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Exploration of the Radiotherapeutic Clinical Target Volume Delineation for Gastric Cancer from Lymph Node Metastases

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Abstract. *Aim: To clarify the clinical target volume of regional lymph nodes (CTVn) delineation of gastric adenocarcinoma. Materials and Methods: The pattern of lymph node metastases (LNM) of a total of 1,473 patients with gastric cancer (GC) who had undergone gastrectomy and lymphadenectomy with more than 15 lymph nodes retrieved was retrospectively examined. Results: A univariate analysis showed that T stage (p<0.001), macroscopic type (p=0.001), tumor differentiation (p<0.001), maximum diameter of tumor (p<0.001) as well as cancer embolus (p<0.001) were closely associated with the rate of LNM. While by multivariate analysis, gender [odds ratio (OR=0.687, p<0.05], maximum diameter (OR=1.734, p<0.001), tumor differentiation (OR=1.584, p<0.001), T stage (OR=2.066, p<0.001) and cancer embolus (OR=4.912, p<0.001) were strongly associated with the rate of LNM. Conclusion: In conclusion, for male patients with GC with large, deeply invasive, poorly differentiated, diffusely infiltration and positive cancer embolus, the radiation fields should be enlarged appropriately.*

As the fourth most common type of cancer worldwide, an estimated 1,000,000 new cases are diagnosed with gastric cancer (GC) each year (1). Despite a steadily declining incidence over the past several decades, particularly in North America and Europe, GC still ranks high, worldwide, with regard to mortality rates among tumor sites (2). At present, R0 resection (no cancer at resection margins) resection is widely accepted as the only radical and standard treatment for GC, and offers excellent long-term survival for early GC. However, for quite a number of patients with advanced GC, the results of surgery are generally unsatisfactory. Indeed, for the majority of patients with GC, a radical resection cannot be performed due to locoregional tumor extent. Alternatively, the growing popularity of multimodality treatments has added to the debate of the role and the optimal extent of surgery. Radiotherapy (RT), as a local treatment, is one of the most important methods of GC treatment, especially for advanced GC. Based on analysis of the pattern of failure after curative surgery (3-7), the target volume of RT included the tumor bed, resection margins, anastomosis site, duodenal stump, and regional lymph nodes in most RT studies of GC. Among them, regional lymph nodes have raised increasing alarm and attention. Certain studies have shown that the lymph node ratio and lymph node status are the most important prognostic factors in patients with resected GC (8, 9). However, at present, there are no general recommendations on the optimal delineation of lymph node regions which are included in the clinical target volume (CTVn) for GC patients. In this study, the implication of lymph node metastases (LNM) in patients with gastrectomy and its impact on CTVn delineation in GC were investigated.

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Patients and Methods

Ethics statement. The current study was approved by the Institutional Review Boards of Yantai Yuhuangding Hospital (201493) and Academy of our Medical Sciences.

Patients. From a total of 3,752 patients diagnosed with GC who had undergone gastrectomy at the Department of General Surgical Oncology at Yantai Yuhuangding Hospital from January 2002 to December 2013, 1,473 patients who conformed to the standard set were retrospectively analyzed. Eligibility criteria included: (a) patients with complete history, physical examination, and endoscopy of the upper gastro-intestinal tract along with computed tomography (CT) of the chest and ultra-sonography or CT of the abdomen, with/without positron-emission tomography (PET) that had been performed to stage and evaluate the resectability of GC; (b) histologically confirmed R0 gastric resection (negative resection margins, en bloc resection of

adherent organs, and en bloc resection of greater and lesser omentum) and pathological evaluation of the total number of resected lymph nodes (≥15) as well as the number of metastatic lymph nodes; and (c) informed consent obtained before treatment. Clinical data of enrolled patients including sex, age, tumor location, macroscopic type, stage of disease, maximum diameter of tumor, tumor differentiation, the number of regional lymph nodes examined, the number of metastatic regional lymph nodes and the status of cancer embolus were recorded. Patient characteristics are shown in Table I.

Pathologic analysis and lymph node classification. The TNM and G staging were performed according to National Comprehensive Cancer Networks (NCCN) Guidelines Version 1.2013 GC (10). Macroscopic type and classification of the lymph nodes were in accordance with Japanese classification of GC (11). The stomach was defined upper, middle, and distal sections through dividing the lesser curvature and the greater curvature into three equal parts by two lines. Accordingly, GC was defined as upper, middle and lower tumor. If a tumor location was situated across two or more areas, it fell into the category of whole GC.

