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ORIGINAL PAPER

Determining of metastatic lymph node ratio in patients who underwent D2 dissection for gastric cancer

Ahmet Bilici · Mesut Seker · Bala Basak Oven Ustaalioglu · Burcak Yilmaz · Alper Doventas · Taflan Salepci · Mahmut Gumus

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Abstract The purpose of this study was to determine outcome of the ratio of metastatic lymph nodes to the total number of dissected lymph nodes (MLR) in patients with gastric cancer. We retrospectively analyzed 111 patients who underwent D_2 lymph node dissection. The prognostic factors including UICC/AJCC TNM classification and MLR were evaluated by univariate and multivariate analysis. The MLR was significantly higher in patients with a larger tumor, lymphatic vessel invasion, blood vessel invasion and perineural invasion, and advanced stage. Moreover, the MLR was significantly associated with the depth of invasion and the number of lymph node metastasis. The univariate analysis revealed for overall survival (OS) that stage of disease, lymphatic vessel invasion, blood vessel invasion, perineural invasion, lymph node metastasis (UICC/AJCC pN stage) and MLR were relevant prognostic indicators. Furthermore, both UICC/AJCC pN stage and MLR were detected as prognostic factor by multivariate analysis, as was perineural invasion. Our results indicated that MLR and UICC/AJCC pN staging system were important prognostic factors for OS of patients with D_2 lymph node dissection in gastric cancer in a multivariate analysis. MLR may be useful for evaluating the status of lymph node metastasis in gastric cancer.

Keywords Metastatic lymph node ratio · Lymph node metastasis · Gastric cancer · Prognosis

A. Bilici · M. Seker · B. B. O. Ustaalioglu · B. Yilmaz · T. Salepci · M. Gumus
Department of Medical Oncology, Dr. Lütfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey

A. Doventas
Department of Internal Medicine, Istanbul Education and Research Hospital, Istanbul, Turkey

A. Bilici (✉)
Menderes Mah, 23.sok, Caglar Apt., No: 16, Daire:1, 34210 Esenler, Istanbul, Turkey
e-mail: ahmetknower@yahoo.com

Introduction

Lymph node metastasis is an important prognostic factor in gastric cancer, but the classification of lymph node status (N categories) is still controversial. In addition, lymph node dissection is a promising treatment for gastric cancer [1–6]. In Japan, the extend of lymph node metastasis is classified by anatomical sites of metastatic lymph nodes according to the the Japanese Classification of Gastric Carcinoma (JCGC) which was proposed by Japanese Research Society of Gastric Cancer (JRSGC) [7]. In 1997 and 2002, the International Union Aganist Cancer (UICC) and the American Joint Committee on Cancer (AJCC), in the 5th edition of the tumor, node, metastasis (TNM) system redefined N categories that was based on the number of metastatic lymph nodes [8, 9].

The prognostic value of UICC/AJCC pN classification has been evaluated, and it has been accepted that UICC/AJCC pN is simple and reproducible method for accurate staging [9, 10]. However, some of the problems of the UICC/AJCC pN classification has been mentioned, such as 'stage migration' phenomenon. UICC/AJCC pN classification needs the examination of at least 15 lymph nodes and extended lymph node dissection can cause a 'stage migration' due to the increase in the number of metastatic lymph nodes [11–14].

Several previous trials have demonstrated that a new prognostic indicator of the ratio of metastatic lymph nodes

to the total number of dissected lymph nodes (MLR) was proposed for patients with gastric cancer who undergo curative resection [2–5, 11, 12, 14–17]. The superiority of MLR classification to location-based or number-based N classifications has been reported by some investigators, and they also showed that it is an independent prognostic indicator for gastric cancer [12, 15–23]. In this study, we aimed to determine the prognostic importance of MLR and compared MLR with UICC/AJCC TNM classifications in patients who underwent D_2 lymph node dissection for gastric cancer. In addition, the relation between the other clinicopathological factors and survival was also evaluated.

