	
ypN stage	ypN0	56.9%	64.7%	0.246
	ypN1	27.5%	21.6%	
	ypN2	5.9%	7.8%	
	ypN3	9.8%	5.9%	
DFS	Median DFS: months	30 (16–62)	44 (25–135)	0.163
	5-Year DFS	28.6%	45.9%	
OS	Median OS: months	34 (22–46)	86 (25–147)	0.203
	5 year OS	31.6%	53.7%	

EUS endoscopic ultrasound, *LN* lymph node, *DFS* disease-free survival, *OS* overall survival

DISCUSSION

In this single-institution, retrospective study, the patients with GC undergoing resection after NACXRT had evidence of improved survival after an extended LAD, particularly those with early N stage disease. Perioperative morbidity did not differ based on extent of LAD. Despite the potential effects of tumor downstaging with preoperative therapy, a thorough locoregional lymphatic resection is recommended.

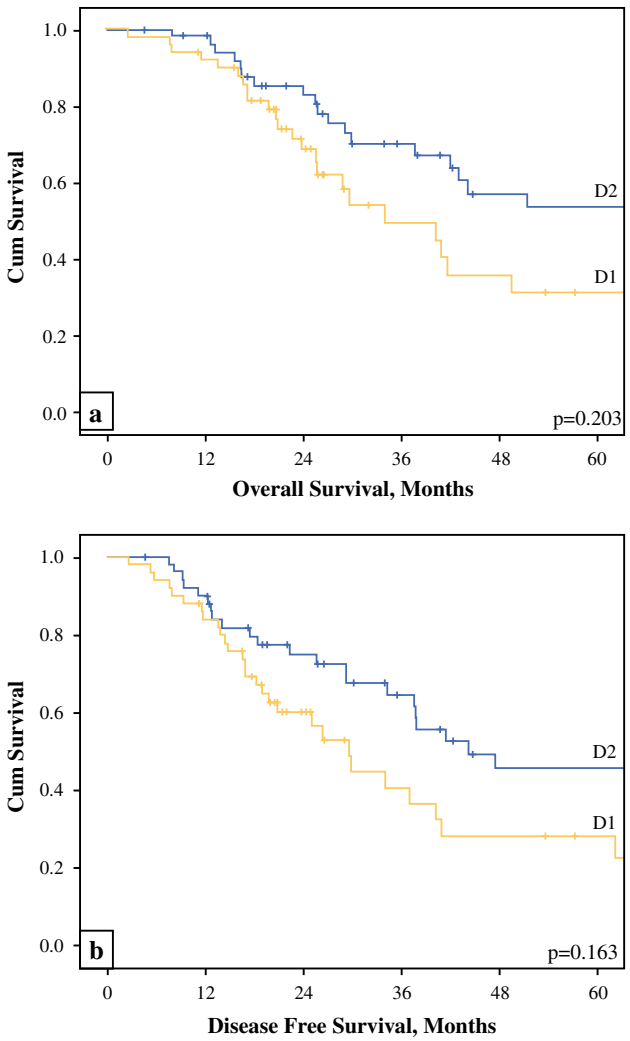

FIG. 3 Kaplan–Maier survival analyses of propensity-matched cohorts (n = 102). **a** Overall survival: D1 versus D2. **b** Disease-free survival: D1 versus D2

At our institution, we often provide NACXRT to various patient populations being considered for curative resection. An important goal of preoperative chemoradiation is to reduce the primary tumor volume to facilitate surgery and increase R0 resection rates, thus resulting in a low local recurrence rate. Other theoretical benefits include a treatment effect on micrometastatic disease and a decrease in the ability of tumor cells to spread at the time of surgical resection. Moreover, patients with aggressive disease biology, who are unlikely to benefit from surgical resection, often progress through neoadjuvant therapy and thus avoid a morbid operation that offers them no survival benefit.[25] In addition, although multimodal treatment clearly is beneficial for patients with GC, adjuvant therapy is delivered only to about 50% of patients after gastrectomy, whereas preoperative therapy is more reliably delivered and may be better tolerated.[26] Finally, a pathologic evaluation of the response to preoperative treatment may offer important prognostic information as well as help with selection of additional therapies.[27]

Beyond our own institutional use of neoadjuvant therapy for GC, support for this strategy also is building internationally. The Dutch ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial showed a survival benefit of NACXRT for patients with esophageal and esophagogastric cancers compared with the use of surgery alone. This study also showed a 29% incidence of pathologic complete response in the NACXRT group.[12] Whereas only a portion of those enrolled in the CROSS trial had GC, several phase 2 clinical trials have demonstrated the safety and efficacy of NACXRT in populations of only GC patients, again showing similarly high incidences (20–30%) of pathologic complete response.[28–30]

The addition of radiation to chemotherapy has been shown to improve primary tumor and nodal downstaging in single-institution and phase 2 single-arm trials.[15,28–30] However, a benefit based on comparative analysis remains to be demonstrated in large randomized phase 3 trials.