The clinicalopathological factors that may influence LNM, such as sex, age, tumor location, maximum diameter of tumor, T stage, G stage, macroscopic type and the status of cancer embolus, were statistically analyzes. All parameters were analyzed with respect to their relationship with LNM by chi-square test. For multivariate analysis, the forward step-wise procedure was performed using a binary logistic regression model. The *p*-values of less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (SPSS 18.0 software package; SPSS, Chicago, IL, USA).

Results

Clinicopathological characteristics. As listed in Table I, the median age of enrolled patients was 58.0 years (range=23-87 years) with a male to female ratio of 2.92:1. Furthermore, as one of the most common complications following tumor, cancer embolus was found in 137 patients.

Relationship between tumor location and LNM. A total of 28817 lymph nodes were studied, the median number of dissected lymph nodes was 21 with a range of 15-92. LNM was found in 1203 out of the 1473 patients (81.7%). According to the site of tumor, the LNM rate was 84.3% (247/293) in upper GC cases, 82.7% (343/415) in those with middle GC, 79.3% (521/657) in those with lower GC and 85.2% (92/108) in those with whole GC (Table II).

Our results showed no statistical difference between different locations of the stomach in terms of LNM (OR=1.003, 95% confidence interval=0.841-1.195, p=0.976; Table III), which is a finding similar to that of a previous study (12). In patients with proximal GC, LNM was detected in stations 1-9, 11 and 110 with a frequency of LNM of 48.6%, 38.2%, 45.2%, 31.3%, 5.9%, 2.9%, 43.3%, 6.1%, 8.7%, 22.7% and 11%, respectively. In patients with middle GC, LNM was detected in all stations 1-16, with a frequency of 18.4%, 62.5%, 42.6%, 32.7%, 35.3%, 18.9%, 22.8%, 15.2%, 11.9%, 21.7%, 15.6%, 13.1%, 11.1%, 4.4%, 3.0% and 22%, respectively. For distal GC, LNM were detected in stations 1-15 with a frequency of 29.3%, 7.1%, 35%, 34.8%, 47.5%, 34.2%, 19.7%, 20.6%, 12.5%, 24.1%, 11.8%, 15.9%, 7.5%, 14.5%, and 18.9%, respectively. Generally, stations 3 and 4 were relatively high-incidence stations for all locations of tumors. Further subgroup nodal involvement by site has been listed in Table IV.

Clinicopathological factors associated with LNM. T-Stage (p<0.001), macroscopic type (p=0.001), tumor differentiation (p<0.001), maximum diameter of tumor (p<0.001) as well as cancer embolus (p<0.001) were significantly associated with LNM by univariate analysis (Table II). While by multivariate analysis, sex (OR=0.687, p<0.05), maximum diameter

Table I. *Clinicopathological features of 1473 patients with gastric cancer.*

Characteristic		Patients	
		No	%
Gender	Male	1097	74.5
	Female	376	25.5
Age	≤60 Years	848	57.6
	<60 Years	625	42.4
Tumor location	Upper third	293	19.9
	Middle third	415	28.2
	Lower third	657	44.6
	Whole GC	108	7.3
Maximum diameter (cm)	≤3.0	280	19
	3.1-6.0	713	48.4
	>6.0	480	32.6
T-Stage	T1	98	6.7
	T2	97	6.6
	T3	191	12.9
	T4	1087	73.8
N-Stage	N0	270	18.3
	N1	237	16.1
	N2	356	24.2
	N3	610	41.4
G-Stage	G1	80	5.4
	G2	3547	23.6
	G3	1042	70.7
	G4	4	0.3
Macroscopic type	1	1	0.1
	2	1015	68.9
	3	113	7.6
	4	309	21
	5	35	2.4
Cancer embolus	Positive	137	9.3
	Negative	1336	90.7
LNM	Positive	1203	81.7
	Negative	270	18.3

GC: Gastric cancer. TNM stage and G stage were performed according to NCCN Guidelines Version 1.2013 Gastric Cancer (10). Macroscopic type and the classification of the lymph nodes were in accordance with the Japanese Classification of Gastric Carcinoma (11).

