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The lymph node ratio as a prognostic factor for gastric cancer

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Abstract

To predict prognosis of gastric cancer, an adequate assessment of the stage of gastric cancer is important. The UICC/AJCC TNM classification is the most commonly used classification system. For adequate N staging at least 15 lymph nodes should be retrieved. In some countries, this amount of lymph nodes is not met, which can lead to understaging. Therefore, the lymph node ratio (LNR) is proposed as an alternative N staging modality. The purpose of this study was to compare the different staging modalities. *Patients and methods.* We included all patients who underwent surgery for gastric cancer, newly diagnosed between 2000 and 2009 and staged patient by UICC/AJCC TNM 5th/6th or 7th and by LNR. We conducted crude survival analysis, univariate and multivariate analyses according to the different staging systems. *Results.* The five-year overall survival rates ranged from 58% for N0 disease to 18% in case of more than 15 metastatic lymph nodes. The distribution of overall five-year survival according to LNR was 58% for LNR0 and 10% for LNR3. Univariate analysis showed that all the UICC/AJCC TNM classification systems as well as the LNR were strong prognostic factors for overall survival. The LNR correlated less with the number of nodes examined. *Conclusion*. LNR is a good prognostic tool for overall survival, it is an independent prognostic factor with a more homogenous spread of hazard ratios and five-year survival rates than UICC/AJCC systems. Furthermore, the LNR has a lower correlation with the number of nodes examined, making it less vulnerable for stage migration.

Gastric cancer is the fourth most common type of cancer worldwide and ranks second with respect to cancer-related death in Europe [1]. In 2009, nearly 2000 people were newly diagnosed and almost 1500 patients died from gastric cancer in the Netherlands [2]. Although incidence and mortality rates are decreasing, survival is worsening [3]. To predict prognosis the assessment of the stage of gastric cancer is important.

The number of metastatic lymph nodes is considered to be the most reliable prognostic indicator for patients with radically resected gastric cancer [4]. In 1968 the Union Internationale Contra le Cancer (UICC) founded the UICC/AJCC Tumor Node Metastasis (TNM) classification system for malignant tumors. Several versions of this classification system have been used. The Japanese Gastric Cancer Association developed another classification for gastric cancer, however, the UICC/AJCC is the superior and most commonly used classification system [5].

However, the difficulty of the UICC/AJCC TNM classification is that for adequate N staging at least 15 lymph nodes should be retrieved. Literature expresses that in some Western countries including the Netherlands, this amount of lymph nodes is not met by surgeons or pathologists, which can lead to understaging [6]. Apart from the UICC/AJCC system, another N staging system was developed, which would not need the required 15 lymph nodes for adequate staging, i.e. the so-called metastatic lymph node ratio (LNR). The purpose of this study is to compare the different UICC/AJCC TNM 5th/6th/7th staging systems comparing number of examined

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lymph nodes with the LNR and to determine which system has the best prognostic value for gastric cancer patients.

Patients and methods

Patients

Data from the Eindhoven Cancer Registry (ECR) were used, which is maintained and hosted by the Comprehensive Cancer Centre South. The ECR collects data on all patients diagnosed with cancer in the south of the Netherlands, an area with about 2.4 million inhabitants. The ECR is served by 10 community hospitals, six pathology departments and two radiotherapy institutes. We included 973 surgical patients with M0 primary gastric cancer, newly diagnosed between 2000 and 2009.

Patient characteristics such as gender, date of birth, postal code, comorbidities and socio-economic status (SES) as well as tumor characteristics such as date of diagnosis, subsite [International Classification of Diseases for Oncology (ICD-O-3)], histology, stage, grade and treatment were obtained routinely from the medical records by specially trained administrators [7]. Follow-up of vital status of all patients was complete up to 2011 January 1. In addition to passive follow-up via the hospitals, information was actively obtained from civil municipal registries and the Central Bureau for Genealogy.