Patients and methods

Totally, 111 gastric carcinoma patients who had undergone curative gastrectomy and D_2 lymph node dissection at Dr. Lutfi Kirdar Kartal Education and Research Hospital, between April 2002 and December 2008, were retrospectively analyzed. The clinicopathologic findings were determined according to the JCGC. All patients undergone either distal partial gastrectomy, proximal partial gastrectomy or total gastrectomy with regional lymph nodes dissection to D_2 with curative intent. Lymph node involvement was classified according to the 1997 UICC/AJCC TNM classification (pN_0, no metastasis; pN_1, 1–6 metastatic lymph nodes; pN_2, 7–15 metastatic lymph nodes; pN_3, >15 metastatic lymph nodes).

Clinical information about age, gender, resection type, tumor location, histopathology, tumor stage, tumor size, histological grade, lymph node involvement, the depth of tumor invasion, lymphatic vessel invasion, blood vessel invasion, perineural invasion (PNI) and resection margins, macroscopic finding, histological type, adjuvant chemotherapy and radiation therapy type, responses to treatment and survival were obtained from patients charts. Paraffin sections of surgical specimens from all patients were stained with hematoxylin and eosin. After histopathological evaluation, PNI was assessed as positive if cancer cells infiltrated into the perineurium or neural fasciculus. All specimens were evaluated by an expert pathologist in the matter of gastric cancer.

The eligibility criteria included histologically confirmed R_0 gastric resection, which was defined as no macroscopic or microscopic residual tumor and postoperative survival time >3 months and having D_2 lymph node dissection in which n_2 lymph node groups according to the Japanese rules were dissected separately and having at least 25 lymph nodes on pathology reports. The patients with distant metastasis at diagnosis were excluded from the study. The peritoneal cytology had not performed perioperatively in this study population. MLR was determined by the best cutoff approach in terms of the long-rank test. MLR 0, 0%; MLR 1, 1–9%; MLR 2, 10–25% and MLR 3, >25%.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software. The significance of the differences among the means were determined by the Mann–Whitney *U*-test and Kruskal–Wallis test. Survival analysis and curves were established according to the Kaplan–Meier method and compared by the long-rank test. Disease-free survival (DFS) was defined as the time from curative surgery to disease progression or recurrence or to the date of death or last known contact. In addition, overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. Multivariate *P* values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All *P* values were two-sided in tests, and *P* values less than or equal to 0.05 were considered to be statistically significant.

Results

One hundred and eleven patients with radically resected gastric cancer and underwent D_2 lymph node dissection for gastric cancer were retrospectively analyzed. Thirty-four patients (30.6%) were women and 77 (69.4%) were men with the median age 58 years (range; 31–79 years). Sixty-two patients were equal or younger than 60 years (55.9%). The median number of dissected and metastatic lymph nodes were 27 (range, 25–67) and 9 (range, 0–62), respectively. Sixteen (14.4%) patients were classified as pN_0, 31 (27.9%) as pN_1, 28 (25.2%) as pN_2 and 36 (32.4%) as pN_3 according to the number of lymph node metastasis. The majority of patients were T3 (58 patients, 52.3%). Eighty-two percent of patients had PNI, while blood vessel invasion and lymphatic vessel invasion were detected in 77.5 and 82.9% of them, respectively. The correlation between the MLR and the clinicopathological findings are summarized in Table 1. MLR was significantly greater in patients with a large tumor, tumors with lymphatic vessel invasion, blood vessel invasion, and PNI and advanced stage. Moreover, MLR was significantly correlated with depth of invasion and the number of lymph node metastasis.

At the median follow-up of 19.3 months (range; 7.7–85), 1-year DFS and OS rates were 72.8 and 76.4% for all patients, respectively. The median DFS interval was