Table II. *Univariate analysis of the clinicopathological factors related to lymph node metastases.*

Factor	Subgroup	Positive nodes, n	Negative nodes, n	Chi-square	*p*-Value
Gender	Male	908	189	3.481	0.062
	Female	295	81		
Age	≤60	688	160	0.386	0.534
	>60	515	110		
Tumor location	Upper third	247	46	4.978	0.173
	Middle third	343	72		
	Lower third	521	136		
	Whole GC	92	16		
Maximum diameter (cm)	≤3.0	169	111	109.448	<0.001
	3.1-6.0	604	109		
	>6.0	430	50		
T-Stage	T1	37	61	213.201	<0.001
	T2	51	46		
	T3	155	36		
	T4	690	127		
Tumor differentiation	G1	53	27	29.048	<0.001
	G2	262	85		
	G3-4*	888	158		
Macroscopic type	1	1	0	20.006	<0.001
	2	806	209		
	3	102	11		
	4	270	39		
	5	24	11		
Cancer embolus	Positive	129	8	15.742	<0.001
	Negative	1074	262		

GC: Gastric cancer. *Only three out of the 1,473 cases were diagnosed as undifferentiated, G3 was combined with G4 according to the principle of Chi-square test to complete the test.

Table III. *Multivariate analysis of the clinicopathological factors related to rate of lymph node metastases in 1473 patients with gastric cancer.*

Variable	B	S.E	Waal's	*p*-Value	OR	95% CI	
						Lower	Upper
Sex	–0.375	0.168	5.002	0.025	0.687	0.495	0.955
Age	–0.009	0.154	0.003	0.954	0.991	0.733	1.341
Maximum diameter	0.551	0.115	22.828	0.000	1.734	1.384	2.174
Location of tumor	0.003	0.090	0.001	0.976	1.003	0.841	1.195
Macroscopic type	0.017	0.089	0.037	0.847	1.017	0.855	1.211
Tumor differentiation	0.460	0.119	15.051	0.000	1.584	1.256	1.999
T-Stage	0.725	0.076	92.299	0.000	2.066	1.782	2.395
Cancer embolus	1.592	0.409	15.169	0.000	4.912	2.205	10.941
Constant	–2.894	0.577	25.173	0.000	0.055		

SE: Standard error; CI: confidence interval; OR: odds ratio.

(OR=1.734, $p<0.001$), tumor differentiation (OR=1.584, $p<0.001$), T-stage (OR=2.066, $p<0.001$) and cancer embolus (OR=4.912, $p<0.001$) were strongly associated with LNM (Table III).

Not completely consistent with the previous studies (12, 13), our results showed that sex, tumor differentiation and cancer embolus also had an effect on LNM. It is interesting to note that the percentage of positive nodes was higher in the male group (82.8%) than in the female group (78.5%) (OR=0.687, $p=0.025$). In addition, our results still highlighted the important role of tumor differentiation in predicting LNM (OR=1.584, $p<0.001$). Noteworthy, the percentage of positive nodes was

higher in the group with poorer differentiation (G3-4, 84.9%) than in the other two groups (G1, 66.3%; G2, 75.5%) ($p<0.001$). Furthermore, the rate of LNM of patients with positive cancer embolus was 94.2%, which is much higher than that for those without cancer embolus ($p<0.001$). Overall, the higher LNM was correlated positively with male sex, deeper, larger maximum diameter tumor, with poorer differentiation, more diffuse infiltration and cancer embolus. All the above unfavorable risk factors should be taken into account while defining the CTVn of GC.

Discussion

Although the incidence is decreasing, due to more timely diagnosis and more standardized operations, the long-term survival of patients with GC remains poor. Because survival rate following curative surgery had changed little over a long period time, experts in GC have turned their efforts to new multimodal strategies. There is an increasing interest in chemoradiotherapy (CRT) in an effort to improve survival and reduce recurrence rates in patients with GC. The Intergroup 0116 (INT-0116) study, a randomized phase III trial which was conducted to compare observation *versus* adjuvant CRT following curative GC resection, showed benefit of the latter for both survival and relapse rates (14). Some other studies have also reported good outcomes of adjuvant CRT (15-20). Recently, an updated analysis of the Southwest Oncology Group-directed Intergroup Study 0116 further confirmed the benefit on overall and relapse-free survival rate from postoperative CRT (21). Furthermore, a meta-analysis of randomized trials for resectable GC implied that adjuvant RT provides an approximately 20% improvement in both disease-free and overall survival (22). On the whole, treatment including adjuvant RT in patients with GC has been universally accepted.