Tumor sub-localization was divided as follows: cardia, middle part fundus, corpus, lesser and greater curvature, pyloric part, overlapping lesions, and not otherwise specified. Furthermore, tumor characteristics included number of lymph nodes examined, number of positive nodes, and grade of tumor differentiation. Relevant comorbidities were recorded from the medical records according to a slightly adapted version of the Charlson Index [8]. SES of the patients was defined at neighborhood level; postal codes were assigned to one of three SES categories: low (1st–3rd decile), intermediate (4th–7th decile), and high (8th–10th decile). For patients residing in nursing homes, a special SES category was assigned.

Registration took place 6–18 months after diagnosis. The quality of the data is high, due to thorough training of the registration clerks and a variety of computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95% [9].

Staging

Patients were classified according to the UICC/AJCC TNM 5th/6th, 7th and to the LNR. LNR is defined as the number of positive lymph nodes divided by the total number of lymph nodes found in the specimen (Table I).

The LNR cut-off points were based on the most common used cut-off points for the LNR used in literature. Second, we compared different cut-off points by means of the distribution of patients on the categories and we used survival as an independent variable and determined by log-rank test.

Statistical analysis

Survival was calculated according to the Kaplan-Meier method and compared by log-rank test. Survival time was calculated from the date of diagnosis to death or 2011 January 1 for those alive. Univariate and multivariate analyses of prognostic factors were performed using the Cox proportional hazard model. The LNR categories were stratified into UICC/AJCC TNM N-categories and vice versa. This was to assess whether LNR or TNM N classification shows any survival benefit where the opposing staging system fails to predict this. The accepted level of significance was $p < 0.05$. The data were analyzed using SAS statistical software (SAS system 9.2, SAS Institute, Cary, NC, USA).

Results

The median age of M0 gastric cancer patients was 69 years (27–94 years). The majority of patients were male and 59% of the patients had one or more comorbidities. Most tumors were found in the

Table I. The different classification systems.

	UICC/AJCC TNM 5/6 N classification	UICC/AJCC TNM 7 N classification	LNR
Stage	*(number of metastatic lymph nodes)*	*(number of metastatic lymph nodes)*	*(percentage of metastatic lymp nodes)*
0	0	0	0%
1	1–6	1–2	0.1–19%
2	7–15	3–6	20–29%
3	≥15	A: 7–15 B: ≥15	≥30%

antrum and pylorus of the stomach and were poorly differentiated. Pre-operative treatment was given to a small proportion of patients and subtotal gastrectomy was the most common type of resection. In the majority of patients were between three and 10 lymph nodes harvested during surgery and/or pathology (41%) (Table II).

Figures 1 and 2 show the crude overall survival according to the UICC/AJCC TNM 5th/6th and 7th classification systems. The five-year overall survival ranged from 58% for N0 disease to 18% in case of more than 15 metastatic lymph nodes. In N1 stage according to the 5th/6th TNM classification overall five-year survival was 19%. In the 7th TNM classification the 5th/6th TNM N1 stage is divided in N1 and N2, with a five-year survival of 27% and 11%, respectively. In this cohort of patients having M0 gastric cancer, N3b stage of the 7th TNM classification showed a better prognosis than the N3a stage in terms of overall survival. The distribution of overall crude five-year survival according to LNR ranged from 58% for LNR0 to 10% for LNR3 (Figure 3). Univariate Cox survival showed that the TNM 5th/6th and 7th classification as well as the LNR were strong prognostic factors for overall survival. The univariate analyses showed similar results as multivariate analyses after adjustment for relevant patient and tumor characteristics listed in Table III.

