

# N staging: the role of the pathologist

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**Abstract:** Gastric cancer is the second cause of cancer-related mortality worldwide. Metastases, including lymph nodes ones, heavily influence the prognosis of this disease. The pathological detection of positive lymph nodes is pivotal for an optimal prognostication and clinical management of affected individuals. Several factors influence the pathological investigation of surgical specimens, ultimately affecting the number of retrieved lymph nodes and, with it, the reliability of N staging. The pathologist plays a central role in optimizing this process. Factors influencing lymph node retrieval and analysis will be herein reviewed, together with the procedures adopted for an optimal pathological analysis of lymph nodes in gastric cancer.

**Keywords:** Lymph nodes; lymphatic metastasis; neoplasm staging; stomach neoplasms

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## Introduction

Gastric cancer is the second cause of cancer-related mortality worldwide (1). Metastases are critical for the prognosis of this disease (2). Regional lymph nodes are the most common site of metastatic localization in affected patients, followed by the peritoneal cavity and distant organs such as liver, lungs and bone. Nowadays, lymph node metastases are a well-established critical prognostic factor and predictor of gastric cancer recurrence and the number of removed and analyzed lymph nodes in radical gastrectomy has been found to be closely related with patients' survival rates (3). We reviewed the current literature with the purpose of investigating factors influencing lymph node retrieval and analysis, with particular emphasis on the role of pathologist in processing surgical specimens. We also focused on the importance of correctly evaluating macro and micro metastases and on the effectiveness and applicability of sentinel lymph node (SLN) procedure, highlighting pitfalls and critical issues.

## Search methods

A literature search was performed in PubMed database for English-language papers published between January 2010 and April 2016 using MeSH terms “lymph nodes”, “gastric cancer AND lymphatic metastasis”, “neoplasm staging” “gastric AND nodal AND neoplasm micrometastasis” and “gastric AND sentinel AND lymph node”. Reference lists of retrieved articles were also considered. Relevant articles were selected.

## Clinical impact of detected lymph nodes

Given the well-established prognostic role of lymph node metastases, highly predictive of gastric cancer recurrence (4-6), extensive investigation of lymphatic metastases assumed a prominent role in both understanding metastatic mechanisms and improving the effectiveness of surgery in gastric cancer (3,7,8). An increasing amount of studies focused on the impact of the number of harvested lymph

nodes on the long-term survival of gastric cancer patients (9). Over the last few years, the number of removed lymph nodes has been demonstrated to be closely related with the survival rate. Seevaratnam *et al.* showed that patients with stage T1–T2 cancer with  $\geq 15$  removed lymph nodes or patients with stage T3–T4 cancer with  $\geq 25$  removed lymph nodes featured significantly higher survival rates compared to patients with cancer of identical stage with fewer removed lymph nodes. The number of removed lymph nodes was found to be an independent prognostic factor (10). The occurrence of lymph node metastases associate with the features of the underlying gastric cancer (11), being related to tumor stage, depth of invasion, size and location; as expected, the bigger the cancer size, the higher the incidence of nodal metastasis (3,12,13). In patients without lymph node metastases, lymph vascular invasion (LVI) should be finely investigated by pathologists, as LVI is a well-known risk factor for distant and nodal recurrences (14,15). Lee *et al.* found LVI to be an indicator of biological aggressiveness and a reliable independent and prognostic factor in pT1–3 pN0 gastric cancer patients, with an impact similar to that of the N1 group (16). Coherently, LVI should be considered in the postoperative management of pN0 gastric cancer.

### Factors influencing the numbers of retrieved lymph nodes

Although preoperative imaging techniques provide an enough accurate determination of the T and M stage, the correct status of lymph nodes can be established only by histology following an optimally extended node dissection (17). In 2010, the International Union Against Cancer (UICC) and the American Joint Committee on cancer (AJCC) proposed the seventh edition of the UICC TNM (an eighth edition is going to be released in 2017), suggesting 16 lymph nodes as the desirable threshold in order to accomplish a proper N staging (18). A low number of analyzed lymph nodes may depend on either the scarcity of lymph nodes in surgical specimens or a suboptimal lymph node retrieval from formalin-fixed specimens by pathologists, or on both of these occurrences. Factors affecting these events will be herein briefly discussed.

