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ORIGINAL RESEARCH

Treatment Outcomes and Prognostic Factors in N3 Stage Gastric Cancer After Curative Resection: A Real World Data

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Purpose: N3 gastric cancer is characterized by a fairly high lymph node metastasis burden and poor outcome despite optimal therapy. Given the limitations of TNM classification, a comprehensive evaluation tool is necessary to predict the prognosis of patients with N3 gastric cancer who underwent curative surgery. This study aims to explore the outcomes and clinicopathologic prognostic factors affecting the overall survival (OS) of patients with N3 gastric cancer after surgery.

Methods: Data on patients with N3 gastric cancer who underwent (sub)total gastrectomy and regional lymph node dissection between November 2005 and September 2018 (n = 169) were analyzed by Cox regression to determine the independent prognostic factors for OS.

Results: The multivariable analysis established that gender, patient performance status, metastatic lymph node ratio (MLNR), tumor grade, and adjuvant chemotherapy are significantly associated with OS. The five-year OS of the study population was 15%. Adjuvant chemoradiotherapy was applied to 72% of the patients, which resulted in an improvement in recurrence-free survival but not OS. Recurrence occurred in 103 (75%) patients, in which the most frequent recurrence site was distant metastasis.

Conclusion: Male gender, poor performance status, grade 3 tumor, MLNR > 0.37, and not receiving adjuvant chemotherapy are predictors of poor prognosis in N3 gastric cancer after curative resection. Considering the high recurrence rates of this group, prospective studies are needed to optimize treatment strategies.

Keywords: gastric cancer, prognosis, N3, lymph node ratio, recurrence pattern

Introduction

According to GLOBOCAN 2018, gastric cancer was globally diagnosed in more than 1 million new cases, which resulted in more than 782,000 deaths. This number of deaths makes gastric cancer the third leading cause of cancer-related deaths.[1] Although the incidence in the United States has decreased in the last decade, gastric cancer continues to be a primary health problem, especially in East Asia.[2,3] The main curative treatment option for non-metastatic gastric cancer is (sub)total gastrectomy with regional lymphadenectomy.[4] Despite recent advancements in surgical techniques and perioperative medical treatment improving long-term outcomes of early gastric cancer, the prognosis of locally advanced diseases is still poor.[5] The AJCC 8th Edition TNM staging system is currently used to predict the prognosis of patients with gastric cancer. However, this system only considers two parameters for non-metastatic gastric cancer, namely, the depth of invasion and the number of metastatic lymph nodes (pT and pN).[6] The N stage is determined by the number of metastatic lymph nodes, which can differ depending on the extent of lymphadenectomy. Failure to remove enough lymph nodes can lead to underestimated nodal status.[7] Therefore, other clinicopathologic features, such as age, tumor size, vascular and nerve invasion, tumor differentiation, and serum markers, whose effects on survival have been shown previously, should be taken into account.[8] Identifying a more accurate evaluation tool to predict the prognosis of patients who underwent curative surgery is essential[9].

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N3 gastric cancer, characterized by a heavy burden of nodal metastases, has an extremely poor prognosis.[10] Despite optimal therapy, the recurrence rate in patients can reach up to 80%.[11] This study aims to determine outcomes and prognostic factors affecting the overall survival (OS) in curatively treated pN3 gastric cancer patients.

Materials and Methods

Study Population

We retrospectively assessed patients with gastric cancer who underwent curative radical gastrectomy between 2005 and 2018. A total of 169 patients with pathologically confirmed pN3/ypN3 gastric adenocarcinoma were enrolled in the present study (Figure 1). All patients underwent ≥D1+ lymphadenectomy. The pathology results of the patients were re-evaluated according to the 8th edition of the AJCC TNM staging system [6]. The eligibility criteria consisted of histopathologically confirmed gastric adenocarcinoma without macroscopic residual tumor. The patients who had distant or peritoneal metastases, recurrent gastric cancer, and other types of cancer were excluded. All patients' medical records were reviewed. Moreover, clinicopathologic parameters, including age, gender, performance status, pathologic TNM stage, tumor location, tumor differentiation, tumor size (maximum tumor diameter), type of surgery, lymphovascular invasion (LVI), and perineural invasion, were collected. The metastatic lymph node ratio (MLNR) was calculated as the ratio of metastatic lymph nodes to the total number of excised lymph nodes.