Table 1 The correlation between the MLR and clinicopathological characteristics

Variables	MLR (mean ± SD)	*P* value
Age		0.10
≤60 ($n = 62$)	0.43 ± 0.33	
>60 ($n = 49$)	0.32 ± 0.30	
Gender		0.16
Male ($n = 77$)	0.36 ± 0.31	
Female ($n = 34$)	0.43 ± 0.32	
Tumor differentiation		0.054
Well differentiated ($n = 8$)	0.19 ± 0.15	
Moderately differentiated ($n = 52$)	0.32 ± 0.29	
Poorly differentiated ($n = 51$)	0.46 ± 0.35	
Tumor size		0.004
≤3 cm ($n = 19$)	0.17 ± 0.26	
≤6 cm ($n = 39$)	0.44 ± 0.30	
>6 cm ($n = 53$)	0.41 ± 0.33	
Depth of invasion		<0.0001
T1 ($n = 5$)	0.06 ± 0.10	
T2 ($n = 40$)	0.23 ± 0.25	
T3 ($n = 58$)	0.47 ± 0.31	
T4 ($n = 8$)	0.64 ± 0.32	
Stage		<0.0001
I ($n = 13$)	0.02 ± 0.06	
II ($n = 19$)	0.06 ± 0.06	
III ($n = 39$)	0.35 ± 0.21	
IV ($n = 40$)	0.68 ± 0.25	
Number of lymph node metastasis		<0.0001
No ($n = 16$)	0	
N1 ($n = 31$)	0.12 ± 0.07	
N2 ($n = 28$)	0.39 ± 0.14	
N3 ($n = 36$)	0.76 ± 0.17	
Lymphatic vessel invasion		<0.0001
Absence ($n = 19$)	0.02 ± 0.05	
Presence ($n = 92$)	0.45 ± 0.30	
Blood vessel invasion		<0.0001
Absence ($n = 25$)	0.12 ± 0.22	
Presence ($n = 86$)	0.45 ± 0.31	
Perineural invasion		<0.0001
Absence ($n = 20$)	0.15 ± 0.26	
Presence ($n = 91$)	0.43 ± 0.31	

MLR the ratio of metastatic lymph nodes to the total number of dissected lymph nodes and *SD* standard deviation

22.2 months [standard error (SE):6, 95% CI; 10.3–34] and the median OS time was 25 months (SE:4.5, 95% CI; 20–29.9) (Figs. 1, 2). Based on the MLR classification, 16 patients (14.4%) were classified as MLR 0, 15 (13.5%) as MLR 1, 20 (18%) as MLR 2 and 60 cases (54.1%) as MLR 3. One-year OS rate was not applicable in MLR 0 and 1 groups. However, 1-year OS rate was 78.8 in MLR 2 and 53.3 in MLR 3. This difference was significant ($P = 0.036$, Fig. 3).

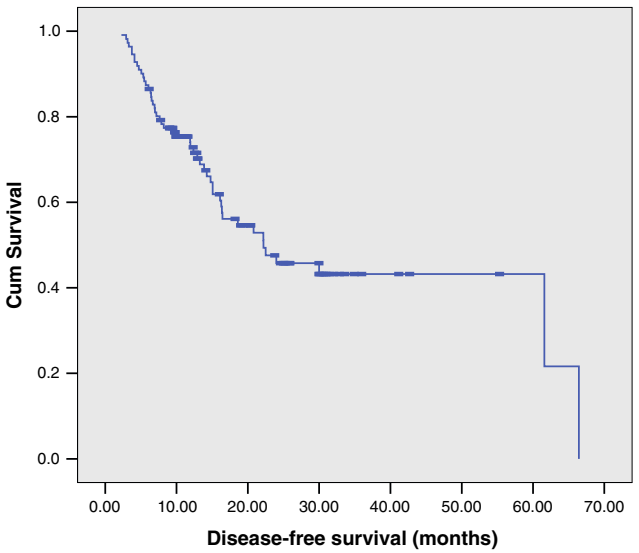

Fig. 1 Disease-free survival in all gastric carcinoma patients who had undergone D2 lymph node dissection

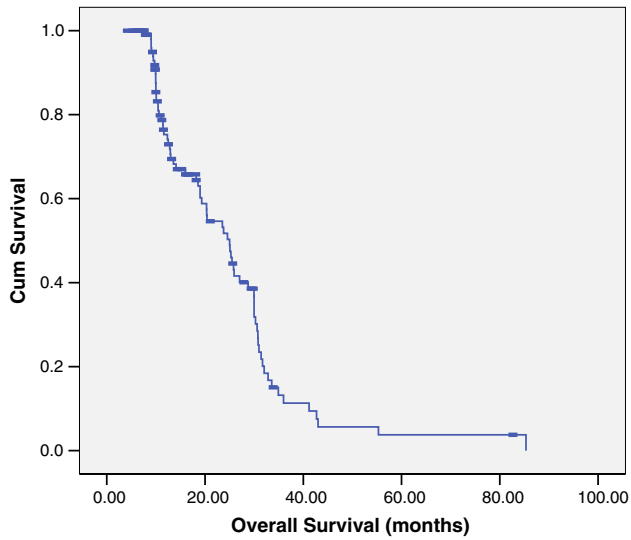

Fig. 2 Overall survival in all gastric carcinoma patients who had undergone D2 lymph node dissection

