

## ORIGINAL ARTICLE

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# Lymph node harvesting in gastric cancer: the crucial role of T stage

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### Summary

**Purpose:** Nodal status represents probably the most important determinant of gastric cancer prognosis. The purpose of the present study was to assess the impact of the primary tumor's T stage on lymph node harvesting after D1 resections for gastric cancer.

**Methods:** Between January 2000 and January 2012, the medical files of patients who presented to our department with the diagnosis of gastric cancer and were submitted to a gastric resection with curative intent were retrospectively reviewed. A total of 134 gastric cancer patients (mean age 67.36±9.64 – 35 females and 99 males) were submitted to a gastrectomy in our department (total or subtotal) with curative intent. The distribution of the tumors within the stomach was as follows: upper third – 37 patients, middle third – 49 patients and lower third – 46 patients.

**Results:** Lymph node retrieval was superior in advanced T

stage patients (T3, T4a/T4b) compared to their low T stage (T1a/T1b, T2) counterparts ( $p=0.0008$ ). Similar findings were encountered when the comparison was reduced to the subtotal gastrectomy subgroup ( $p=0.0047$ ). However, although there was a distinct trend, statistical significance was not reached for the patient group submitted to total gastrectomy ( $p=0.1088$ ).

**Conclusion:** The results of the present study seem to add another value i.e. tumor's T stage in the equation of lymph node retrieval in gastric cancer resection specimens. Lymph node retrieval in gastric cancer patients appeared to be dependent to the primary tumors T stage in the given patient sample.

**Key words:** gastric cancer, lymph nodes, prognosis, T stage, lymph node ratio

### Introduction

The extent of lymph node dissection in gastric cancer has been the field of a constant intercontinental debate. Generally, extended lymph node dissections (D2) carry increased morbidity and mortality risks and mainly failed to demonstrate the expected favorable impact on survival apart from probably advanced (T3+) tumors [1] (Table 1). However, the vast majority of researchers agree on the lack of high quality studies comparing the standard (D1) with the extended (D2) lymph node dissection [1] (Table 1). What is universally agreed though

is that a minimum number of lymph nodes, more than 10-15 depending on the trial, are required for an appropriate N staging [2]. On the other hand from the pathologist's viewpoint, gross examination and careful inspection of the surgical specimens remain the traditional modalities of routine lymph node detection and subsequent analysis in the vast majority of centres worldwide.

In the present study, based on the results of the intra-departmental audit evaluating the quality of surgical treatment of gastric cancer, we observed

that the determinant of lymph node harvesting was not what appeared at first to be as the logical assumption i.e. surgeon-dependent. The number of lymph nodes retrieved out of the gastric cancer resection specimens varied significantly even in single surgeons audits. Namely, we observed that often the number of lymph nodes picked on the pathology analysis of surgical specimens in early tumors (low T stage) was not always within the desired range. Conversely, the respective amount in cases of large tumors (advanced T stage) usually exceeded the minimum requirements set from the literature. Thus, the purpose of the present study was to assess the impact of the primary tumor's T stage on the number of lymph nodes retrieved after D1 resections for gastric cancer.

## Methods

Internal board approval and ethics committee permission for accessing patients' data was obtained prior to the initiation of this study. Between January 2000 and January 2012, the medical files of patients who presented to our department with the diagnosis of gastric cancer and were submitted to a gastric resection with curative intent either total or subtotal were retrospectively reviewed. As there is no clear cut evidence in the literature suggesting the superiority of the extended (D2) over the standard (D1) lymph node dissection, we have adopted the D1 lymph node dissection as the standard of care

in all gastric cancer patients. Thus, during surgery the aim from the surgeon's point of view was, apart from resecting the gastric primary tumor in accordance to the oncological principles, to achieve an adequate dissection of all lymph node stations comprising the N1 lymph node station group (Table 1). All procedures were performed under the same standardized principles, as mentioned, by 5 surgeons with years of experience in upper GI surgery.

Regarding pathology, after the procedure the surgical specimen was sent out to the pathology lab for the final pathology analysis. Then, 2 pathologists specialized on gastric malignancies performed a meticulous dissection of the specimen in order to retrieve lymph nodes. The standard Hematoxylin and Eosin (HE) staining was used for the histological examination of frozen section slices in order to assess the presence of malignant cells within the retrieved lymph nodes.

