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Research Article

Predictive Factors of Lymph Nodes Invasion and Factors Associated with Advanced Lymph Nodes Invasion in Gastric Cancer: Retrospective Study of 145 Cases

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ABSTRACT

Introduction: The detection of risk factors for lymph node extension in gastric cancers is crucial to standardize the indications of endoscopic treatment in early tumors, to rationalize the extension of lymphadenectomy and to adapt adjuvant and neoadjuvant therapies in locally advanced tumor. This study aimed to identify the clinical, biological, and histological predictive factors of lymph node involvement in gastric cancer.

Patients and Methods: Clinical and histological data of 145 patients treated for gastric adenocarcinoma have been enrolled. Univariate and multivariate analyzes of risk factors for lymph node involvement were performed.

Results: Lymph node invasion was found in 82.1% of cases. Among our patients, 32.4% were staged at pN3, 28.3% at pN2, and 21.4% at pN1. In univariate analysis, lymph node metastasis was significantly associated with the presence of Lymphovascular Invasion (LVI) (p=0.04), Perineural Invasion (PNI) (p=0.006), the degree of differentiation (p=0.04), the depth parietal invasion (p=0.019) and a high levels of Carcinoembryonic Antigen (CEA) (p=0.027). In multivariate analysis, the depth of parietal invasion (HR: 4.97, 95% CI:1.46-16.88, p=0.01), the presence of LVI (HR:0.053, 95% CI:0.004-0.70, p=0.026), PNI (HR:41.24, 95% CI: 2.86-59.36,p=0.006), and the CEA level (HR:5.40, 95% CI:1.21-22.58, p=0.021) were the independent predictive factors of lymph node metastasis.

Conclusion: The high level of tumor markers, the depth of parietal infiltration, the presence of LVI, and PNI are the main risk factors of lymph node metastases in gastric cancer.

Keywords: Gastric cancer; Surgery; Lymph node; Metastasis; Risk factors

INTRODUCTION

Stomach cancer is the fourth-largest cancer in the world with just under a million cases a year (6.8% of cancers in 2012, or 952.000 cases) but the third leading cause of cancer deaths in the world. The incidence of stomach cancer is subject to wide geographical variations, which can be explained by exposure to different (mainly dietary) risk factors. More than 70% of cases are in developing countries [1]. In Tunisia, the standardized incidence rates were 6.2/100.000 for men and 3.7/100.000 for women. This cancer is found at a stage of metastasis in about half of the cases. The trend is downward between 1994 and 2009, for both sexes with an average annual change in percentage equal to -2.4% for men (p<0.05) and -2.1% (p<0.05) for women [2]. Despite a declining incidence, the poor prognosis of stomach cancer is evidenced by a 5-year survival of less than 30% at all stages.

Detecting risk factors of lymph node invasion is fundamental whether in the case of early gastric cancer or locally advanced tumors [3]. Indeed, many studies have analyzed the lymph node extension risk mainly in early gastric cancer in order to standardize endoscopic mucosectomy and submucosal dissection indication. However, some teams investigated factors related to nodes invasion even in the case of advanced tumors so that they can justify the extension of lymphadenectomy even to the para-aortic territories as well [4].

The identification of a population which is highly exposed to node

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invasion risk may better standardize lymphadenectomy choice, improve oncologic results, and reduce morbidity. This study attempts to identify the predictive factors of lymph node invasion in gastric cancer.

PATIENTS AND METHODS

We conducted retrospective study involving 145 patients that were treated at Salah Azaiez Institute between January 2005 and December 2015 for gastric adenocarcinoma, and that received curative surgery. Lymphadenectomy was classified into three types according to the site of the tumor and the type of gastrectomy: D1 dissection, D1.5 dissection, and D2 dissection. A D1.5 lymphadenectomy corresponds to a D2 lymphadenectomy with no dissection of the hilar and the splenic artery (relay 10 and 11). This study did not include all metastatic patients at the moment of the diagnosis, cardia siewert I and II tumors, patients being operated for palliative intent, all patients treated through neoadjuvant chemotherapy for gastric adenocarcinoma with no surgery and patients having other associated cancers. Patients with an incomplete clinic and anatomopathological data were excluded.