The univariate analysis for OS indicated that stage of disease, lymphatic vessel invasion, blood vessel invasion, PNI, lymph node metastasis (pN category of UICC/AJCC classification) and MLR were important prognostic indicators. The correlation between tumor size and OS was not detected ($P = 0.29$). The results of univariate analysis are shown in Table 2. However, when the univariate analysis was performed for DFS, we found that tumor size, lymphatic vessel invasion, blood vessel invasion, PNI, T stage, stage of disease, UICC/AJCC pN stage and MLR were important prognostic factors (Table 3).

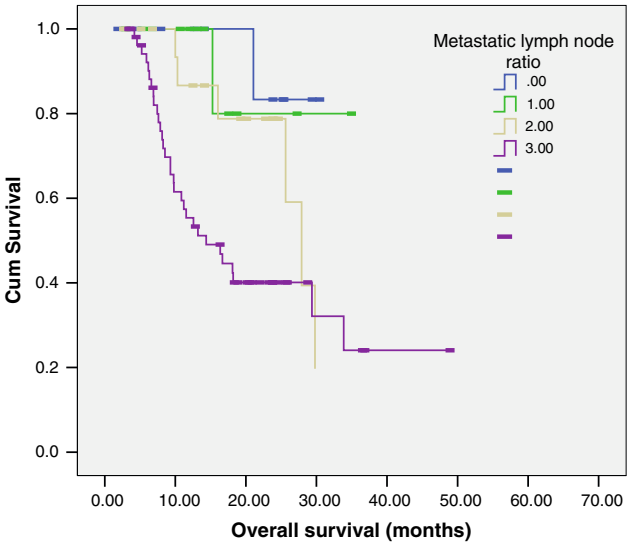

Fig. 3 Overall survival curves according to the metastatic lymph node ratio

The multivariate analysis with Cox proportional hazards model was performed in order to further evaluate the prognostic significance of MLR and UICC/AJCC pN stage, because MLR and lymph node metastasis are closely associated with OS of patients with radically resected gastric cancer in a univariate analysis. Multivariate analysis indicated that UICC/AJCC pN stage and MLR were independent prognostic factors (χ^2: 4.23, $P = 0.023$, HR: 6.45; 95% CI:1.54–31.3 and χ^2: 8.9, $P = 0.03$, HR: 0.33; 95% CI: 0.16–0.69, respectively), as was PNI. Table 4 shows the results of multivariate analysis according to OS. Furthermore, a multivariate analysis was carried out for DFS, and we detected that only UICC/AJCC pN stage was an independent prognostic indicator (χ^2: 4.32, $P = 0.03$, HR: 3.66; 95% CI:1.07–12.4, Table 5).

In our study, 86.5% of patients were treated with adjuvant chemoradiotherapy (CRT) (5-fluorouracil 425 mg/m^2 per day, plus leucovorin 20 mg/m^2 per day, for five days, followed by 4,500 cGy of radiation at 180 cGy per day, given five days per week for five weeks, with modified doses of fluorouracil and leucovorin on the first four and the last three days of radiotherapy), while 15 patients (13.5%) were not received adjuvant CRT, because of early stage disease in 13 patients and patient's refusal in two patients. One-year OS rate was 78.8% in patients who received adjuvant CRT and 60.2% in patients who were not administered CRT. This difference was not significant ($P = 0.54$).

Discussion

This study showed that both MLR and UICC/AJCC pN stage is an independent prognostic factor for OS of patients who had undergone D_2 lymph node dissection in gastric cancer by multivariate analysis. In addition, only UICC/AJCC pN stage was found to be prognostic indicator for DFS by multivariate analysis. However, the superiority of MLR to lymph node metastasis could not be indicated in our study.