The study was approved by the local ethics committee of our institution. The local regulations in our country do not mandate patient consent for retrospective chart reviews. The waiver was granted with due consideration of patient data confidentiality and strict adherence to the principles of the Declaration of Helsinki.

Treatment

Adjuvant chemotherapy was routinely recommended to patients with pathological N3 disease who can tolerate adjuvant treatment according to performance status and comorbidities. The chemotherapy regimen consisted of either a 5-FU or a combination of 5-FU and cisplatin/oxaliplatin. Adjuvant chemoradiotherapy(CRT) was administered to patients who had completed the adjuvant chemotherapy, had a good performance status, and showed no progression. These patients received a total radiation dose of 4500 cGy, delivered at a daily dose of 180 cGy over five weeks concurrently with either 5-fluorouracil (5-FU) or capecitabine following the completion of adjuvant chemotherapy.

Follow-Up and Recurrence

All patients were routinely followed up in the clinic with physical examinations and laboratory tests, including tumor markers, chest X-ray or CT, abdominal CT, or ultrasonography. Follow-up visits were done every three months for the first two years, every six months for up to five years, and then annually. Recurrence was determined with imaging modalities and biopsies of suspicious lesions.

The recurrence sites of the disease were classified into three categories: a) locoregional recurrence, defined as recurrence in the anastomosis line or surrounding regional lymph nodes; b) peritoneal recurrence, defined as a malignant tumor deposit on the visceral peritoneum; and c) distant recurrence, defined as a distant organ metastasis (liver, bone, lung) or non-regional metastatic lymph nodes.

Recurrences within one year after curative resection were reported as early recurrences.

Statistical Analysis

Descriptive statistics of numerical variables are summarized as mean ± standard deviation or median–interquartile range (IQR) according to the normality of the groups. Categorical variables were represented as frequencies and percentages. The optimal cut-off value for mLNR and tumor size was determined by calculating the AUC of receiver operating characteristic (ROC) analysis. In the evaluation of AUC, the maximal joint point of sensitivity and specificity was determined by the Youden Index. Mann–Whitney *U*-test and Pearson chi-square or Fisher's test were used to compare continuous and categorical variables of two groups, respectively. The Kaplan-Meier test was used for survival analyses. The duration of time between the date of diagnosis and the date of last control for alive patients or death from any cause was defined as overall survival (OS). The interval between the time of