Table II. Descriptives of the study population (n = 973).

	n	%
Median age (range) (years)	69 (27–94)	
Gender		
Males	625	64
Females	348	36
Socio-economic status		
Low	286	29
Intermediate	352	36
High	280	29
Institutionalized	29	3
Unknown	26	3
Comorbidity		
None	320	33
1	293	30
≥ 2	283	29
Unknown	77	8
Tumor site		
Cardia	183	19
Middle part	236	24
Antrum and pylorus	364	37
Overlapping, unknown	190	20
Stage		
IA	123	13
IB	259	27
II	307	32
IIIA	213	22
IIIB	36	4
IV	35	4
Differentiation grade		
Moderate/well	275	28
Poor	563	58
Unknown	135	14
Preoperative treatment		
Chemo- and/or radiotherapy	133	14
None	840	86
Type of resection		
Total gastrectomy	223	59
Subtotal gastrectomy	571	23
Esophageal-cardiac resection	126	13
Multi-organ resection	31	3
Unspecified type of resection	22	2
Number of lymph nodes evaluated		
0	58	6
1/2	69	7
3/6	198	20
7/10	203	21
11/14	151	16
≥ 15	145	15
Exact number unknown	145	15
Unknown	4	0

In multivariate analysis, the 5th/6th TNM N stage, age, comorbidities and 6th TNM T stage had an independent effect on survival in the first model. UICC/AJCC 5th/6th TNM N2 stage had a higher hazard ratio than N3 stage, 3.48 (95% CI 2.64–4.59) versus 2.51 (95% CI 1.33–4.72). In our models concerning TNM 7th and LNR the aforementioned factors also had an independent effect on survival. In the second model UICC/AJCC 7th TNM N2 and N3a stage had a higher hazard ratio then N3b stage. In the last model the hazard ratios for the various LNR stages increased from 1.72 (95% CI 1.25–2.37) in LNR1 to 3.22 in LNR3 (95% CI 2.59–4.10) (Table III). This table also shows that patient distribution among different classification systems is best in UICC/AJCC TNM 7th.

There was a significant correlation between number of lymph nodes examined and the UICC/AJCC TNM 7th (correlation coefficient = 0.33; $p < 0.001$) or TNM 5th/6th N classification (correlation coefficient = 0.33; $p < 0.001$). The LNR correlated less but was still significant (correlation coefficient = 0.11; $p = 0.0019$). There was no significant difference in survival after stratifying LNR stage 3 in different UICC/AJCC TNM N stages. For the other LNR groups, stratification for N stage was not possible due to small numbers and little variation within the LNR group. The LNR showed significant differences within N1 stage of the 5th/6th or 7th TNM in terms of survival. In the 7th TNM classification patients with a N1 stage and a LNR1 had a five-year overall survival of 39%, while patients with a LNR stage 3 had a five-year overall survival of 15% ($p = 0.0404$). For TNM 6th N1 patients similar survival differences were found (Table IVa and b).

Discussion

The results of this study show that the various versions of the TNM classification and the LNR are

