

LYMPH NODE METASTASIS IN GASTRIC CANCER AND THE RATIO OF METASTATIC LYMPH NODES (RLN)

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Keywords: gastric cancer, lymph nodes, staging

Abstract: The routine identification and removal of regional lymph nodes (LN) in solid neoplasm is essential. The proportion between metastatic and examined lymph nodes (N-ratio) has been proposed as an independent prognostic factor in patients with gastric cancer. We analysed the postoperative survival of 124 patients with gastric cancer, having 96 intraoperative lymphography with colorant (methyl blue). For lymph nodes status (N, PN), two classifications were assigned: TNM, UICC/AJCC and the JSCA: (NR₀: 0%, NR₁ ≤20%, NR₂ >20%). The impact concerning staging and survival of patients with gastric cancer and R0 resection was compared in the study group. A total of 124 patients with gastric cancer from our institution were studied retrospectively between 1998 and 2007. Results: a significant difference in survival was seen in the patients with NR₁ versus NR₂. In our multivariate analysis study, only NR with pT and histologically G (grading) were found to be independent prognostic factors. With JSCA classification, in the patients with gastric cancer operated between 2000 and 2007, stage migration was present in 43 cases (51%), with the UICC/AJCC TNM classification, in the patients operated between 1998 and 2007, 15 cases (18%) and when NR was applied, stage migration was found only in 14 (11%) of cases. Conclusion: the NR is a simply reproducible staging system, with a very good prognostic significance.

Cuvinte cheie: cancer gastric, noduli limfatici, stadializare

Rezumat: Identificarea de rutină și îndepărtarea nodulilor limfatici (NL) regionali este esențială în tumorile solide. Raportul dintre nodulii limfatici metastatici (N+) și cei examinați (Rația – N) – RN, a fost propus ca factor prognostic independent la pacienții cu cancer gastric. Am analizat supraviețuirea postoperatorie la 124 pacienți cu cancer gastric, din acest lot fiind efectuate 96 de limfografii intraoperatorii cu colorant (albastru de metilen). Stabilirea stării NL- (N,PN) s-a efectuat pe baza a două clarificări: TNM, UICC/AJCC și JSCA: (NR₀: 0%, NR₁ ≤20%, NR₂ >20%). Impactul asupra studiului și supraviețuirii din cancerul gastric rezecat cu rezecție R0 a fost comparat la nivelul lotului studiat. Lotul de 124 de bolnavi cu cancer gastric din clinică a fost evaluat retrospectiv, intervalul studiat fiind 1998-2007. Rezultate: studiul prezent a arătat o diferență semnificativă în supraviețuire la pacienții NR₁ în raport cu NR₂. Analiza multivariată din studiul nostru a arătat că numai NR cu pT și gradul de diferențiere histologică G, sunt factori prognostici independenți. Prin clasificarea JSCA la pacienții cu cancer gastric, operați în intervalul 2003-2007, migrația stadială a fost prezentă în N3 (51%) din cazuri. Prin clasificare NICE/A7CC-TNM-ed a 6-a, migrația a fost absentă în lotul studiat din 1998-2007 în 15 (18%) din cazuri, iar când s-a aplicat NR, atunci acest procent a fost 14 (11%) din cazuri. Concluzie: NR este un sistem de stadializare simplu și ușor de reprodus, având semnificație prognostică foarte bună.

INTRODUCTION

The prognostic significance of the number of metastatic lymph nodes (N+) with gastric cancer has been revealed by several reports and some authors suggested that the number of lymph nodes with metastasis exerts a larger effect on survival than the anatomic level of involved nodes.(1-4)

Anatomical distribution of regional lymph nodes is determined by the JSCA (5), but the numbering (N=1-16) and grouping (Gr 1-3) depends of the location and extension of tumours and it is too complicated to be used routinely in hospitals worldwide. Therefore, Adachi et al (2) classified the level of lymph nodes metastasis as level I nodes (perigastric 1-6), level II nodes (intermediate 7-9) and level III nodes (distant 10-16) of the tumour location.