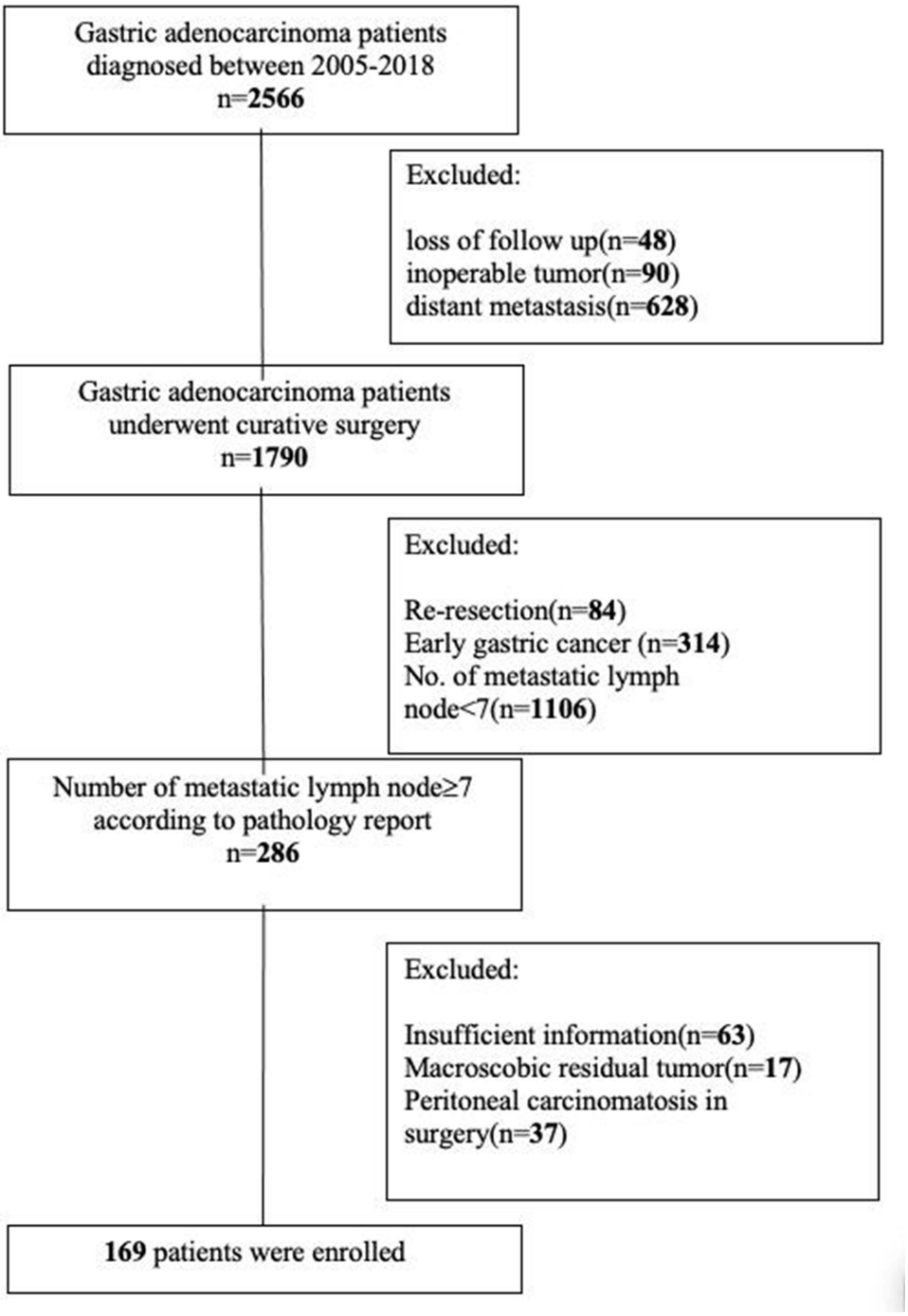

Figure 1 Patient flow chart.

diagnosis and recurrence was defined as disease-free survival (DFS). Univariate and multivariate analyses for OS and DFS were performed by Cox proportional hazards regression model.

All statistical analyses were performed using IBM SPSS Statistics version 22. The level of significance was $p < 0.05$.

Results

Demographic and Pathologic Characteristics

The clinicopathologic characteristics of the patients are listed in Table 1. Among the 169 patients, 134 (79.3%) were males and 35 (20.7%) were females. The median age of the patients was 56.0 years (IQR: 49.50–64.50 years). The

Table 1 Clinicopathologic Characteristics of the Patients (n=169)

Parameter	Number of Patients [n(%)]
Age (mean(IQR))	56.0 (49.50–64.50)
<65	127 (75.1)
≥65	42 (24.9)
Sex	
Male	134 (79.3)
Female	35 (20.7)
ECOG	
0	45 (26.6)
1	99 (58.6)
2	25 (14.8)
Tumor Localization	
Upper	39 (23.4)
Middle	69 (41.3)
Lower	59 (35.3)
Multifocal	2 (1.2)
Surgical treatment	
Subtotal gastrectomy	63 (37.3)
Total gastrectomy	106 (62.7)
Grade	
2 (moderate)	57 (34)
3 (poor)	110 (65)
Unknown	2 (1)
Pathologic T stage	
T1	–
T2	6 (3.6)
T3	62 (36.9)
T4a	85 (50.6)
T4b	15 (8.9)
Number of total retrieved lymph nodes (median(IQR))	29 (21–39)
≥ 16 lymph nodes	149 (88.2)
< 16 lymph nodes	20 (11.8)
Lymph node dissection	
D1	29 (17.2)
D2	140 (82.8)
N stage	
N3a	90 (53.3)
N3b	79 (46.7)
Number of metastatic lymph nodes (median(IQR))	14 (9–21)
LNR (median(IQR))	0.58 (0.40–0.77)
Tumor size (the maximum diameter of the tumor as cm)(median)(IQR)	6.0 (4.5–9.00)
Surgical border	
Negative	138 (82.1)
Positive	31 (17.9)

(*Continued*)

Table 1 (Continued).