We started identifying medical files, clinic (age, gender, the reason of counseling, WHO status), endoscopic (tumors site, size, aspect) data, tumors markers (CA 19-9 and CEA level), histological data (histological type, tumors size, differentiation grade, number of removed nodes, parietal infiltration depth, Lymphovascular Invasion (LVI), Perineural Invasion (PNI), lymph node status and the Lymph Node Ratio (LNR) that corresponded to the ratio between metastatic and dissected lymph nodes, namely the number of metastatic lymph nodes to that of dissected lymph nodes with dividing patients up into 03 groups according to the LNR value: LNR 0: LNR=0, LNR 1 : 0<LNR<0.1; LNR2: 0.1 ≤ LNR ≤ 0.25 and LNR 3: LNR>0.25). The lymph nodes metastasis (N stage) and the depth of invasion (T stage) were classified according to the TNM staging system 8th edition elaborated by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system. (AJCC/UICC). In this study, histological classification was based on WHO classification [5] and Lauren classification into 03 subgroups: intestinal type, diffuse type, and mixed type. Poorly differentiated tumors included moderately differentiated tubular adenocarcinoma, independent signet ring cells adenocarcinoma, and mucinous adenocarcinoma.

Continuous variables with a normal distribution were expressed on mean ± Standard Deviation (SD). In the case of no normality, variables were expressed through their medians and interquartile (Q1,Q3). Categorical variables are set in the form of percentages and absolute values. Test$\chi 2$, fischer exact test, and logistical regression models were respectively deployed for univariate and multivariate analysis of lymph nodes risk factors. Statistical signification was fixed on p (alpha error) <0.05. We conducted statistical analysis through Statistical Package for the Social Sciences (SPSS) program version 20.0.

RESULTS

This study included 145 patients with a mean age of 61.46 ± 12.86 years old.

The tumor was located at the lower third of the stomach in 77 cases (53.1%). Thirty-five patients (24.1%) had a tumoral stenosis. Table 1 recapitulates all patients' clinic and therapeutic data.

Table 1: Clinical, therapeutics and histological data of patients treated for gastric adenocarcinoma.

Variables		Effectifs	%
Age (mean ± SD, min, max, years)	-	61.48 ± 12.86	(26-85)
	≥ 70	44	30.3
	<70	101	69.7
Gender	Male	93	64
	Female	52	36
Site	Upper third	21	14.5
	Middle third	45	31
	Lower third	77	53.1
	Pangastric	2	1.4
CA19-9	Normal	87	87.9
	High	12	12.1
CEA	Normal	87	64.4
	High	48	35.6
Gastrectomy	Total	77	53.1
	Partial	68	46.9
Multi organ resection	No	111	76.6
	Yes	34	23.4
Lymphadenectomy	D1	15	10.3
	D1.5	36	24.8
	D2	94	64.8
Therapeutic sequence	Surgery	47	32.4
	CT-surgery-CT/RTCT	13	9
	Surgery+ADJCT	27	18.6
	Surgery+RTCT/RT ADJ	58	40
Size (mean ± SD, min, max, years)	-	64.86 ± 34.49 [12-22]	-
	<50	58	40
	≥ 50	87	60
Lauren classification	Intestinal	109	75.2
	Mixed	4	2.8
	Diffuse	32	22.1
Differentiation	Well	63	43.4
	Moderately	47	32.4
	Poorly	35	24.2
LVI	No	73	50.3
	Yes	72	49.7
PNI	No	76	52.4
	Yes	69	47.6
pT stage	pT1	8	5.5
	pT2	32	22.1
	pT3	61	42.1
	pT4	43	30.3
Lymph node	N-	26	17.9
	N+	119	82.1
pN stage	pN0	26	17.9
	pN1	31	21.4
	pN2	41	28.3
	pN3a	28	19.3
	pN3b	19	13.1
Number of lymph node	-	23.63 ± 10.856 [5-57]	-

The surgical procedure was a Total Gastrectomy (TG) for 77 patients (53.1%) and a Partial Gastrectomy (PG) in 68 patients (46.9%). Associated multi-organ resection was performed in 34 patients (23.4%). The D1 limited lymphadenectomy was performed in 15 patients (10.3%) and 130 patients (89.7%) had an extended lymphadenectomy. A D2 lymphadenectomy was associated with a splenectomy in 11 patients and with a splenopancreatectomy in 3 cases or 11.7% of D2 dissections. We performed a D1.5 dissection on 60% of gastric corpus tumors, 32% of lesser curvature tumors, 71.4% of proximal tumors, and 50% of pan-gastric tumors. The resection was macroscopically incomplete (R2) for one elderly patient (61 years old) who had a total gastrectomy for an antropyloric tumor involving the head of the pancreas. The mean tumor size was 64.86 mm ± 34.49. According to Lauren classification, the intestinal subtype was the most common histological form in 109 cases (75.2%). The mean number of examined lymph nodes was 23.63 ± 10.85. The distribution of the number of dissected lymph nodes according to the extent of lymphadenectomy was summarized in Table 2.