#### *Factors independent of pathological handling*

Surgery, the cornerstone in the treatment of gastric cancer, can consist of conventional open gastrectomy or

laparoscopy-assisted gastrectomy. Complete resection along with lymph node dissection has been accepted as the only possibly curative surgical treatment for gastric cancer (19). Benefits of minimally invasive approach are worldwide known and laparoscopic techniques for treating patients with early gastric cancer have improved and are being increasingly employed, resulting in oncologic follow-ups and long-term survivals comparable to the open technique, with fewer complications and recurrences (20,21). Different surgical techniques, implying various possible modalities of lymph node dissection, can affect the number of examined lymph nodes, possibly influencing the detection of metastatic ones. The optimal schedule of lymph node dissection for gastric cancer is still matter of debate. Median values of 25 or 43–52 lymph nodes per patient were identified respectively after extended lymph node dissection or super-extended lymph node dissection (22,23). The demonstration that laparoscopy-assisted gastrectomy with extended (D2) lymph nodes dissection is a feasible and safe procedure for advanced gastric cancer is relevant (24,25) since 60–80% of gastric carcinoma patients are diagnosed in advanced-stage.

Current guidelines of Eastern and Western countries support D2 lymph node dissection as a standard treatment for a potentially curative resection and to maximize patients' benefit, primarily because of the higher number of lymph nodes obtained with respect to the more limited (D1) dissection (26–29).

The extension of routinely performed lymphadenectomy has been found to differ significantly in the past between Eastern and Western countries (30,31). In fact, Western population-based studies often reported a median of about ten examined lymph nodes per patient, inadequate for a proper staging (32–34). The type of gastric resection can also influence the number of retrieved lymph nodes. Finally, patient's age and neoadjuvant therapy can both negatively affect the number of analyzed lymph nodes, by decreasing both their actual number and their size, with the latter event in turn hampering lymph node pathological detectability (35).

#### *Factors related to pathological handling: procedures for lymph node retrieval and analysis*

Differences in specimen handling methods have been invoked for explaining differences in the number of retrieved lymph nodes after gastric cancer surgery. In Japan and in many specialized Western institutions, lymph node retrieval is generally performed by the surgeon itself on the

fresh specimen, correctly allocating the nodes according to their anatomical site for the purpose of proper anatomy-based staging (36). Conversely, in some western and/or in non-specialized institutions, lymph node retrieval is generally performed from formalin-fixed specimens by pathologists or by pathology technicians, often losing the proper anatomical allocation (35). Most pathologists detect lymph nodes for histologic evaluation by sight and palpation. This is termed the “manual method”. Alternatively, “lymph node clearing techniques” highlight lymph nodes by employing fat dissolving solutions. The resulting translucent mesentery allows nodes as small as 1.0 mm to be retrieved. The use of such “clearing solutions” has been considered able to up-stage some patients because of the detection of additional small positive lymph nodes not detected by the manual method (37). The benefit of using an acetone-based clearing method has been proved in colon cancer. Vogel *et al.* showed an average additional identification of 4.4 lymph nodes in comparison to the manual method (38). A recent survey showed that only 43% of pathologists use fat clearing solutions, such as acetic acid (39). Acetone-based fat clearing solution employment in gastric cancer specimens produced statistically higher numbers of retrieved lymph nodes with respect to manual dissection; however, this advantage was paid with longer times and higher costs per pathological analysis, without a clear benefit in terms of detection of positive lymph nodes (40). Therefore, with regard to colorectal cancer, a prolonged fixation of pericolonic/perirectal fat for 24 hours or more (which increases the solidity difference between lymph nodes and fat, improving the manual detection of the former) was proposed as a compromise solution (41).

Despite optimal surgical resection and fixation of pathological specimens, several factors may contribute to inappropriate pathological processing, including distraction often due to workload increase (42). To reduce the latter, “pathologists’ assistants” have been trained to take over some of the pathologists’ recurrent tasks. A Dutch study concerning colorectal cancer sampling demonstrated that well-trained pathologist’s assistants significantly contribute to patient safety, because their work results in an improved harvest of lymph node (43). Once a lymph node is retrieved, another possible issue is the number of slices to be performed in order not to miss metastases. With this regard, as proved for lymph node metastases assessment in colorectal cancer, histological analysis of the whole lymph nodes through serial slicing significantly increases laboratory workloads without producing significant clinical

benefits (44). As a matter of fact, the role of a learning curve for pathologists, similar to surgeons, aimed at lymph node retrieval in gastric cancer specimens should not be underestimated, with particular regard to non-dedicated western centers (45).