In RT of GC, popular 3-dimensional conformal RT and intensity-modulated RT require more accurate determination of the target volume, which is a key factor affecting curative effect. The INT-0116 and GIWP-ROG trials provided some definitive guidelines on adjuvant and neoadjuvant RT of GC (14,23). Obviously, CTVn was not appropriately considered in creating CTV in both, which may lead to the high post-RT local lymph node recurrence. However, there have been no explicit provisions on how to define CTVn. At present, clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound, computed tomography (CT), combined PET and CT, magnetic resonance imaging, and laparoscopic staging (24-26). Even so, the accuracy of CT scanning, which is the common base for RT planning, is low for nodal disease (27). According to our results, the number of macroscopically positive nodes found by imaging diagnosis (n=5627) was far less than the number of microscopically positive nodes found by pathological diagnosis (n=10145). In other words, if radiation oncologists only define the primary tumor and its invasion area according to CT examination, the RT field is not adequate and subclinical LNM may be missed. To compensate for these limitations of pre-therapeutic imaging on defining CTVn, we retrospectively examined 1,473 patients with GC who had undergone gastrectomy, and analyzed the pattern of the LNM.

Table IV. *Lymph nodes involved in each subgroup.*

Factor		Station
Depth of tumor invasion		
T1-2	M	3, 4, 7, 8,
	L	3, 4, 5, 6, 7, 8, 15
T3-4	U	1, 2, 3, 4, 5, 6, 7, 8, 11, 110
	M	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 110
	L	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17
Gender		
Male	U	1, 2, 3, 4, 7, 8, 11, 110
	M	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16
	L	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17
Female	U	1, 2, 3, 4, 7,
	M	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 15
	L	3, 4, 5, 6, 7, 8, 11, 12, 14, 15
Tumor differentiation		
G1-G2	U	1, 2, 3, 4, 7, 9
	M	1, 3, 4, 5, 6, 7, 8, 9, 11, 12
	L	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15
G3-G4	U	1, 2, 3, 4, 7, 8, 9, 11, 110
	M	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 110
	L	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17
Maximum diameter of tumor, cm		
≤3.0	U	1, 2, 3, 4, 7, 8, 110
	M	3, 4, 5, 7, 8, 9
	L	1, 3, 4, 5, 6, 7, 8, 9, 12, 14, 15
3.1-6.0	U	1, 2, 3, 4, 7, 8, 9, 11, 110
	M	3, 4, 5, 7, 8, 9, 10, 11, 12, 13
	L	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
>6.0	U	1, 2, 3, 4, 6, 7, 8, 9, 11, 110
	M	3, 4, 5, 7, 8, 9, 10, 11, 12, 13
	L	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,14, 15

U, Upper gastric cancer (GC); M, middle GC; L, lower GC.

Matzinger *et al.*, defined the guidelines for preoperative irradiation of adenocarcinomas of the stomach by performing a systematic review (23). The results from EORTC-ROG were also partly verified by Yi *et al.* (12). Both had provided a guideline about target volume irradiation of elective lymph node stations corresponding to the different localization. However, in addition to the location, there are still other aspects affecting the delineation of the CTVn, including tumor differentiation, tumor size, and depth of tumor invasion. Therefore, we carried out further subgroup analysis in our study to clarify the detail CTVn delineation in GC as much as possible.