Parameter	Number of Patients [n(%)]
PNI	
No	61 (31)
Yes	118 (69)
LVI	
No	34 (21)
Yes	135 (79)

Notes: Frequency(percentage), and median–interquartile range (IQR).
Abbreviations: mLNR, metastatic lymph node ratio; PNI, perineural invasion; LVI, lymphovascular invasion.

performance status of the patients was evaluated according to the Eastern Cooperative Oncology Group Performance Score (ECOG-PS). The majority of the patients had an ECOG-PS of 0 or 1, while only 15% had an ECOG-PS of 2. D2 dissection was performed in 82.8% of the patients. Most of the following patients were in pathological T4a (50.3%), while 36.7% were in pT3.

The median follow-up time was 82 months. Approximately 87% of the patients received adjuvant chemotherapy, and dose reduction was applied in 30% of these patients. Only 30 patients (18%) received neoadjuvant chemotherapy(NACT). No statistical difference was observed in the OS (median OS 24.6 vs. 19.7 months, $p > 0.05$) and RFS (median RFS 17.9 vs. 13.3, $p>0.05$) between those who did not receive NACT and those who did. Adjuvant CRT was administered in 72% of the patients (Table 2). Information about the recurrence status of 35 patients could not be obtained. The analysis regarding RFS was conducted on 134 patients. Recurrence occurred in 103 (75%) patients. The median recurrence-free survival (RFS) was found to be 17 months (13.4–20.6). The median RFS of the patients who received adjuvant CRT was significantly higher than those who did not receive adjuvant CRT (19.5 vs. 8.1 months; $p < 0.001$, see Table 3). However, no significant difference was found between the OS of the patients who received and did not receive adjuvant CRT ($p = 0.084$). Meanwhile, the median RFS and OS of the patients who received adjuvant chemotherapy were significantly higher than those who did not receive adjuvant chemotherapy (mRFS 17.9 vs 9.7, $p=0.046$; mOS 23.2 vs 11.5 months; $p = 0.007$).

Identification of Prognostic Factors of RFS and OS

The OS curve for all patients is shown in Figure 2A. The one-year survival rate of the patients was 82%, the three-year survival rate was 29%, and the survival rate in the fifth year was 15%. The median OS of all patients was 21.8 months (95% CI: 19.1–24.6).

Table 2 Treatment-Related Features of Patients

	Number of Patients (%)
Adjuvant chemoradiotherapy	
No	19 (11)
Yes	122 (72)
Unknown	28 (17)
Adjuvant chemotherapy	
No	8 (4)
Yes	148 (87)
Unknown	15 (9)
Perioperative chemotherapy	
No	139 (82)
Yes	30 (18)

Table 3 Comparison of OS and RFS According to Treatment

Characteristics	OS	p value	RFS	p-value
(Neo)adjuvant Chemotherapy		**0.007**		**0.046**
No	11.5 (5.4–17.5)		9.7 (1.2–18.2)	
Yes	23.2 (20.2–26.3)		17.9 (14.7–21.2)	
Adjuvant chemoradiotherapy		0.084		**<0.001**
No	18.7 (12.2–25.3)		8.1 (5.5–10.7))	
Yes	23.9 (20.7–27.1)		19.5 (16.9–22.2)	

Notes: Median (IQR), Bold p-value: p<0.005 statistically significant.
Abbreviations: OS, overall survival; RFS, recurrence-free survival.

ROC analysis was performed to determine the prognostic value and a cut-off for the mLNR ratio by defining death from any cause as the endpoint. The AUC was 0.73 (CI: 0.54–0.82) ($p < 0.05$). The maximal joint point of sensitivity and specificity was determined using the Youden Index. The optimal cut-off value for mLNR was 0.37 with 88% sensitivity and 48% specificity. The same cut-off value was used for recurrence with 88% sensitivity and 42% specificity (AUC: 0.70, CI: 0.60–0.80). For mLNR grouped according to the threshold, the median OS of patients with LNR < 0.37 was significantly higher than the survival time of patients with LNR ≥ 0.37 (55.9 vs. 19.7 months; $p < 0.001$, see Figure 2B). Also, the median RFS of patients with LNR<0.37 was significantly higher than the other group (NR vs. 15.5 months, p=0.002). The median OS of the patients with tumor size < 3.6 cm was also significantly higher than that of patients with tumor size ≥ 3.6 (36.8 vs. 21.4 months); $p = 0.014$, Figure 2C).