Further complicating the issues of radiation efficacy in GC, radiation fields and technique used in NACXRT vary by institution in the United States. The international, multicenter TOPGEAR trial[14] is a currently ongoing phase 3 study comparing survival of patients with resectable gastric or gastroesophageal adenocarcinoma receiving preoperative chemotherapy or NACXRT. This trial, in addition to other trials such as the ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach (CRITICS-II), should offer high-quality data for a better resolution of the questions surrounding the efficacy of preoperative radiation for GC.[31]

The debate surrounding neoadjuvant therapy for GC remains unsettled, and the debate surrounding extent of LAD in GC has been ongoing for years. A randomized Dutch study showed no significant survival benefit of D2 over D1 LAD for patients with GC due to an increase in perioperative mortality in the D2 group.[1,32] In contrast, a more recent Italian trial showed that with the elimination of pancreaticosplenectomy, short-term or perioperative mortality rates did not differ between patients undergoing D1 and D2 LAD, but the subgroup analysis showed a long-term survival benefit with D2 LAD.[33,34] These studies offer some guidance for patients who undergo a surgery-first approach, but to date few data exist to guide LAD after neoadjuvant therapy. Given the increased popularity and use of neoadjuvant therapy, this is an important knowledge gap. Our results support the association of D2 LAD with improved survival after preoperative therapy for GC. Additionally, in our current study, perioperative complications did not differ based on the extent of LAD. Based on interpretation of the randomized clinical trials, current

national guidelines, and our own institutional results, we routinely perform a D2 LAD and recommend this as best practice for others.[22]

Our study had several limitations. Numerous measurable and likely immeasurable differences between the patients who received D1 and D2 resections likely contributed to bias between the two experimental cohorts that could not be completely controlled with advanced multivariate statistics. Decisions whether to perform a D1 or a D2 resection were dependent on surgeon preference.

As mentioned earlier, our D2 LAD is defined as removal of stations 8, 9, and 10, whereas our D1 LAD is defined as regional nodes including station 7, which differs slightly from current NCCN guidelines.[35] However, we have shown that metastases to station 7 nodes is common, supporting our decision to align this aspect of our LN classification with the Japanese guidelines.[21] Additionally, other reasons for performing a D1 resection by our surgeons could be the perceived increased risks associated with extended LAD and the assumption of improved locoregional control from neoadjuvant therapies. Thus, a less extensive LAD may have been performed for certain patients. Our institutional preference is a routine offering of induction chemotherapy followed by chemoradiation based on our phase 2 trials and single-institution results for this approach.[15,28–30] Although this is included in the current NCCN guidelines, we acknowledge that it is unique and a limitation to the generalizability of our work. Still, a benefit based on comparative analysis remains to be demonstrated in large randomized, phase 3 trials.

Because we routinely offer chemoradiation as part of neoadjuvant therapy, not enough patients have undergone chemotherapy alone to provide an adequate comparison with NACXRT. Only a small portion of patients received less than the planned 45 Gy radiotherapy, so we were unable to compare outcomes based on radiation doses and regimens. Because NACXRT may cause fibrosis of LNs, the minimum number of LNs sufficient for adequate staging or assessment of prognosis is not known for this population. Due to the size limitation of this data set, and because the vast majority of patients had an LNY of at least 10, we were not able to perform an assessment of optimal LNY after NACXRT. Due to the limited population size, we were unable to assess stage-specific outcomes such as those for patients with advanced nodal disease. In addition, stage migration has a possible effect, which is a concern as with all retrospective comparisons of D1 and D2 dissections.

Finally, the technique used for preoperative radiation therapy changed during the course of the study period. In most cases, 3D-CRT was used before 2009 and IMRT after 2009. The extent of the radiation field also varies, but typically does not include extra-regional LNs such as paraaortic LNs or hepatoduodenal ligament LNs unless they are found to be enlarged and suspected for metastasis. Despite these limitations, this study represents the largest evaluation of the important question concerning the necessary extent of LAD after NACXRT.

In conclusion, the optimal extent of LAD after NACXRT for GC is not defined because existing trials have studied patients who have undergone upfront surgery. Despite the known benefits of preoperative therapy, our results provide further support for the current national guidelines and the practice of D2 LAD after preoperative multimodal therapy for GC. Further studies with analysis of separate LN basins will be beneficial for accurately defining the necessary extent of LN removal in patients with GC who have completed preoperative therapy.

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DISCLOSURE That the authors declares that they have no conflict of interest.

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