Some Japanese authors clarified that not the anatomical level but the total number of positive LN (1-6 vs ≥7)

was an independent prognostic indicator for N+ gastric cancer.(2)

Many authors have suggested that the extended lymphadenectomy D2 or even D3, has potential for a more appropriate pathological staging, better regional disease control and survival advantage.(6,7,8)

The degree of curative efficacy of the lymphadenectomy will remain unknown until prospective randomised trials show evidence of disease control and survival.(9,10)

In Europe and in USA, extended lymph nodes dissection is not randomly performed despite the fact that more than 50% of patients with gastric resection for carcinoma show N+ disease.(11,12)

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In the TNM system, the number of LN to be removed and examined for adequate staging is unclear, varying from 10 to 15 or greater than 25.(13,14,15)

In JSCA, an extended lymphadenectomy is mandatory for N-stage classification (5). The rate of „stage migration” for both systems is over 15% (16,17,18).

In current opinion, the absolute number of metastatic locoregional lymph nodes (TNM-N category) is the most reliable prognostic indicator for patients with radically resected gastric cancer.(21,20,19)

The UICC/AJCC classification, which is the most widely used for the staging of gastric cancer, suggests that at least 15 LN should be examined for a correct assessment of N-category and this implies that D1 dissection, limited to the level I (1-6 group, perigastric), LN might not guarantee an accurate staging, but D1-lymphadenectomy is routinely performed in Europe, which is supported by the fact that D2 dissection is associated with higher rates of postoperative morbidity and mortality.(14,22-26)

The ratio between metastatic and examined lymph nodes (N-ratio) has been recently proposed, for identifying prognostic subgroups among patients with N1 and N2 disease and reduce the phenomenon of stage migration.(17,21,26-30)

The incidence of gastric cancer has decreased over the past 30 years, the disease remains the second leading cause of cancer death.(31)

Today, surgery is the only potentially curative treatment for gastric cancer. Lymph node metastasis occurs during the early stages of the disease and lymphadenectomy is recommended as a main component of radical surgery. The extent of lymphadenectomy has been a controversial topic for a long time without a worldwide consensus as yet. In the 1960s, Japanese surgeons first introduced the extended lymphadenectomy procedure (D2) with systematic dissection of LN in the first tier (D1) and in the second tier (D2). In addition to D2 lymphadenectomy, LN around the upper abdominal aorta are dissected (D3) on the basis that 20% to 30% of patients with not-early gastric cancer (>T1) had microscopic metastasis present in para-aortic nodes.(32,33,34,35)

In the present study, we retrospectively evaluated the prognostic significance of the NR in 124 gastric cancer patients.

PURPOSE

The aims of our study were to validate the value in prognostic of N ratio, compared to traditional prognostic systems and to see whether the N ratio has a prognostic power in patients with limited (D1) lymphadenectomy.

METHODS

In this study, 124 patients with gastric cancer admitted between 1998 and 2007 were included. D1 lymphadenectomy was performed in 100 patients and 24 D2 lymphadenectomy, according to JSCA and UICC recommendations.

For comparative purposes, we classified all patients by three staging systems:

- JSCA: p0, pn1, pn2, pn3;
- UICC/AJCC/TNM: pN0, pN1, pN2, pN3;
- NR: NR0(ratio 0%), NR1(ratio \leq 20%), NR2(ratio>20%).

Lymph node status classification:

The 124 evaluated patients were divided into two groups according to the number of examined LN: Group 1 consisted of 98 patients with less than 15 LN and 26 patients with more than 15 LN were in group 2.

Lymph node involvement was classified according to both the 1997 UICC/AJCC TNM classification (N0: no

metastasis, N1: 1-6 LN+, N2: 7-15 LN+, N3: more than 15 LN+) and the 1981 JRSC classification (n0= no LN+, n1= LN+ to group N1, n2=LN+ to group N2, n3=LN+ to group N3).