In the univariate analysis focusing on disease-free survival (RFS), significant prognostic factors were identified as mLNR, adjuvant chemotherapy, and adjuvant CRT (Table 4). However, when assessing overall survival (OS) through univariate analysis, factors such as age, grade, performance status, mLNR, tumor size, pT, and pN stage, as well as LVI, were found to be significant prognostic indicators (Table 5).

A subsequent multivariate analysis employing the Cox proportional hazards model aimed to further evaluate the notable prognostic factors uncovered during the univariate analysis, specifically within the context of N3 gastric cancer patients. This analysis revealed that mLNR remained an independent prognostic factor, alongside the significance of adjuvant CT for RFS (Table 4). Additionally, the multivariate analysis for OS highlighted gender, performance status, grade, mLNR, and adjuvant chemotherapy as independent prognostic indicators (Table 5).

Recurrence Patterns

Recurrence occurred in 103 (61%) patients in the study population. About half of those who had recurrence were observed within the first year. The most common form of recurrence was distant metastasis. The recurrence patterns of the patients and the rates of these patterns are schematized in Figure 3.

Discussion

In the past decades, locally advanced gastric cancer treatment has evolved from frontline surgery to perioperative chemotherapy in the United States and other Western countries.[12] In Asia, different approaches are available, and they vary according to the region.[13,14] Despite new treatment approaches improving OS and RFS, not all patients benefit from perioperative chemotherapy.

For more than 50 years, TNM classification has been used in gastric cancer staging, and much debate on the definition of N3 has been going on for years. During this period, the definition of N3 has been revised several times.[15,16] According to the eighth edition of the AJCC TNM classification, the division of N3 into N3a (7–15 MLNs) and N3b (>15 MLNs) has shown improvement in prognosis estimation.[6] This system, which is based on the preservation of the removed metastatic lymph node, may be affected by several clinical and surgical factors, such as the extent of lymphadenectomy and variation in the number of individually owned lymph nodes. Therefore, different prognoses may be encountered even in the same nodal stage.[10] However, a more comprehensive evaluation is needed to better identify the prognostic factors