## Statistics

The statistical package for social sciences v15 (SPSS) software was used for the statistical analysis. The unpaired t-test was used to compare means  $\pm$  standard deviations. A result was considered statistically significant when p value was under 0.05.

## Results

A total of 134 gastric cancer patients (mean age  $67.36 \pm 9.64$  years – 35 females and 99 males) were submitted to a gastrectomy in our depart-

**Table 1.** Lymph node stations in gastric cancer

Lymph node stations	Anatomic location	Group	Lymphadenectomy
1	Right cardia	N1	D1
2	Left cardia		
3	Lesser curvature		
4	Greater curvature		
4a	Short gastric vessels		
4b	Left gastroepiploic vessels		
4c	Right gastroepiploic vessels		
5	Suprapyloric		
6	Infrapyloric		
7	Left gastric artery		
8	Common hepatic artery		
9	Celiac trunk		
10	Splenic hilus		
11	Splenic artery		
12	Hepatoduodenal ligament	N3	D3 (N1 + N2 + N3)
13	Posterior surface of the head of the pancreas		
14	Root of the mesentery		
14A	Superior mesenteric artery		
14V	Superior mesenteric vein	N4	D4 (N1 + N2 + N3 + N4)
15	Para-aortic		
16	Paracolic		

**Table 2.** Mean  $\pm$  standard deviation number of lymph nodes identified during the histologic assessment of the surgical specimen categorized according to the primary tumor T stage (T1a/T1b, T2, T3 and T4a/T4b) for the whole patient sample and for the total and subtotal gastrectomy patient subgroups, as well.

T stage	Total / subtotal gastrectomy		Subtotal gastrectomy		Total gastrectomy	
1a/1b	10.85 $\pm$ 8.38 N: 20	12.51 $\pm$ 7.52 N: 53	9 $\pm$ 7.01 N: 15	11.37 $\pm$ 6.69 N: 38	16.4 $\pm$ 10.5 N: 5	15.4 $\pm$ 8.9 N: 15
2	13.52 $\pm$ 6.88 N: 33		12.91 $\pm$ 6.13 N: 23		14.9 $\pm$ 8.57 N: 10	
3	18.48 $\pm$ 9.93 N: 47	17.91 $\pm$ 9.63 N: 81	18.82 $\pm$ 10.63 N: 33	16.63 $\pm$ 9.61 N: 52	17.64 $\pm$ 8.34 N: 14	20.21 $\pm$ 9.39 N: 29
4a/4b	17.15 $\pm$ 9.28 N: 34		12.84 $\pm$ 6.09 N: 19		22.6 $\pm$ 9.93 N: 15	
P value		0.0008		0.0047		0.1088

ment (total or subtotal) with curative intent. The distribution of the tumors within the stomach was as follows: upper third – 37 patients, middle third – 49 patients and lower third – 46 patients. Based on the location of the primary tumor and the desired specimens' tumor-free borders, patients were submitted either to a total gastrectomy (44 patients) with a Roux-en-Y reconstruction or to a subtotal gastrectomy (90 patients) where the gastrointestinal tract continuity was re-established with a Billroth II reconstruction. In all cases, the standard (D1) lymph node dissection was performed.

Table 2 shows the mean  $\pm$  standard deviation number of lymph nodes identified during the histologic assessment of the surgical specimen categorized according to the primary tumor T stage (T1a/T1b, T2, T3 and T4a/T4b) for the whole patient sample and for the total and subtotal gastrectomy patient subgroups, as well. According to the results of the statistical analysis, the mean number of lymph nodes identified by the pathologist was greater for patients of advanced T stage disease (T3 and T4a/T4b) compared to the early T stage patients (T1a/T1b and T2) for the whole patient sample (total and subtotal gastrectomy -  $p=0.0008$ ) and for the subtotal gastrectomy subgroup ( $p=0.0047$ ). However, although there was a trend, statistical significance was not reached for the total gastrectomy patient subgroup ( $p=0.1088$ ).

## Discussion

The short- and long-term prognosis of gastric cancer and generally of all gastrointestinal epithelial malignancies as well, is determined after a careful TNM staging out of information derived from both pathology and radiology. The nodal status appears to be of most importance as it usually dictates the need for subsequent adjuvant therapies [3,4]. Recently, there are supporting data from

a significant number of publications highlighting the importance of lymph node ratio, namely the ratio of positive to resected lymph nodes, on the prognosis of gastric, pancreatic and colorectal cancer [3-6]. One of the most important features of lymph node ratio is the fact that it maintains its prognostic value even after neo-adjuvant therapy as it is already well-known that preoperative treatments, i.e. chemotherapy or radiotherapy, can limit the efficiency of lymph node harvesting leading to a false downstaging [3-6]. By definition, alterations to either part of this fraction, i.e. nominator or denominator (as in our case), can have prognostic significance.