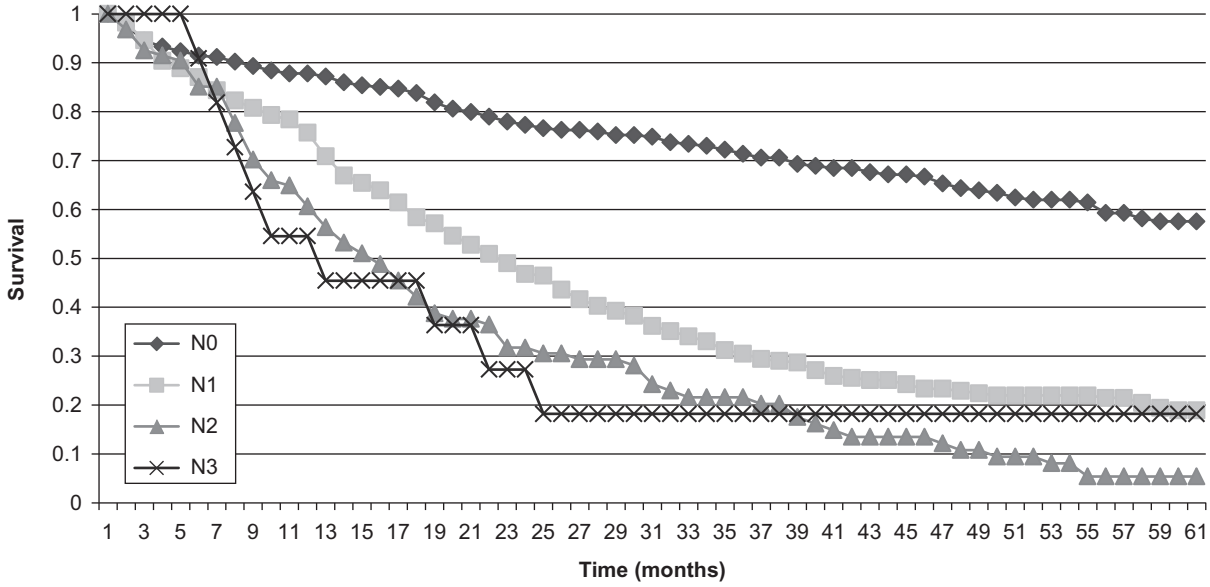

Figure 1. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to TNM6 N stage. Log rank $p < 0.001$.

independent prognostic factors for overall survival. The LNR had the best homogenous spread of overall crude five-year survival and hazard ratios, and correlated the least with the total amount of lymph nodes examined.

In 1997 the UICC/AJCC introduced the 5th edition of the UICC/AJCC TNM Classification of Malignant Tumors [10]. At this time N stage was defined as: N1 having metastases in 1–6 lymph nodes, N2 having metastases in 7–15 lymph nodes and N3 as having metastases in more than 16 lymph nodes. Subsequently in 2002, the UICC/AJCC came with the 6th edition of the UICC/AJCC TNM staging system, which was only slightly different from the previous one and remained the same in terms of N stage. After the 7th edition was published in 2010 there was a reclassification for the T and the N stage, which resulted in a shift from stage IV to stage III disease [11]. In this edition N stage was defined as N1 having metastases in 1–2 lymph nodes, N2 in 3–6 lymph nodes, N3a in 7–15 lymph nodes, and N3b in more than 15 lymph nodes [12]. A minimum of 15