Lymph node invasion was found in 119 patients (82.1%) of cases. Among our patients, 32.4% were staged at pN3, 28.3% at pN2, and 21.4% at pN1. The mean number of involved lymph nodes was 8.16 ± 7.85 and 64 patients had a lymph nodes ratio LNR3 ≥ 25%.

In univariate analysis, lymph node invasion was significantly correlated to LVI (87.5% vs 76.7%; p=0.04), to PNI (91.3% vs 73.7%; p=0.006), to differentiation degree (91.4% in a poorly or undifferentiated tumors vs 73% in well-differentiated tumors; p=0.04), to the depth of parietal invasion (86.7% in pT3/T4 stages vs 70% in pT1/2 stages; p=0.019) and to a high level of CEA (p=0.027) (Table 3). No significant association was found between tumor size and lymph node invasion (p=0.061). In a multivariate analysis, the depth parietal invasion, the presence of LVI and PNI, and high CEA level were the independent factors of lymph nodes involvement (Table 4).

Table 2: Distribution of the number of dissected lymph nodes according to the extent of lymphadenectomy.

Lymphadenectomy	N	Number of dissected lymph node		
		<15	15-24	>=25
D1	15	12 (80%)	3 (20%)	0
D1.5	36	5 (13.9%)	12 (33.3%)	19 (52.8%)
D2	94	10 (10.6%)	46 (48.9%)	38 (40.4%)
Total	145	27 (18.6%)	61 (42.1%)	57 (39.3%)

Table 3: Univariate analysis of predictors of lymph node invasion.

Variables		Lymph node status			
		N	N-	N+	p-value
Age (mean ± SD, min, max, years)	-	145	58.61 ± 13.91	62.11 ± 12.59	0.279†
Gender	M	93	19 (20.4%)	74 (79.6%)	0.249*
	F	52	7 (13.5%)	45 (86.5%)	
ACE	Normal	87	18 (20.7%)	69 (79.3%)	0.027*
	High	48	3 (6.3%)	45 (93.8%)	
CA 19-9	Normal	87	19 (21.8%)	68 (78.2%)	0.072*
	High	12	0	12 (100%)	
Site	Distal	77	16 (20.8%)	61 (79.2%)	0.391
	Other	68	10 (14.7%)	58 (85.3%)	
Tumor size (mean ± SD, min, max, years)	-	145	53.96 ± 26.26	67.24 ± 35.68	0.061†
pT stage	T1-T2	40	12 (30%)	28 (70%)	0.019*
	T3-T4	105	14 (13.3%)	91 (86.7%)	
Lauren classification	Intestinal	109	22 (20.2%)	87 (79.8%)	0.219*
	Mixed/diffuse	36	4 (11.1%)	32 (88.9%)	
Differentiation	Well	63	17 (27%)	46 (73%)	0.04*
	Moderately	47	6 (12.8%)	41 (87.2%)	
	Poorly	35	3 (8.6%)	32 (91.4%)	
LVI	No	73	17 (23.3%)	56 (76.7%)	0.04*
	Yes	72	9 (12.5%)	63 (87.5%)	
PNI	No	76	20 (26.3%)	56 (73.7%)	0.006*
	Yes	69	6 (8.7%)	63 (91.3%)	

LVI: Lymph Vascular Invasion; PNI: Peri Neural Tumor Invasio; †: p-value using T test of student; *: p value using chi² Test of Pearson; SD: Standard Deviation

Table 4: Multivariate analysis of predictors of lymph node invaasion.