From the pathologists' viewpoint, various techniques have been proposed in order to increase the efficiency of lymph node harvesting out of gastrointestinal cancer resection specimens such as fat clearing, methylene blue staining, fat stretching and the use of a dedicated pathology assistant [7]. However, although some of the aforementioned techniques appear more efficient than others, there are insufficient data in the literature to suggest that a certain technique can actually increase positive lymph node count leading to upstaging [7]. Generally, lymph node retrieval out of gastric cancer surgical specimens is pathologist-dependent with the various alternatives used as adjuvants in order to increase lymph node retrieval efficiency. Pathologists' specialization and increased case volume can further contribute favorably [7,8].

In the present study, we used data extracted out of gastric cancer patients' medical files to delineate the correlation of the primary tumor's T stage with the total number of lymph nodes (metastatic or not) reported on the pathology report. All patients were treated with surgical resection up front without neo-adjuvant manipulation and they were submitted to an intradepartmental standardized procedure depending on the site of the primary

malignancy. The same standard pathology analysis of the specimen was performed in all cases by two pathologists. Because of the limited number of patients in each T stage, i.e. T1a/T1b, T2, T3, T4a/T4b, we grouped low T stage patients (1a/1b and 2) and advanced T stage patients (3 and 4a/4b) together for comparison purposes. We certainly did not mean to implement prognosis similarities on the resulting groups.

According to our data, lymph node retrieval was superior in advanced T stage patients (T3,T4a/T4b) compared to their low T stage (T1a/T1b,T2) counterparts ( $p=0.0008$ ). Similar findings are encountered when the comparison is reduced to the subtotal gastrectomy subgroup ( $p=0.0047$ ). However, although there was a distinct trend, statistical significance was not reached for the total gastrectomy subgroup ( $p=0.1088$ ). Perhaps, the limited number of patients ( $n=44$  patients) in the total gastrectomy subgroup might be responsible for this finding.

Since 1997, the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) tumor, lymph node, metastasis (TNM) staging system has classified lymph node status according to the absolute number of metastatic lymph nodes. Lymph node stage can be determined appropriately when the number of total examined lymph nodes is 16 according to the latest TNM staging system [9-12]. Although mainly inappropriate due to the existing limitations of the present study, filtering this statement through the results of the present study, we could dare to propose that a T stage adjusted lymph node number threshold might be of more prognostic and staging accuracy. Certainly, including larger number of patients in each T stage and operative category (total and subtotal gastrectomy) optimally within the context of a multicenter record would be a more objective approach in order to jump into more accurate and informative conclusions. However, this study can definitely be the stepping stone to initiate further research on this field.

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The results of the present study seem to add another value in the equation of lymph node retrieval in gastric cancer resection specimens i.e. that of the primary tumor's T stage. Aiming to find the pathophysiology behind our findings, we could assume that a cancer volume dependent host's reaction to cancer might cause lymph node enlargement rendering larger number of nodes detectable from the pathologists. Inflammation might be on one side but other parameters, not as obvious, needing more thorough clarification might supervene as well.

However, although interesting, a few things should be kept in mind before interpreting the results of the present study and seek for correspondence in clinical practice. Pathologists' vigilance and insight are logically stimulated in cases of large tumors and conversely these human features are blunted in cases of small tumor. Seeking to "find the expected" i.e. metastatic lymph nodes in large tumors probably acts as an extra motive for a more thorough analysis of the specimen. On the other hand, the "search for the unlikely", i.e. metastatic nodes in early cancers, can subconsciously reduce the intensity of the effort to find scattered lymph nodes within the fat surrounding the gastric resection specimen. Furthermore, the fact that patients operated by several surgeons were included in the study represents a notable limitation. Although surgical technique had been standardized, differences in the applied technique probably exist. Optimally, a prospectively created database detached from the limitations of a retrospective audit would be of more scientific value.

In conclusion, lymph node retrieval in gastric cancer patients appeared to be dependent to the primary tumors' T stage. Lymph node harvesting proved to be more efficient in patients with advanced tumors than in those with early tumors in the given patient sample.

## Conflict of interests

The authors declare no conflict of interests.

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