Two main staging systems for gastric cancer includes the UICC and JCGC. The most important difference between these staging systems is the method of evaluating the status of lymph node metastasis, which influences survival in resectable gastric cancer. Accurate and uniform disease staging is essential to predict prognosis and to determine treatment modality in gastric cancer. In the JCGC system, the regional lymph nodes are classified into three groups (n_1–n_3) based on the location of positive lymph nodes in relation to the primary tumor, whereas UICC system are based on the number of metastatic lymph nodes alone [7, 8]. Although it remains unreliable as to which is the most important, the location or number of metastatic lymph nodes, some studies showed that the number of metastatic lymph nodes, but not their level, is an independent prognostic indicator [24, 25].

Previous reports have emphasized the superiority of the UICC/AJCC TNM staging system, because of its simplicity, reliability and stratification [5, 26]. On the other hand, in this staging system, the number of resected lymph nodes are very important, because, stage migration occurs in 5–15% of cases [11]. To resolve these limitations, recently, MLR as a new prognostic factor has been proposed by several authors [11, 12, 15, 23]. MLR indicates the number of metastatic lymph nodes and extend of lymph node dissection. Moreover, it has proved to be good alternative to prevent the 'stage migration' phenomenon, and it is also usable in patients with <15 lymph nodes dissected or D_1 lymphadenectomy or non-curative resection [11–18]. Sun et al. in their recent study, indicated that MLR had more potential advantages in minimizing stage migration phenomenon for patients with insufficient number or level of lymph nodes retrieved [27].

However, a recent study performed by Yamashita et al. [28] indicated that the JCGC system was superior to the UICC system for the prognostic stratification of stage IIIA, IIIB and IV gastric cancer. The authors used the JCGC system for prognostic validation with respect to depth of invasion in cancers of the same stage, and they found that there was an outstanding difference between the muscularis propria and subserosa. Thereafter, they concluded that the invasion into the muscularis propria had an earlier propensity than expected, and the JCGC system might provide a better stratification of prognosis than the UICC system.

In our study, we compared UICC/AJCC staging system with MLR. The means of MLR were significantly greater in patient with gastric tumor with greater size, with

Table 2 Overall survival (OS) univariate analysis according to clinicopathological factors

Factor	No. of patients	1-year OS rate (%)	95% CI	*P* value
All	111	76.4	20–29.9	
Gender				0.68
Male	77 (69.4)	97	16.2–30.8	
Female	34 (30.6)	90.1	22.5–27.6	
Age (year)				0.83
<60	62 (55.9)	74	22.8–22.1	
>60	49 (44.1)	77.1	12.5–28.2	
Tumor site				0.19
Upper	25 (22.5)	76.5	17.4–31.6	
Middle	34 (30.6)	76.7	12.5–39	
Lower	47 (42.3)	73.9	18.3–1.8	
Diffuse	5 (4.5)	NA	–	
Tumor size (cm)				0.29
<3	19 (17.1)	52.6	7.1–31.5	
<6	39 (35.1)	82.6	22.7–8.8	
>6	53 (47.7)	72.3	15.3–32.1	
Surgery type				0.79
Proximal	25 (22.5)	76.5	17.4–1.6	
Distal	43 (38.7)	74.3	16.6–3.4	
Total	43 (38.7)	72.7	7.0–0.1	
Tumor differentiation				0.52
Well differentiated	8 (7.2)	NA	–	
Moderately differentiated	52 (46.8)	75.8	18.3–0.8	
Poorly differentiated	51 (45.9)	76.9	15.5–1.5	
Macroscopic finding				0.30
Type I	4 (3.7)	NA	–	
Type II	8 (7.2)	71.8	11.3–7.2	
Type III	35 (31.5)	69.0	13.6–3.4	
Type IV	64 (57.6)	73.2	19.4–0.5	
Histological type				0.45
Intestinal	46 (41.5)	72.6	18.1–2.3	
Diffuse	65 (58.5)	71.9	17.2–9.7	
Lymphatic vessel invasion				0.033
Absence	19 (17.1)	85.7	22.9–2.5	
Presence	92 (82.9)	65.1	6.4–20.5	
Blood vessel invasion				0.006
Absence	25 (22.5)	92.9	22.8–7.3	
Presence	86 (77.5)	62.0	7.5–27.4	
Perineural invasion				0.03
Absence	20 (18)	76.9	20.1–9.8	
Presence	91 (82)	62.3	7.6–20.1	
T stage				0.17
T1	5 (4.5)	NA	–	
T2	40 (36)	79.0	17.3–9.1	
T3	58 (52.3)	66.2	15.7–4.1	
T4	8 (7.2)	NA	–	
Stage				0.01
I	13 (11.7)	NA	–	
II	19 (17.1)	78.9	15.9–8.4	