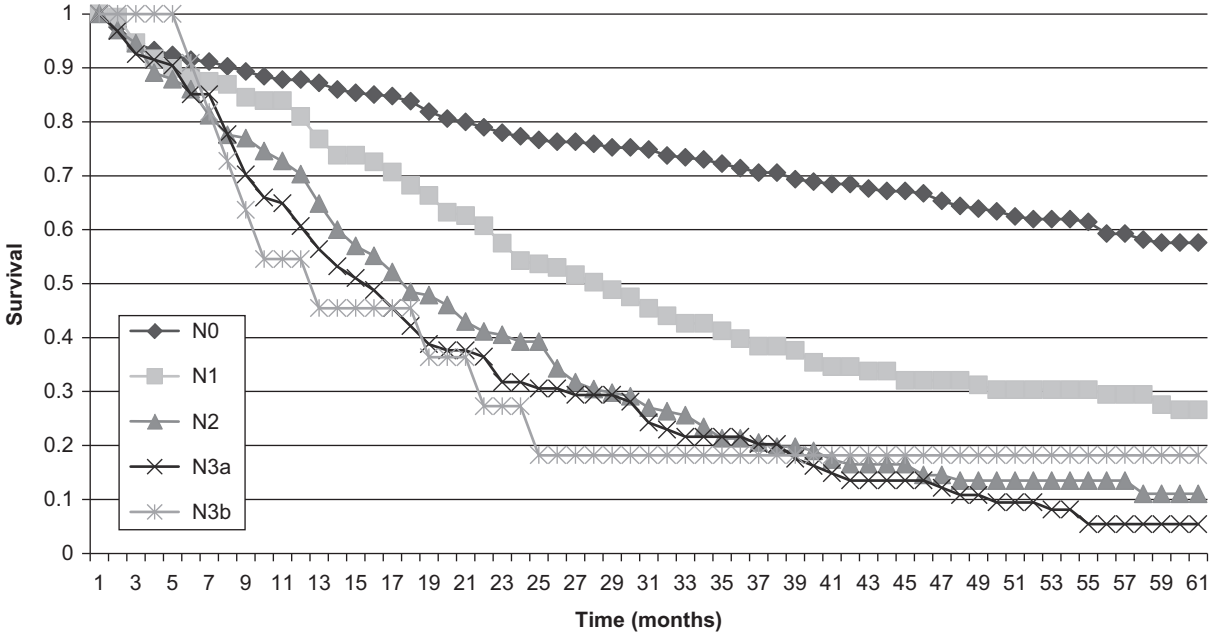

Figure 2. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to TNM7 N stage. Log rank $p < 0.001$.

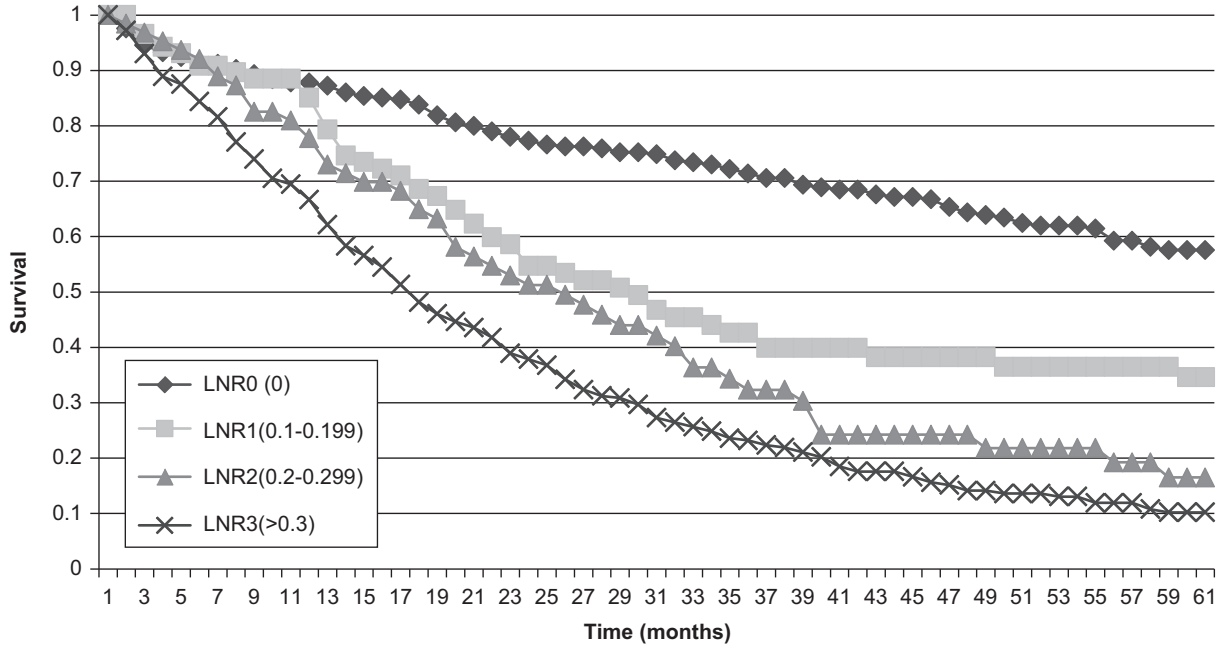

Figure 3. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to N ratio. $p < 0.001$.

lymph nodes examined is necessary for adequate staging using the TNM classification system. In the Netherlands and various other countries this amount is often not met. Previous research done in the Comprehensive Cancer Centre South showed that this can partly be explained by differences between the various pathology departments [6], showing a difference in the median number of detected lymph nodes. The region of the Comprehensive Cancer Centre South is served by six departments of pathology and the number of lymph nodes assessed varied between five and nine lymph nodes per patient, with a median number of seven in the whole region. Also after adjustment in a multi-level analysis for relevant factors, differences between departments of pathology remained, probably suggesting variation in diligence and effort put in these time-consuming examinations. They did not find an effect of age, gender or operating volume. The latter would make centralization of surgery for gastric cancer less effective for harvesting more lymph nodes.