The median number of involved LN was 50 (mean 10 \pm 11).

N-ratio:

In survival and stage migration analysis, the NR parameter was the best cut off approach in terms of the log-rank test. Rate of stage migration was calculated to each staging system; for this evaluation only perigastric lymph nodes (N1 station) were considered (D1-lymphadenectomy).

Statistical analysis:

Overall survival (OS) rates and 95% confidence intervals were determined using the Kaplan – Meier estimation (cit 16).

The following were analysed: age <70 years, age >70 years, tumour site, type of surgical resection, T-category (T1: mucosa or submucosa invasion; T2: muscularis propria or subserosa; vs T3: serosa; vs T4: infiltration of extra-gastric space), grading: G1 vs G2 vs G3 vs G4, Lauren type, anatomical location of LN+ (n0 vs n1 vs n2 vs n3), number of LN+ (TNM:N0 vs N1 vs N2 vs N3), N-Ratio between metastatic LN and examined LN (N-Ratio 0 vs N-Ratio 2 vs N-Ratio 3).

The Cox's proportional hazard model was used for multivariate survival analysis.(36,37)

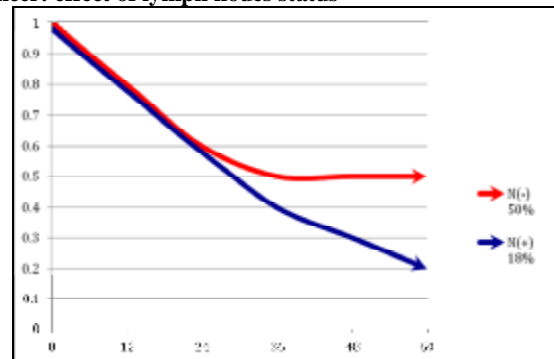
The value of p<0.05 was considered significant and for NR the calculation was by the Pearson correlation coefficient (r).

RESULTS

Classification of N and the elements for survival:

For all 124 patients, the 5-year survival rate was 28% and in N negative patients was 50%, 18% for node-positive patients (P<0.0001) figure no. 1.

Figure no. 1. The survival of patients with resected gastric cancer: effect of lymph nodes status



In table no. 1 the clinical and histopathological record of 124 patients and the 5-year survival rates are shown.

In this study, the tumour diameter, G grading, pT, residual tumour and TNM-stage were the most important prognostic factors. Lauren classification is important on survival, the patients with intestinal type having a significantly higher survival rate.

The 5-year survival rates of the patients staged by UICC AJCC pN classification were 46% to pN1, 18% for pN2.

In the classification by the ratio based pN classification, the 5-year survival rate was: 39% for NR1 and 18% for NR2.

Both the NR1 and the NR2 groups in the ratio-based classification system discriminated patients who would have been included in different prognostic categories according to the JSCA and TNM classifications (table no. 2).

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Table no. 1. Date of clinical and histopathological records for the 124 patients, 5-year survival rates

		Cases n=124	5-year survival (%)	SE	P
Tumour diameter	≤4,0 mm	44	46	4.5	<0.0001
	≥4,0 mm	80	30	5.1	
Lauren type	Diffuse	48	36	5.2	0.049
	Intestinal	76	48	5.4	
Grading	G1-2	34	50	6.9	<0.0001
	G3	90	39	4.5	
Residual tumor (R)	R0	90	49	3.7	<0.0001
	R1-2	34	15	6.7	
PN	N0	12	50	5	<0.0001
	N1	76	46	8.2	
AJCC/TNM	N2	76	18	-	<0.0001
	N3	-	-	-	
NR	NR0	14	50	5.0	<0.0001
	NR1	76	39		
	NR2	40	18	4.7	

Table no. 2. NR distribution, among TNM and JSCA staging systems in N

		NR	
		NR1	NR2
TNM	N1	38	9
	N2	6	12
	N3	-	-
7GCA	N1	28	11
	N2	12	24
	N3	-	-

About the survival, we have a statistically significant differences between patients with a different NR stage (for n1 patients: NR1/NR2 $p < 0,0001$, for n2: NR1/NR2 with $p = 0,002$) and pN stage (for n1: NR1 versus NR2 with $p = 0,014$).