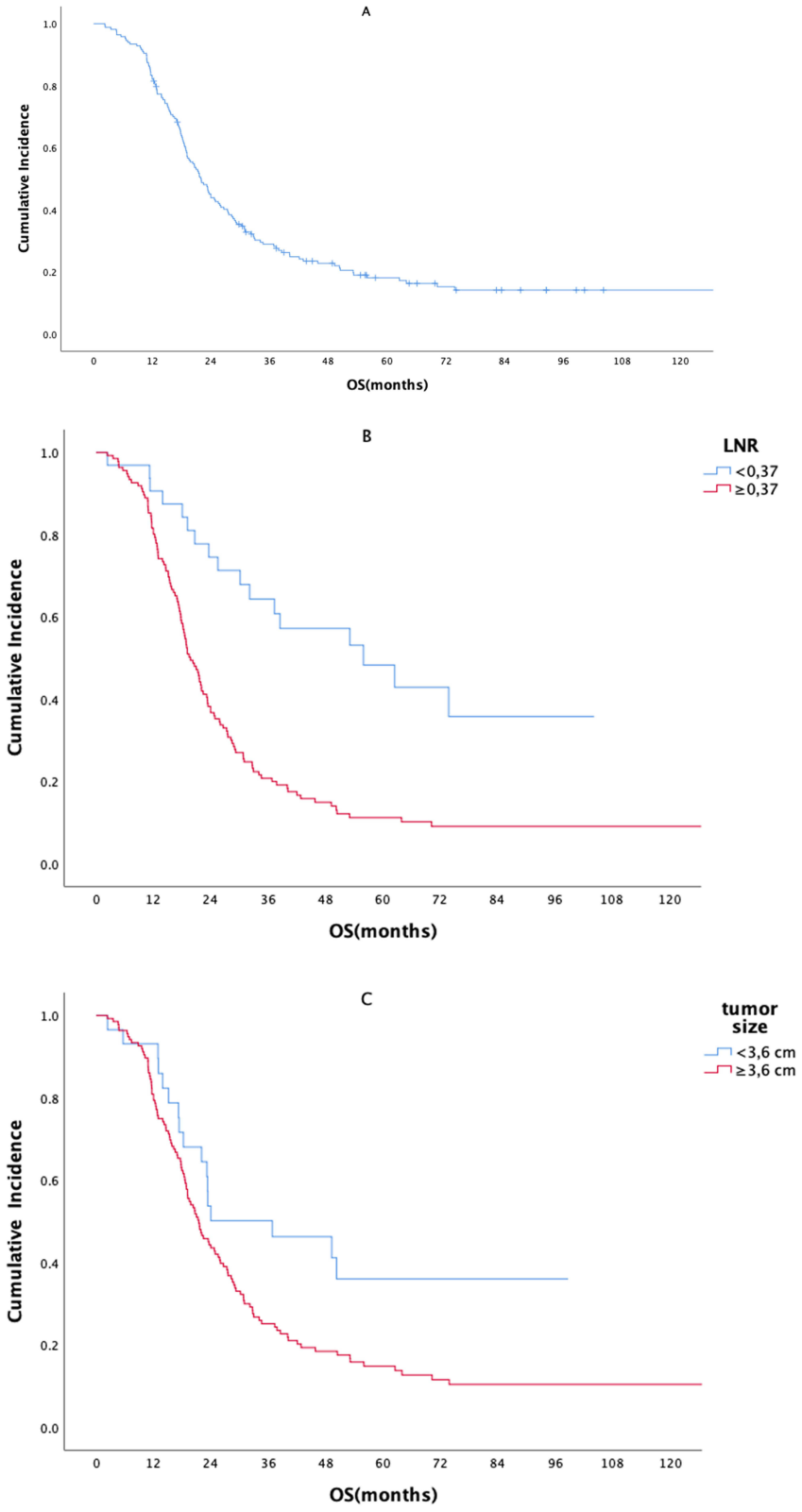

Figure 2 (**A**) Overall survival curve for all patients. (**B**) The effect of LNR on OS in gastric cancer patients. (**C**) The effect of tumor size on OS in gastric cancer patients.

and manage patients with N3 gastric cancer. There is no well-defined optimal treatment strategy for N3 gastric cancer. This group is underrepresented in clinical trials[14,17,18] (not more than 10% of the study population), and current guidelines recommend treating them like other locally advanced gastric cancers.

Table 4 Univariable and Multivariable Analyses of prognosis Factors to predict RFS

		Univariable Analysis		Multivariable Analysis	
Parameter	**Subgroup**	**HR (95% CI)**	**p- value**	**HR (95% CI)**	**p-value**
Age	<65 ≥65	1.52 (0.97–2.40)	0.066	– –	–
Gender	Female Male	1.40 (0.87–2.25)	0.159	– –	–
Ecog	Well Moderate Poor	1.31 (0.83– 2.0) 1.58 (0.82– 3.0)	0.241 0.165	– –	–
mLNR	<0.37 ≥0.37	2.52 (1.37–4.63)	**0.003**	1 2.60 (1.37–4.95)	**0.003**
N stage	N3a N3b	1.34 (0.90– 1.98)	0.140	– –	–
Grade	II (moderate) III (poor)	1.19 (0.79–1.79)	0.398	– –	–
Surgical border	Negative Positive	1.59 (0.97– 2.60)	0.066	– –	–
PNI	No Yes	1.41 (0.85– 2.35)	0.181	– –	–
LVI	No Yes	1. 37 (0.76– 2.47)	0.283	– –	–
Adjuvant radiotherapy	No Yes	4.02 (2.25– 7.19)	**< 0.001**	1 1.93 (0.64–5.82)	0.242
Adjuvant chemotherapy	No Yes	3.75 (1.49–9.42)	**0.005**	1 3.03 (1.61–5.70)	**0.001**

Note: Bold p-value: p<0.005 statistically significant.
Abbreviations: mLNR, metastatic lymph node ratio; PNI, perineural invasion; LVI, lymphovascular invasion; HR, hazard ratio.