Table 2 Overall survival (OS) univariate analysis according to clinicopathological factors

Factor	No. of patients	1-year OS rate (%)	95% CI	*P* value
III	39 (35.1)	82.9	20.7–32	
IV	40 (36)	61.1	7.5–20.9	
Number of lymph node metastasis				<0.001
N0	16 (14.4)	83.3	7.6–42.5	
N1	31 (27.9)	90.0	24.0–5.9	
N2	28 (25.2)	69.6	11.5–9.0	
N3	36 (32.4)	36.1	6.8–11.7	
Metastatic/resected nodes				0.036
MLR 0	16 (14.4)	NA	–	
MLR 1	15 (13.5)	NA	–	
MLR 2	20 (18)	78.8	18.2–2.1	
MLR 3	60 (54.1)	53.3	8.6–21.5	

CI confidence interval, *NA* not applicable and *MLR* the ratio of metastatic lymph nodes to the total number of dissected lymph nodes

lymphatic vessel invasion, vascular vessel invasion, PNI and advanced stage. Furthermore, MLR was significantly correlated with depth of invasion and the number of lymph node metastasis. Our results were compatible with the literature [23].

Univariate analysis for OS indicated that stage of disease, lymphatic vessel invasion, blood vessel invasion, PNI, lymph node metastasis and MLR were statistically significant prognostic factors. Moreover, MLR, lymph node metastasis and PNI were the most significant prognostic factors by using multivariate analysis. On the other hand, while tumor size, lymphatic vessel invasion, blood vessel invasion, PNI, T stage, stage of disease, UICC/AJCC pN stage and MLR were found to be important prognostic indicators for DFS in a univariate analysis, the multivariate analysis indicated that only UICC/AJCC pN stage was independent prognostic factor for DFS. Although several authors have shown the superiority of MLR compared with UICC/AJCC pN staging system in the literature [22, 23], we did not find that MLR was superior to UICC/AJCC pN stage. In addition, it may be considered superior toUICC/AJCC pN staging, because of its simplicity, especially in patients with D_2 lymph node dissection.

Bando et al. reported that there was a statistically significant difference between the survivals of patients with MLR groups [12]. Similarly, Siewert et al. evaluated the 10-year results of 1,654 patients and identified MLR ($\leq$20 vs. $\geq$20%) and the residual tumor status (R classification) as the major independent prognostic factors in patients with resected gastric cancer [29]. In their analysis, Kodera et al. analyzed 656 gastric cancer patients who had D_2 lymphadenectomy, and they reported that there were significant prognostic differences among MLR groups [15]. In the study carried out by Inoue et al., MLR was selected as the most significant prognostic factor in 474 patients who underwent an R_0 resection and D_2 lymph node dissection for gastric cancer [14].

In our study, we found significant differences in OS for both MLR groups of 0, 1–9, 10–25 and >25% ($P = 0.036$), and UICC/AJCC pN stage groups ($P < 0.001$) by univariate analysis. Furthermore, in a multivariate analysis, both lymph node metastasis and MLR were detected to be independent prognostic factor, as was PNI. Saito et al. studied 777 gastric cancer patients who had undergone curative gastrectomy. They reported that the MLR, but not the number of lymph node metastases, was an independent prognostic factor. Authors concluded that the MLR was useful for evaluating the status of lymph node metastasis in gastric cancer [23]. On the other hand, in their study, Celen et al. showed that macroscopic findings, pN category of UICC/AJCC classification and MLR were the most significant prognostic factors, and a higher hazard ratio was obtained for MLR than UICC/AJCC pN staging [22]. Our findings are not compatible with Saito et al.'s results, while they are correlated with Celen et al.'s findings.