In multivariate analysis, including prognostic factors, NR, pT and S-grading were found to be independent prognostic factors.

No correlation was found between the number of total harvested LN and NR ($r = 0,07$; $p = 0,3$), but there was a significant correlation between the number of N+ LN and the NR ($r = 0,8$; $p < 0,0001$).

DISCUSSIONS

This study confirmed that N-Ratio has a prognostic value independent of both traditional prognostic factors and extent of lymphadenectomy (≤ 15 LN or ≥ 15 LN). Several staging systems for LN-metastasis considering the level and number of positive nodes were assessed using multivariate analysis and the most important LN information associated with survival was determined by using multivariate analysis.(38,39,40) The results indicated that 5-year survival rate significantly decreased when the number of positive level II nodes (N2) was greater than one.(40)

Multivariate analysis confirmed that survival rate was significantly influenced by the anatomical level of N+ LN, total number of N+, number of N+ level I nodes and number of N+ level II nodes. The multivariate analysis clarified that the number of positive level I and level II nodes was the most important prognostic indicator in patients with node-positive gastric cancer.(41,42,43)

Recent studies demonstrated that the TNM classification (UICC/AJCC) based on the total number of

positive LN is a better staging system compared with the Japanese classification based on the anatomical level of lymph node metastasis.(44) The efficacy of LN-dissection in gastric cancer is still controversial.(45,46,47) The JSCA nodal staging is considered by western surgeons and pathologists too complicated for clinical use, on the other hand, the UICC/AJCC TNM system, even though easily reproducible, may be influenced by the surgeon's attitude with respect to nodal dissection and by the pathologist examination.(48,49)

Both staging systems imply the phenomenon of stage migration in a significant percentage of cases.(16,17)

The lymph node ratio (NR) is becoming increasingly considered as an important prognostic factor in gastric cancer after curative resection and has been proposed as an alternative LN staging system for reducing the stage migration rate.(16,17,46)

Many published studies compared the prognostic impact and stage migration rate of JSCA and UICC/AJCC LN classifications with the NR in resectable gastric cancer with curative intent gastrectomy.

Our data agree with authors' studies, indicating that the NR is a powerful prognostic parameter following resection of gastric cancer.

Multivariate stepwise Cox regression analysis of all three lymph nodes classifications together, revealed that only the NR is an independent prognostic value ($p = 0,0002$), our data agree with this results from USA and western and Japanese studies.(50,51)

The data from Wagner et al, in agreement with our study with in vivo and ex vivo lymphography showing that the number of perigastric and celiac LN has great anatomical variations.(52)

Some studies show a direct relationship between the NR and the number of N+ but this correlation don't exists between the NR and total number of harvested LN. Today is unknown the reason why the NR is an independent prognostic factor as proposed by Bando et al. (17), these findings suggest that the NR may reflect the interaction between the lost immune defence mechanism (tumour aggressiveness, number of N+ as the numerator), and the total number of dissected LN as the denominator.

Some studies observe increased survival in presence of larger number of removed nodes, explained by introducing the concept of stage migration. In Japan, surgeons usually dissect as many LN as possible while in western hospitals, systematic lymphadenectomy (D2±D3) is not routinely performed.

CONCLUSIONS

One great advantage of extensive lymph node dissection (> 15 LN) is that it allows improved staging of the disease and this is of utmost importance when survival rate in different series is compared. Lymphadenectomy is the only prognostic factor that can be influenced by the surgeon. The prognostic impact of the NR is less influenced by the number of dissected nodes and by the individual presence of lymphatics. The NR may be considered a simple reproducible staging system at institutions.

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