Table 5 Univariable and Multivariable Analyses of prognosis Factors to predict OS

		Univariable Analysis		Multivariable Analysis	
Parameter	**Subgroup**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	<65 ≥65	1.55 (1.06–2.26)	**0.022**	1.37 (0.87–2.15)	0.174
Gender	Female Male	1.56 (0.99–2.45)	**0.051**	1.96 (1.13–3.40)	**0.016**
Ecog	Well Moderate Poor	1.52 (1.00– 2.3) 2.09 (1.22– 3.58)	 **0.045** **0.007**	 1.33 (0.81–2.17) 2.81 (1.40–5.56)	**0.012** 0.254 **0.004**
mLNR	<0.37 ≥0.37	2.91 (1.74- 4.87)	**<0.001**	2.95 (1.56–5.56)	**0.001**
Tumor–size	<3.6 ≥3.6	1.87 (1.12- 3.12)	**0.016**	1.49 (0.83–2.65)	0.173

(*Continued*)

Table 5 (Continued).

		Univariable Analysis		Multivariable Analysis	
Parameter	**Subgroup**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Tumor localization	Upper Middle Lower	 1.31 (0.84- 2.05) 1.18 (0.75- 1.87)	 0.222 0.464	–	–
N stage	N3a N3b	 1.69 (1.20- 2.89)	**0.002**	1.18 (0.78- 1.80)	0.419
Grade	II (moderate) III (poor)	 1.49 (1.03–2.15)	**0.032**	1.73 (1.11–2.71)	**0.015**
Surgical border	Negative Positive	 1.44 (0.95- 2.21)	0.085	–	–
PNI	No Yes	 1.43 (0.91- 2.24)	0.117	–	–
LVI	No Yes	 1.77 (1.04- 2.99)	**0.033**	1.07 (0.58- 1.96)	0.815
T stage	T3 T4a T4b	 1.27 (0.88–1.82) 1.11 (0.59–2.11)	0.083 **0.036** 0.074	–	-
Adjuvant radiotherapy	No Yes	 0.63 (0.18- 1.03)	0.077	–	–
Adjuvant chemotherapy	No Yes	 0.38 (0.18–0.78)	**0.009**	0.14 (0.05–0.37)	**< 0.001**

Note: Bold p-value: p<0.005 statistically significant.
Abbreviations: mLNR, metastatic lymph node ratio; PNI, perineural invasion; LVI, lymphovascular invasion; HR, hazard ratio.

The five-year survival rate for this study population was 15% and the median OS was 21.8 months. These results are relatively similar to those of Pachaury et al[19] in their study (16.3%) despite the NACT receiving group being larger than our study.

Since the effect of TNM classification is limited to predicting the survival rate of this highly specific group of patients, our study considered all clinical and pathological characteristics that can influence the prognosis of the patients. In addition, the effect of adjuvant radiotherapy and/or chemotherapy on survival was evaluated in this study. The multivariate Cox regression analysis represented that gender, performance status, grade, MLNR, and adjuvant chemotherapy were independent prognostic indicators for OS in N3 gastric cancer.

The mLNR reflects not only the number of metastatic lymph nodes but also the extent of lymph node dissection.[20] The mLNR also provides additional information regarding the number of non-metastatic lymph nodes that have shown the potential to host immune responses.[21,22] The main issue with the mLNR is that the cut-off value varies among studies.[23] In this study, we determined the cut-off value of mLNR as 0.37, which is relatively similar to the study of Komatsu et al.[10] Specifically in the N3a patient group, mLNR < 0.37 can significantly distinguish a better prognostic subgroup but not in the N3b group.

Even though D2 lymph node dissection is a standard procedure for locally advanced gastric cancer in European and American guidelines, it cannot be performed at times because of various reasons, such as surgical experience and technical conditions.[24,25] In this study, D2 dissection was applied in 82.8% of the patients. Although patients with high nodal involvement after preoperative chemotherapy and patients with less than D2 dissection are rarely included in studies, we encounter these patients in our daily practice; thus, they were included in our study population.