The UICC advised that when less than 15 nodes examined, UICC/AJCC pN stage cannot be applied accurately [11, 12, 14]. Because the number of lymph node metastases is sometimes affected by the number of lymph nodes dissected, in cases who underwent D_1 lymphadenectomy, the stage migration might occur. In our study, we included the patients with D_2 lymph node dissection in order to maintain the homogeneity.

PNI is a process by which cancer cells invade the perineurium or neural fascicles and wrap around nerves. However, PNI is reported to be a common route of spread in carcinomas of the pancreas and biliary tract but is relatively rare in rectal carcinoma. It is a crucial route for the local spread of tumor associated with poor prognosis. There were only a few studies which had investigated on the presence and prognostic significance of PNI in gastric cancer and had not reached a consensus [30, 31]. Duraker et al. [31] found that PNI was positive in 59.6% of patients, and the incidence of PNI increased with the progression of

Table 3 Disease-free survival (DFS) univariate analysis according to clinicopathological factors

Factor	No. of patients (%)	1-year DFS rate (%)	95% CI	*P* value
All	111	72.8	10.3–34	
Gender				0.59
Male	77 (69.4)	73.9	8.4–30.8	
Female	34 (30.6)	70	12.7–31.6	
Age (year)				0.91
<60	62 (55.9)	71.3	7.9–40	
>60	49 (44.1)	74.7	16.8–27.5	
Tumor site				0.29
Upper	25 (22.5)	74.8	24.4–37.7	
Middle	34 (30.6)	62.3	10.1–19.9	
Lower	47 (42.3)	75.5	6.9–38	
Diffuse	5 (4.5)	NA	–	
Tumor size				0.026
<3 cm	19 (17.1)	84.2	29–37.5	
<6 cm	39 (35.1)	69.2	7.1–30	
>6 cm	53 (47.7)	72	13.9–27.6	
Surgery type				0.14
Proximal	25 (22.5)	74.8	14.4–33.7	
Distal	43 (38.7)	81.3	23.1–36.1	
Total	43 (38.7)	63	9.1 –23.5	
Tumor differentiation				0.63
Well differentiated	8 (7.2)	NA	–	
Moderately differentiated	52 (46.8)	65	4.1–40.1	
Poorly differentiated	51 (45.9)	76.5	12.6–31.7	
Macroscopic finding				0.23
Type I	4 (3.7)	NA	–	
Type II	8 (7.2)	75.5	10.7–37.2	
Type III	35 (31.5)	72.9	12.8–47.1	
Type IV	64 (57.6)	73.6	14.4–33.1	
Histological type				0.70
Intestinal	46 (41.5)	79.5	13.3–23.8	
Diffuse	65 (58.5)	70	9.4–19.4	
Lymphatic vessel invasion				0.04
Absence	19 (17.1)	90.9	29.7–32.5	
Presence	92 (82.9)	68.9	12.6–24.5	
Blood vessel invasion				0.006
Absence	25 (22.5)	89.6	9.8–47.9	
Presence	86 (77.5)	67.8	6.5–23	
Perineural invasion				0.028
Absence	20 (18)	89.4	16.1–39.3	
Presence	91 (82)	69.1	9.9–22.9	
T stage				0.03
T1	5 (4.5)	NA	–	
T2	40 (36)	82.5	18.8–40.3	
T3	58 (52.3)	68	9.7–6.1	
T4	8 (7.2)	NA	–	
Stage				<0.001
I	13 (11.7)	NA	–	
II	19 (17.1)	94.7	29.3–58.7	

Table 3 Disease-free survival (DFS) univariate analysis according to clinicopathological factors