Centralization of gastric cancer surgery has been a frequently discussed topic in the Netherlands. Recent literature on the difference between low (1–5 gastrectomies) and high (over 20 gastectomies) volume hospitals confirmed the improved harvesting of lymph nodes in high volume hospitals [13]. On the other hand, this study fails to show if they meet the minimal amount of lymph nodes needed, making an alternative N staging modality still necessary. However, since 2012 gastrectomies in the Netherlands are centralized to a minimum of 10 per year and as of 2013 to a minimum of 20 per year.

Further known factors associated with a higher detected number of lymph nodes are younger age, comorbidity, female gender, Asian race, obesity and more radical surgery [6,14–16]. Obviously, in a total gastric resection more surrounding tissue is removed, resulting in more lymph nodes retrieved and assessed. In the Netherlands, mostly a D1 resection is performed. The type of lymph node dissection during surgery is still subject to discussion and there is no worldwide consensus about this. There are different types of lymphadenectomy. In a D1 resection perigastric lymph nodes are removed, while in a D2 resection additionally the lymph nodes around the left gastric artery, the common hepatic artery and splenic artery are removed, depending on location of the tumor [17]. Limited research has been done for LNR for gastric cancer treated with a limited lymphadenectomy, as usually conducted in the Western world including the Netherlands. Nevertheless adequate research has been done in extended lymphadenectomy and for various other types of carcinomas [18].

This study implicates that LNR is a good prognostic tool for overall survival in a population with a limited lymphadenectomy and a minimal amount of lymph nodes harvested during surgery and/or examined during pathology. The results show that LNR is an independent prognostic factor with a more homogenous spread of hazard ratios and crude five-year overall survival rates than UICC/AJCC TNM classification systems 5th, 6th and 7th version. Furthermore, the LNR has a lower correlation with the number of lymph nodes examined, making it less vulnerable for stage migration: finding metastases that had previously been

Table III. Overall multivariate survival analysis for M0 gastric cancer patients.

		Hazard Ratio (95% Confidence Interval)		
	N	Model 1	Model 2	Model 3
TNM 5/ 6 N stage				
N0	387	1.0		
N1	372	2.32 (1.92–2.80)*		
N2	99	3.48 (2.64–4.59)*		
N3	12	2.51 (1.33–4.72)*		
Exact number unknown	49	2.35 (1.64–3.34)*		
TNM 7 N stage				
N0	387		1.0	
N1	189		1.85 (1.48–2.32)*	
N2	183		3.07 (2.46–3.84)*	
N3a	99		3.56 (2.70–4.70)*	
N3b	12		2.54 (1.35–4.78)**	
Exact number unknown	49		2.39 (1.68–3.41)*	
N ratio				
0 (0)	382			1.0
1 (0.01-0.19)	87			1.72 (1.25–2.37)*
2 (0.20–0.29)	63			2.54 (1.81–3.55)*
3 (0.30–1.00)	288			3.22 (2.59–4.10)*
missing	207			2.29 (1.81–2.91)*
Age (years)				
<70	491	1.0	1.0	1.0
70+	482	1.25 (1.06–1.47)*	1.29 (1.09–1.52)*	1.28 (1.08–1.51)**
Gender				
Males	625	1.0	1.0	1.0
Females	348	0.92 (0.78–1.09)	0.94 (0.80–1.12)	0.98 (0.83–1.17)
Comorbidity				
None	320	1.0	1.0	1.0
1	293	1.23 (1.00–1.50)**	1.21 (0.99–1.48)	1.18 (0.97–1.45)
2 or more	283	1.51 (1.23–1.86)*	1.54 (1.25–1.90)*	1.45 (1.18–1.78)**
unknown	54	1.17 (0.82–1.67)	1.20 (0.84–1.71)	1.09 (0.76–1.56)
TNM 6 T stage				
T1	152	0.52 (0.38–0.70)*	0.54 (0.40–0.73)*	0.47 (0.35–0.64)*
T2	528	1.0	1.0	1.0
T3	255	1.28 (1.07–1.52)**	1.28 (1.07–1.53)*	1.31 (1.09–1.56)**
T4	35	1.87 (1.28–2.74)**	1.97 (1.34–2.89)*	1.92 (1.31–2.81)**
Number of lymph nodes examined				
<7	325	1.18 (0.98–1.42)	1.18 (0.98–1.42)	1.00 (0.84–1.20)
≥ 7	499	1.0	1.0	1.0
Tumor site				
Cardia	183	0.89 (0.65–1.22)	0.87 (0.64–1.19)	0.90 (0.66–1.23)
Middle part	236	0.82 (0.66–1.02)	0.83 (0.67–1.04)	0.84 (0.68–1.05)
Pyloric part	364	1.0	1.0	1.0
Other/unknown	190	1.10 (0.87–1.38)	1.08 (0.86–1.36)	1.03 (0.83–1.29)
Type of resection				
Total gastrectomy	191	1.18 (0.96–1.46)	1.19 (0.96–1.47)	1.31 (1.06–1.61)*
Subtotal gastrectomy	571	1.0	1.0	1.0
Eesophageal-cardia resection	126	1.28 (0.91–1.81)	1.30 (0.92–1.83)	1.41 (1.00–1.99)
Multi-organ resection	31	1.29 (0.83–2.00)	1.26 (0.81–1.96)	1.43 (0.92–2.22)
Neoadjuvant treatment				
No	840	1.0	1.0	1.0
Yes	133	0.99 (0.76–1.28)	1.00 (0.77–1.30)	1.07 (0.83–1.40)