In 2010, Yi *et al.* summarized the LNM of all stations from 875 patients with GC and gave a specific figure for each station involved by site (12). Based on this, we delineate the

CTVn when its LNM is larger than 10% in small-scale GC. Combined with the results from Bando *et al*., (8) and Matzinger *et al*., (23), the results showed that the CTVn we delineated covered most high-risk areas, without serious complications of extensive RT. Therefore, in the current study, sites with a LNM rate higher than 10%, an empirical cutoff value, were considered as high-risk and included in the CTVn of patients with GC. Tumor invasion into the gastric submucosa could cause regional LNM. Deeper tumor invasion may lead to more opportunities for tumor cells to invade lymphatic vessels and higher rates of LNM. The present study showed that the rate of LNM from GC increased with increasing T stage (37.8% in T1, 52.6% in T2, 81.2% in T3 and 88.3% in T4) which was similar to findings of previous studies (12, 28, 29). The results of the subgroup analysis suggest that radiation oncologists should design individualized radiotherapeutic CTVn for patients with GC with different tumor invasion. Accordingly, as shown in Table IV, for T3-4 upper GC, we suggest that stations 1-8, 11 and 110 should be included. Therefore, we argue for the exclusion of supra-pancreatic nodes which are included in the NCCN guidelines (10) in order to reduce radiation damage to organs at risk. In our opinion, more comprehensive coverage for middle GC with T3-4 should be considered because the bidirectional transfer probability of both sites is higher. For middle GC with T3-4, CTVn should include stations 1-16 and 110. While for middle GC with T1-2, CTVn including stations 3, 4, 8 and 7 may be adequate. With regard to the T3-4 lower GC, the CTVn should cover stations 1-12 and 14-17, whereas for T1-2 lower GC, only stations 3-8 and 15 should be included.

In addition, it is important for the radiation oncologist to recognize that tumor size should be included in the classification of disease stage. Previous studies provided some cues that tumor size was associated with depth of invasion and LNM rates (12, 30). According to tumor size (maximum diameter of tumor), we divided the patients into three groups: with tumor 3.0 cm or less, 3.1-6.0 cm, and 6.0 cm or greater with LNM rates of 60.4%, 84.7% and 89.6%, respectively. Further analysis provided some information for the delineation of CTVn of GC. For patients with upper GC with tumors measuring 3.0 cm or lesser, stations 1-4, 7, 8 and 110 should be included. In addition to these stations, for patients with tumors measuring 3.1-6.0 cm, stations 9 and 11 should also be included, as well as stations 6, 9 and 11 for tumors measuring 6.0 cm and more. For patients with middle GC with tumors measuring larger than 3.0 cm, stations 3-5 and 7-13 should be included in the CTVn. However, for patients with middle GC with tumors measuring 3.0 cm or less, stations 10-13 can be abandoned. Likewise, for patients with lower GC with tumors measuring 3.0 cm or less, the CTVn should include stations 1, 3-9, 12, 14 and 15 without stations 10, 11 and 13 which should be included in patients with lower GC with tumors measuring 3.1-6.0 cm or 6.0 cm and more.

According to our results, the incidence of LNM was significantly higher in patients with poorly differentiated tumors than in those with well-differentiated tumors (G1, 66.3%; G2, 75.5%; G3-4, 84.9%), which has been confirmed in previous studies (29, 31). In the same way, we carried out further subgroup analysis. For patients with middle GC with G3-4, stations 1, 3-13, 15, 16 and 110 should be included in the CTVn, while for G1-2, stations 1, 3-9, 11 and 12 may be enough. For patients with lower GC with G1 and G2 tumors, the CTVn should cover stations 3-12 and 15 without stations 14, 16 and 17, which should be included in G3-4 lower GC.

Our study showed that sex is also a prognostic factor for LNM, and further subgroup analysis suggest that for male patients with middle GC, the CTVn should include stations 1-13, 15 and 16, while for female cases, stations 10, 11, 13 and 16 should be abandoned. For female lower GC, stations 3-8, 11, 12, 14 and 15 should be included, while for the same site in males, stations 9, 10, 16 and 17 should be added.

Moreover, Table IV shows the LNM of different site with different status of cancer embolus. However, we were unable to draw clear conclusions due to a great difference in sample size between the two subgroups.

In conclusion, as applicable parameters for delineating the CTVn, LNM as well as the related clinicopathological factors are significant for RT of GC. CTVn should be customized by experienced radiation oncologists according to the tumor and its clinicopathological elements. Selective regional lymph node radiation including correlated lymphatic drainage regions according to clinicopathological characteristics should be well performed. The radiation fields should be enlarged appropriately for male patients with GC, with large, deeply invasive tumor, with poor differentiation, diffuse infiltration and cancer embolus.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in regard to this study.

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