Variables	P	Exp beta	95% IC pour beta
pT stage	0.01	4.978	[1.46-16.88]
LVI	0.026	0.053	[0.004-0.70]
PNI	0.006	41.24	[2.86-59.36]
CEA	0.021	5.4	[1.29-22.58]

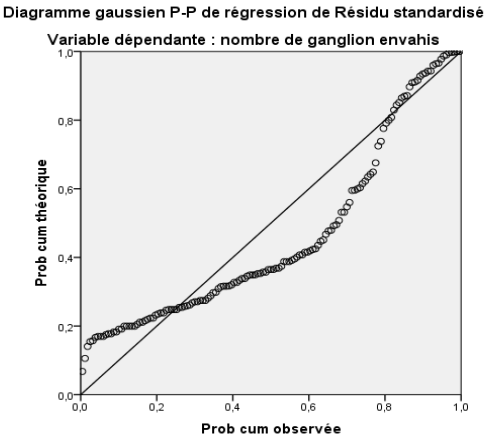

Figure 1: Linear correlation between number of involved lymph nodes and tumor size.

Table 5: Factors associated to involved lymph node number.

Variables		Number of N+ (means ± SD)	p-value
Tumor site	Distal	5.42 ± 6.612	0.04†
	Others	8.15 ± 8.886	
CA 19-9 level	Normal	6.22 ± 7.420	p=0.037†
	High	13.58 ± 10.587	
Tumor size (mm)	-	-	R=0.237*
			p=0.004
pT stage	T1-T2	3.83 ± 4.560	<0.0001†
	T3-T4	7.78 ± 8.562	
Lauren classification	Intestinal	5.44 ± 7.068	0.001†
	Diffuse/mixed	10.50 ± 8.936	
Differenciation	Well	4.17 ± 6.288	<0.0001†
	Moderately	7.68 ± 7.899	
	Poorly	9.91 ± 8.998	
LVI	No	5.19 ± 6.567	0.02†
	Yes	8.22 ± 8.757	
PNI	No	4.84 ± 6.456	0.03†
	Yes	8.74 ± 8.751	

LVI: Lymph Vascular Invasion; PNI: Peri Neural Tumor Invasion; SD: Standard Deviation; *: Coefficient rho of spearman; †: Test t of student

In the group of patients with lymph node metastasis, the number of involved lymph nodes increased linearly with the tumor size (p=0.004, R=0.237) (Figure 1). Moreover, there was a significant increase in the number of metastatic LN in the case of middle third and upper third tumors and pan-gastric tumors compared to the others tumor sites (p=0.004), in poorly differentiated tumors (p<0.0001), and mixed and diffuse type according to Lauren classification (p=0.001); in pT3-T4 stage tumors (p<0.0001), in case of LVI (p=0.02) and PNI (p=0.03) (Table 5).

DISCUSSION

In our study, the depth of parietal infiltration, the presence of LVI and PNI, and high CEA level were the independent risk factors of lymph nodes invasion. Since the determination of the N stage depends on the number of metastatic lymph nodes, we analyzed the factors associated with the increase in the number of invaded LN and therefore an increase in the pN stage. Indeed, in this study, in patients with lymph node involvement, locally advanced tumors, and the presence of PNI and LVI were associated with a higher number of invaded lymph nodes. In addition, we were able to identify other factors associated with an increase in the number of metastatic LN, especially the proximal tumor site, the large tumor size, the mixed and diffuse type according to the Lauren classification, and the low degree of differentiation.

Due to proximal gastric tumors spreading mainly in Central Asia and Western Countries, several studies compared clinical, histological and prognostic particularities that distinguish between proximal gastric tumors and distal ones [6-8]. Indeed, in most of these studies, proximal tumors were characterized by a higher rate of lymph node involvement compared to distal tumors. Jang's study comparing 9929 distal tumors to 1260 proximal ones has revealed a lymph node invasion rate of 48.7% for distal tumors and 67.9% for proximal ones (p=0.001) [9].

In our study, the rate of lymph node invasion was higher in proximal tumors compared to distal tumors with no statistically significant (85.3% vs 79.2 respectively, p=0.391), However, in patients with lymph node metastasis, the mean number of invaded lymph nodes were found to be significantly lower in distal tumors compared to other locations (5.42 vs 8.15, p=0.04). Our results do not seem strictly comparable to those of the literature which can be explained by the reduced number of proximal tumors and the exclusion of cardial tumors. On the other hand, some studies have shown that lymph node involvement in early tumors does not correlate with tumor site [9,10].

The prognostic value of tumor markers in gastric cancer remains a matter of debate. Indeed, the impact of some makers such as CA19-9, CEA, and CA72-4 on survival data and especially on the prediction of lymphatic and distant extension was mentioned in several articles. Nevertheless, there is no consensus defining markers choices, their reliability, their associations nor their monitoring in gastric cancer treatment. In a meta-analysis published in 2014, Shimada et al. [11], included 46 studies evaluating these three tumor markers impact on survival data in gastric cancers and their associations with histoprognostic characteristics notably lymph node involvement.