Model 1. Multivariate analysis with TNM 5/6 N-stage, model 2 : Multivariate analysis with TNM 7 N-stage, model 3: Multivariate analysis with lymph node ratio.
*$p \leq 0.001$; **$p < 0.05$.

Table IVa. Five-year overall survival for N stage 1 and N stage 2 (TNM 7) according to lymph node ratio.

	TNM 7 N1 n = 187		TNM 7 N2 n = 183	
	n	5-year overall survival (%)	n	5-year overall survival (%)
Lymph node ratio				
1 (0.1–0.19)	78	39*	8[a]	
2 (0.20–0.29)	38	18	20	18
3 (0.30–1.00)	52	15	137	11
Missing	19	21	18[a]	

*$p < 0.05$; [a]not available due to small numbers.

Table IVb. Five-year overall survival for N stage (TNM 6) according to lymph node ratio.

	TNM 6 N1 n = 370		TNM 6 N2 n = 183	
	n	5-year overall survival (%)	n	5-year overall survival (%)
Lymph node ratio				
1 (0.1–0.19)	86	35*	8[a]	
2 (0.20–0.29)	58	18	20	17
3 (0.30–1.00)	189	12	137	11
Missing	37	11	18[a]	

*$p < 0.05$; [a]not available due to small numbers.

unidentified which results in upstaging of patients. The identification of metastases can be done by examining and/or harvesting more (metastatic) lymph nodes during surgery and pathology [19]. In a small population the LNR showed a survival benefit where the conventional staging system failed to predict any benefit (Table IVa and b). Patients with a UICC/AJCC TNM 5th/6th or 7th N1 stage and a LNR stage 3, have a prognosis that is closer to an UICC/AJCC TNM N2 stage disease.

Compared to the 5th/6th version of the UICC/AJCC TNM classification, the 7th version had a more homogenous spread in five-year overall survival. Although the 7th TNM N3b stage had a better five-year overall survival then N2 and N3a, the spread among all curves is more homogenous when comparing UICC/AJCC TNM 5th/6th with 7th. Nevertheless it failed to show a benefit in multivariate survival analysis, with 7th TNM N3b stage having a better prognostic value then N2 and N3a stage. This is probably due to the small amount of patients in N3b stage. UICC/AJCC 7th TNM classification correlated as strong as the 5th and 6th version with the total number of lymph nodes examined, making it more vulnerable for stage migration. It seemed to be less influenced by confounding factors when comparing univariate with multivariate analysis.