Factor	No. of patients (%)	1-year DFS rate (%)	95% CI	*P* value
III	39 (35.1)	79.4	15–44.9	
IV	40 (36)	50	7–16.8	
Number of lymph node metastasis				<0.001
N0	16 (14.4)	88.9	10.2–30.5	
N1	31 (27.9)	90.0	23.7–35.2	
N2	28 (25.2)	81.6	12.5–30	
N3	36 (32.4)	43.1	4.5–11.1	
Metastatic/resected nodes				<0.001
MLR 0	16 (14.4)	88.9	23.2–51.7	
MLR 1	15 (13.5)	NA	–	
MLR 2	20 (18)	85	8.2–47.7	
MLR 3	60 (54.1)	57.3	11.7–17.7	

CI confidence interval, *NA* not applicable and *MLR* the ratio of metastatic lymph nodes to the total number of dissected lymph nodes

Table 4 Multivariate analysis of various clinicopathological factors in patients with radically resected gastric cancer according to overall survival

Factors	Wald	*P*	HR	95% CI
Gender	0.45	0.50	1.29	0.60–2.77
Age (≤60 vs. >60)	0.31	0.57	0.83	0.45–1.55
Tumor location	1.49	0.22	1.29	0.85–1.96
Tumor size	2.21	0.33	1.25	0.54–2.59
Depth of invasion	0.70	0.40	1.72	0.48–6.10
Macroscopic finding	2.18	0.13	1.62	0.85–3.08
Histological type	0.05	0.81	1.07	0.57–2.01
Lymphatic vessel invasion	1.86	0.17	0.34	0.07–1.59
Blood vessel invasion	2.55	0.11	2.65	0.80–8.7
Perineural invasion	10.6	0.016	2.61	1.19–5.74
Tumor differentiation	5.65	0.55	1.20	0.65–2.19
Number of lymph node metastasis (UICC/AJCC pN stage)	4.23	0.023	6.45	1.54–31.3
MLR	8.9	0.03	0.33	0.16–0.69

HR hazards ratio, *CI* confidence interval and *MLR* the ratio of metastatic lymph nodes to the total number of dissected lymph nodes

Table 5 Multivariate analysis of various clinicopathological factors in patients with radically resected gastric cancer according to disease-free survival

Factors	Wald	*P*	HR	95% CI
Gender	1.07	0.30	0.66	0.31–1.43
Age (≤60 vs. >60)	0.16	0.68	0.86	0.43–1.71
Tumor location	0.24	0.62	1.12	0.69–1.81
Tumor size	0.99	0.31	1.34	0.75–2.38
Depth of invasion	1.38	0.24	1.57	0.73–3.36
Macroscopic finding	0.88	0.34	1.37	0.70–2.67
Histological type	0.05	0.81	0.91	0.45–1.86
Lymphatic vessel invasion	0.73	0.39	3.25	0.21–6.79
Blood vessel invasion	0.59	0.44	0.46	0.06–3.25
Perineural invasion	1.05	0.30	0.53	0.16–1.76
Tumor differentiation	0.04	0.95	0.98	0.51–1.85
Number of lymph node metastasis (UICC/AJCC pN stage)	4.32	0.03	3.66	1.07–12.4
MLR	0.29	0.59	0.76	0.28–2.05

HR hazards ratio, *CI* confidence interval and *MLR* the ratio of metastatic lymph nodes to the total number of dissected lymph nodes

gastric cancer, but it did not provide any additional information to the classical prognostic parameters. In a recent study performed by Tianhang et al. [32], they found that PNI was positive in 518 of the 1,632 patients (31.7%) with gastric cancer. Their results indicated that the incidence of PNI was high in gastric cancer, and that it corresponded to the progression of disease. In our study, we detected PNI in 91 of the 111 patients (82%). The rate of PNI was very high relative to the literature in this study. Also, OS was very poor, and the reason for this dismal result may be related to our high rate of PNI. Moreover, we did not obtain significant difference for OS according to adjuvant CRT. The reason for this difference according to the literature may be related to small sample size of our study.

In conclusion, our study indicated that MLR and UICC/AJCC pN staging system were important prognostic indicators for OS for patients with D_2 lymph node dissection in gastric cancer by both univariate and multivariate anaysis. In addition, the multivariate analysis indicated that perineural invasion was also independent prognostic factor. MLR may be useful for evaluating the status of lymph node metastasis in gastric cancer.

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