As a result, the level of these three markers was significantly correlated with overall survival and the risk of recurrence but also with the depth of parietal invasion and lymph node extension with a better sensitivity of CA72-4 for stage detection, and a CA19-9 positive predictive value Valor Predictivo Positivo (VPP) ranging from 78% to 96% in the prediction of lymph node involvement. In our series, a high CEA serum level was significantly predictive of lymph node involvement in a univariate analysis (93.8% vs 79.3% in case of normal level case; p=0.027) and represented an independent risk factor in multivariate analysis (p=0.021, HR=5.406, IC=1.294- 22.585). These results are similar to those

presented in several studies that are included in Shimada's meta-analysis [11], especially in Ishgami's large series [12] including 549 patients where 72% of patients who had a high CEA level had a lymph node involvement (p<0.001). Nevertheless, in Yu et al. study [13], the CEA level wasn't correlated to lymph node status since among patients with high CEA, 18.93% had lymphatic extension and 19.72% did not (p=0.986).

Tumor size is currently considered as a risk factor for lymph node involvement that is decisive in endoscopic mucosectomy indications and submucosal dissection for superficial cancers. However, there is a disagreement in tumoral diameter cutoff among western guidelines [14,15] that consider a tumor size going beyond 2 cm as a risk factor for lymph node involvement and the Asian guidelines [16] which, conversely, recommend a 3 cm cutoff for well-differentiated tumors and a 2 cm cutoff for poorly differentiated superficial tumors. Furthermore, the association between the tumor size and the risk of lymph node invasion in gastric cancer, independently to parietal invasion depth, is widely debated. In the retrospective study of Kunisaki including 1215 patients, a tumor size exceeding 10 cm was identified as an independent risk factor for lymph node invasion (HR=7.487, 95% CI=2.600-16.181, p<0.001) [17]. Jun et al. analyzed the correlation between tumor size and clinicopathological data by dividing 1284 into two groups: a Small Group (SG=tumor size <3.5 cm) and a Large Group (LG=tumor size ≥ 3.5 cm). The appropriate cutoff value of tumor size determined by the receiver-operating characteristic curve for cancer-related deaths was 3.5 cm (sensitivity=73.8%, specificity=59.3%) [18].

In this large study, the tumor size going beyond 35 mm was significantly associated with lymph node extension in 61.3% of cases, and only 38.3% of patients were classified at pN0 in the case of tumors going beyond 35 mm (p<0.0001). Using tumor volume 90th percentile as a cutoff, Li et al. have demonstrated that lymph node invasion was significantly associated with tumor size (85% vs 69.8%; p<0.001) [19].

In our series, the univariate analysis has shown no significant association between lymph node involvement and tumor size (p=0.061) which in line with the results published in 2017 by Chen et al. where the tumor size where tumor size was associated with LN metastasis only in the univariate analysis without being an independent factor in multivariate analysis (OR=0.911, 95% CI=0.469-1.770, p=0.784) [3] Withal, in patients with lymph node metastasis, we found that the number of invaded nodes number increased linearly with tumor size (p=0.004, R=0.237) which is similar to Hung et al. results, who have reported a positive linear correlation between the number of invaded lymph nodes and the tumor size (R=0.987, p<0.05) [20].

In our series, the depth of the parietal invasion was identified through univariate and multivariate analysis as an independent factor of lymph node invasion. These results match the data cited in the literature. Indeed, the invasion of the submucosa is recognized by all academic communities as an essential predictive parameter of lymph node involvement on which depend endoscopic treatment indications in early gastric cancers [14-16], and consequently in nonsuperficial tumors (T2-T3-T4). In Chen et al. study [3], including gastric tumors ranging from T1 to T4, the depth of parietal invasion was identified, in multivariate analysis, as an independent risk factor for lymph node involvement. Moreover, in our series, in patients with LN metastasis, the number of involved lymph nodes was significantly associated with the depth of parietal invasion with a mean number of involved nodes of 7.78 in pT3-T4 tumors and 3.83 inpT1-T2 tumors (p<0.0001). These funding are in line with the study of Huang with a significant association between the number of metastatic LN and the depth of invasion in multivariate analysis [20].