When reviewing the literature for the prognostic impact of LNR compared to the 5th/6th UICC/AJCC TNM classification, most studies demonstrate that LNR is a better prognostic tool than the 5th/6th UICC/AJCC TNM classification. The LNR is proven to be the strongest independent prognostic factor in terms of overall survival and a prognostic factor for recurrence of disease [20,21]. It also minimizes stage migration by being an independent prognostic factor without being influenced by the amount of lymph nodes examined [18]. Whereas stage migration is suggested to be at least 10% and up to 25% in the conventional TNM classification systems, LNR halves the stage migration phenomenon [22,23]: in a study done by Persiani et al. [24], stage migration was found in 19% of the cases classified by the 5th/6th UICC/AJCC TNM-system, and in only 11% of the cases when LNR was applied [24]. As stated by our results and in the literature the LNR gives a more homogenous stratification of the survival curves [25]. In addition, literature shows that LNR can make a prognostic difference between different UICC/AJCC TNM N stages: N1 patients having a LNR less than 9% have similar survival as patients with N0 gastric cancer, and patients with a LNR between 10% and 25% have a prognosis similar to a TNM 5th/6th N2 stage. On the contrary, UICC/AJCC TNM N stages cannot significantly distinguish in survival between different LNR groups [26]. The power of our research prevents us from drawing this conclusion, but our evidence suggests a prognostic benefit for LNR within different TNM stages in terms of survival. Several studies also endorse these benefits for a D1 lymph node dissection, but all studies have a higher average amount of lymph nodes harvested [23].

When comparing literature about the 5th/6th UICC/AJCC TNM classification with its successor, conclusions vary. Some evidence suggests the 7th edition being the best classification for predicting overall survival: they found that the 7th edition N stage is an independent factor for predicting overall survival instead of the 5th/6th edition N stage multivariate survival analysis. They also showed a statistically significant difference between survival in 7th N1 and N2 stages, but not in 5th/6th N2 and N3 stages. This research has been done in both extended as limited lymph node dissection [12,17], and could not be confirmed by our results. Others suggest the new TNM system to be a major reclassification, without improving the assessment of patient prognosis even showing inferior distribution in survival curves. In this study, the type of lymph node dissection is not mentioned [27]. Our results do also show a major redistribution but also a more homogenous spread of survival curves.

Little is published about the prognostic value of the 7th UICC/AJCC TNM classification compared

to the LNR. However, it has been reported that in the 7th edition of the TNM staging system the proportion of advanced TNM N stage increases when the number of examined lymph nodes increases, being prone to stage migration. This in contrast to the LNR which was constant regardless of the number of lymph nodes examined. It also showed better patterns of patient distribution between LN stages and a better distribution of survival curves. The research has been done in both limited as extended lympadenectomy. Literature showing small numbers of lymph nodes after surgery demonstrated the LNR to be of low clinical utility due to a small number of patients in the first LNR stage [28,29]. The latter was not being reproduced in our research, nor did the LNR show a better distribution of patients, but it did show a better distribution of survival curves.

From a critical point of view the weaker aspect of this study might be found in the cut-off points of the LNR. These are chosen by the authors and could be chosen in favor of this study or LNR itself. Another point of criticism is that this research used overall survival instead of disease specific survival. Unfortunately the use of disease specific survival was not possible because the ECR does not register the cause of death.

Conclusion

In this population-based study on patients with M0 gastric cancer who usually underwent a limited lymph node dissection and who thus generally have a small number of lymph nodes examined, the lymph node ratio is a good and simple prognostic instrument. It has the best homogenous spread of overall crude five-year survival and hazard ratios and it is less vulnerable for stage migration then the UICC/AJCC TNM classification and might be able to make a significant difference within different N stadia.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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