### Micrometastases

In spite of the achievement of apparently curative resections with tumor free lymph nodes, recurrence in gastric cancer patients is a common event (46). Histological subtypes and stage at the time of diagnosis may have a relevant prognostic impact. Undetected lymph node micrometastases, representing an early stage of metastatic spread, have also been reported to affect prognosis (47). Currently, microscopic tumor involvement of lymph nodes is classified as micrometastases or isolated tumor cells (ITC) according to size. Micrometastases range between 0.2 and 2.0 mm in greatest dimension. ITC are defined as single tumor cells or small tumoral clusters less than 0.2 mm in size (48). The seventh TNM classification does not distinguish between micrometastases and ordinary lymph node metastases in gastric cancer; classification of gastric cancer ITC is not peculiar with respect to ITC as treated in the chapter concerning cancer in general (18). Whatever their biological meaning, micrometastases and ITC can escape detection in routine pathological examination with H & E staining. Immunohistochemistry (IHC) is a widely accepted technique for detecting lymph node micrometastasis in gastric cancer (49-51). IHC is routinely performed with anti-cytokeratin (CK) antibodies such as AE1/AE3 and CAM 5.2, allowing the detection even of single tumor cells (52). Various clinicopathologic parameters appear associated with the occurrence of micrometastases. IHC-detected lymph nodes micrometastases were found to be significantly more frequent in Lauren’s diffuse histotype (53-55). This finding is secondary to the loss of E-cadherin expression, a critical event occurring in diffuse type gastric carcinoma (56) which, decreasing intercellular adhesion, ultimately leads to tumor cell dissociation (57). The higher probability of micrometastasis and ITC occurrence in diffuse gastric cancer (50,55,56) potentially supports the importance of lymph node immunostaining in this cancer type. Although lymph nodes harboring IHC-detected micrometastasis are considered positive nodes in gastric carcinoma, their clinical impact is unclear (58). Gastric cancer patients classified as N0 by routine histology turned out to bear micrometastases and/or ITC after IHC have been proposed

for additional treatment after surgery (59). Despite judging controversial the prognostic role of ITC in gastric cancer lymph nodes based on a review of literature, Tavares *et al.* proposed this descriptor as a valid prognosticator provided proper definitions, methodology, stage groups, extension of lymphadenectomy and follow-up are used, implying a possible impact on therapy (58).

## SLN

SLN navigation surgery, i.e., the removal of the first(s) lymph node(s) only along the lymphatic drainage from a malignancy, followed by a thorough pathological analysis, is an accepted standard treatment procedure for malignant melanoma and breast cancer. Several studies have been performed on SLN in gastric cancer (60,61). However, the benefit of this technique remains unclear in this tumor (62), probably due to both a low sensitivity and a relevant inter-study variability. Recently, a multicentre prospective study from the Gastric Cancer Surgical Study Group of the Japanese Clinical Oncology Group (JCOG) revealed a high false-negative rate, highlighting the necessity of a learning curve and the common pathological examination of one frozen section only as major limitations for a reliable SLN procedure (63). It appears increasingly clear that, in order to usefully apply the results of SLN examination to surgery, accurate intraoperative diagnosis is required. Multistep level sections, IHC (64), reverse transcription polymerase chain reaction (RT-PCR) (65), and the one-step nucleic acid amplification assay (OSNA) (66), have all been developed for both reducing the false negative rate and providing additional tools for diagnosing micrometastases in sentinel lymph node biopsies. Whatever the technique applied for the pathological analysis of resected SLN, a major limitation to the use of SLN in gastric cancer is the complexity of the gastric lymphatic drainage, ultimately implying numerous potential SLNs to be analyzed. If SLN navigation surgery eventually reveals a valid procedure, more conservative lymphadenectomies and gastric resections will be possible in selected cases, perhaps increasingly supporting pylorus-preserving gastrectomy (PPG). This topic is still matter of debate, since there are no published prospective randomized control trials comparing the patient's postoperative quality of life between distal gastrectomy and PPG (62).

Despite controversial findings in recent literature, SLN navigation surgery could ultimately reveal a safe procedure even in countries with non-endemic gastric cancer levels, especially if associated with minimally invasive surgery (67),

potentially offering better quality of life, low rates of postoperative complications, and shorter hospitalizations for many patients.

## Conclusions

In conclusion, the number of retrieved lymph nodes after surgery influences patients' survival by affecting the reliability of the pathological assessment of N status. The surgical and pathological techniques heavily impact on the number of retrieved lymph nodes, justifying an accurate training of dedicated medical and technician personnel. Further studies are warranted for establishing a possible biological meaning of lymph node ITC in gastric cancer, implying both a refinement and a standardization of the procedures employed for their detection. SLN technique in gastric neoplasms deserves also further investigations since currently concerns seem to largely exceed advantages.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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