Perineural tumor invasion, defined through the presence of infiltration of neural sections by tumoral cells in at least 33% of the circumference [21], is recognized as a dissemination way that has a prognostic value validated in several tumoral locations. Nevertheless, in gastric cancer PNI prognostic value remains a controversial topic, and there is no consensus on the therapeutic impact of this parameter [22]. Furthermore, the correlation between PNI and lymph node invasion was investigated by a few studies. In fact, in Deng et al. [23], meta-analysis which enrolled 24 studies analyzing the PNI impact on survival, only 7 studies reported a significant association between PNI and lymph node invasion (HR: 1.322, 95% CI: 1.249-1.400, P=0.000). In our series, univariate analysis has shown that 91.3% of patients with PNI had a lymph node involvement and in multivariate analysis, PNI was an independent risk factor for lymph node involvement (HR=41.243, CI=2.865-593.616, p=0.006).

LVI incidence in gastric cancer varies widely in studies ranging from 5.4% to 86% according to identification techniques used by both Immunohistochemistry (IHC) and standard coloring with hematoxylin and eosin that presents difficulties in recognizing lymphatic and vascular chains [24,25]. The incrimination of the presence of vascular embolus in the emergence of lymphatic and hematological metastasis was evaluated in several studies and represents a decisive parameter in the therapeutic care especially in early gastric cancers [26]. Indeed, Kim et al. have demonstrated that LVI was significantly correlated, not only to macroscopic node invasion but also to microscopic node invasion detected in the IHC [27]. Du et al. have analyzed the LVI prognostic value in stage II gastric cancers on a population of 487 patients and suggested an increase in the incidence of lymph node invasion from 30.6% in case of tumors without LVI to 58.2% in case of tumors with LVI (p<0.001) with a significant linear correlation between the number of invaded nodes and LVI [28]. These results are consistent with our results.

In our study, the degree of tumor differentiation was predictive of lymph node involvement only in univariate analysis. However, we noticed that the mean number of invaded nodes was significantly higher in poorly differentiated tumors compared to well-differentiated (9.91 vs 4.17, p<0.001). This result is reminiscent of Huang's finding where the number of invaded nodes was significantly higher in undifferentiated tumors (p<0.001) on the univariate analysis and the multivariate analysis identified tumor size and pT stage as the only independent parameters correlated with the number of involved lymph nodes [20].

In the literature, the gastric signet ring cell carcinoma presents epidemiological, prognostic, and therapeutic particularities that distinguish them from other histological types. In fact, several studies have shown that these tumors are characterized by a higher risk of metastatic spread because they are significantly associated

with a higher rate of initial lymph node involvement and more advanced stages [29-31]. A large Korean study including 2643 patients, conducted by Shim et al., have shown that lymph node involvement wasn't notably higher in the presence of signet ring cell component compared to other histological types (p=0.9757) [32]. In our series, mixed and diffuse histological types according to Lauren classification and especially the presence of signet ring cells don't expose to a higher risk of lymph node invasion (p=0.219). However, in patients with LN metastasis, the number of invaded nodes was significantly higher in the presence of signet ring cells (p=0.001).

Our study has certain limitations related to its retrospective and unicentric nature, the relatively small number of patients included but especially the existence of a group of patients with a number of removed lymph node less than 15 lymph nodes in 18.6% of cases which may explain the underestimation of lymph node status.

CONCLUSION

CEA high level, parietal infiltration depth, and the presence of lymphovascular invasion and peri-neural tumor invasion are the independent risk factors for lymph node involvement. The determination of clinical and histological risk factors of lymph node invasion in gastric cancers is a crucial phase in the therapeutic process. It allows, in early cancers, the selection of appropriate patients for endoscopic treatment and, in locally advanced cancers, the justification of the indication of an extended lymphadenectomy and to well rationalize the indication of adjuvant therapies in the case of insufficient lymph node dissection under estimating lymph node status.

In patients with lymph node involvement, proximal tumor site, the large tumor size, the mixed and diffuse type according to the Lauren classification, the low degree of differentiation as well as locally advanced tumors, PNI and LVI were associated with a higher number of invaded lymph nodes and therefore a higher pN stage. Since the determination of the N stage depends on the number of metastatic lymph nodes, these factors may be useful to improve the estimation of the survival according to the N stage especially in patients with insufficient lymph node dissection leading to an underestimation of the N stage.

ETHICS APPROVAL

The ethics review board approved this study and did not require informed consent from study participants since this was a strictly registry-based study

CONFLICT OF INTEREST

None declared.

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