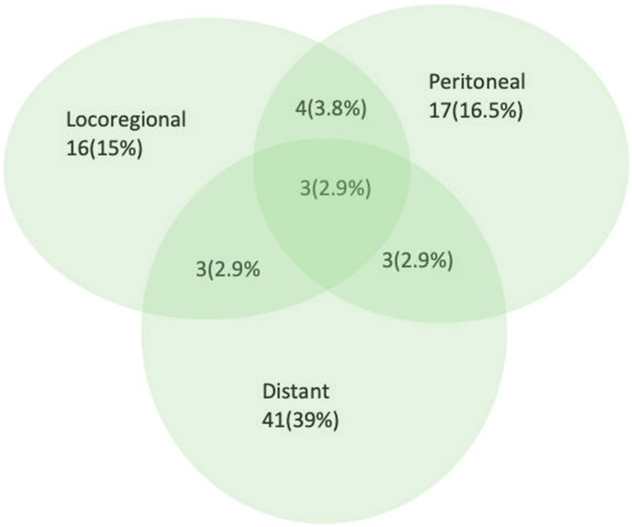

Figure 3 Pattern of recurrences.

Our study comprises an advanced-stage patient population with a high T4 tumor rate (around 60%), leading to a higher than expected R1 resection rate of approximately 20%. Pachaury A. et all reported R1 resection rate was 12% in their study on N3 gastric cancer.[19] However, the T4 tumor rate in this study is below 50%. Despite this, our analysis did not find a significant impact on disease-free survival (RFS) or overall survival (OS).

Only 18% of the study cohort consisted of patients receiving NACT. The median OS of the patients who received NACT was 19.7 months, whereas that of the patients who did not was 26.4 months ($p > 0.05$). Almost the same median OS values were obtained in the study of Pachaury et al,[19] where statistically meaningful OS difference was shown, unlike this study. In their study, MLNR > 0.5 and ypN3 after NACT were reported as independent prognostic factors affecting the OS. To date, there is only one study comparing the pathological TNM stage with the ypTNM stage after NACT in terms of stage-matching gastric cancer OS.[26] The ypTNM stage had a worse prognosis than a similar pTNM stage. In this study, although numerically worse survival was noted in patients with ypN3, no statistically significant difference can be obtained due to the small number of patients who received NACT.

Postoperative radiotherapy has been widely discussed in the last few decades. An updated analysis of the Intergroup 0016 trial demonstrated that adjuvant chemoradiotherapy has an ongoing advantage on OS and RFS; however, only 10% of the study population underwent D2 dissection.[27] Although the ARTIST-2 trial showed that adjuvant chemoradiotherapy or doublet chemotherapy prolonged RFS compared with monotherapy, the addition of radiotherapy to chemotherapy did not decrease the recurrence rate after D2 dissection.[28] However, the median mLNR was smaller than 0.2 in both arms, suggesting the predominance of patients with early nodal stage. This study showed that adjuvant radiotherapy significantly improves RFS in N3 gastric cancer but not OS. Our findings are consistent with the results of Zhou et al, who investigated the addition of radiotherapy to adjuvant chemotherapy, particularly in N3 gastric cancer.[29] Although the effect of radiotherapy in addition to chemotherapy on RFS and OS was not shown in two large clinical studies (CRITICs and ARTIST-2), the representation rate of N3 gastric cancer in these studies was very low, so the effect of radiotherapy on RFS and survival in this group remain uncertain.

This study has several limitations. First, it is a retrospective study, which means it may include inevitable bias. The number of patients undergoing NACT was limited. One reason for this is that the ypN3 rate after NACT was already low; another reason is that patients were included over a long period, existing the period when NACT was not a standard treatment in Turkey. Another limitation is treatment heterogeneity, that is, different adjuvant and neoadjuvant chemotherapies were administered. Despite all these limitations, this is an important study that encompassed a substantial number of patients in a very specific gastric cancer subgroup, which is N3.

Conclusion

This study reflects the real-world data of N3 (pN3, ypN3) gastric cancer patients. Male gender, poor performance status, poor differentiation, and mLNR≥0.37 are associated with poor prognosis. Considering the recurrence patterns, the combined use of different treatment modalities for this subgroup requires further investigations.

Ethics Statement

The study was approved by the Ethics Board of Ankara City Hospital.

Disclosure

The authors report no conflicts of interest in this work.

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