Lymph node sampling in colorectal cancer: still many lessons to be learned

Bence Kővári[1], Cord Langner[2]

Abstract

The tumor stage based on the American Joint Committee on Cancer / Union for International Cancer Control tumor node metastasis (TNM) system is considered the most important prognostic factor for patients with colorectal adenocarcinoma. Clinical decision-making including the application of adjuvant chemotherapy is greatly influenced by the presence of lymph node metastasis. The number of retrieved lymph nodes mainly depends on tumor-related factors, such as tumor size and depth of penetration, as well as procedure-related factors, including the extent and technique of surgical mesocolon/mesorectum removal and the skills and thoroughness of the pathologist. The lymph node ratio, defined as the number of positive lymph nodes divided by the total number of evaluated nodes, is a new marker. It may imply a higher prognostic significance than the absolute number of positive nodes alone. It is of note, that the pathologist's lymph node harvest is dependent on the size of the lymph nodes. Thus, the diameter of lymph nodes, which are relevant to be histologically evaluated is a frequent matter of debate. The size of the lymph nodes is related to the risk of metastatic involvement, with the larger nodes more commonly positive for metastatic deposits than the smaller ones. However, statistical analysis based on multiple series of lymph nodes so far failed to determine a reliable cut-off value to predict metastatic disease. Thorough specimen dissection and the examination of lymph nodes smaller than 2mm can cause upstaging in approximately 30% of cases, but usually cannot identify additional node positive patients.

[1] Department of Pathology, University of Szeged, Állomás u. 1, 6720 Szeged, Hungary
[2] Institute of Pathology, Medical University of Graz, Auenbruggerplatz 25, 8036 Graz, Austria

Bence Kővári
Department of Pathology
University of Szeged
Állomás u. 1
6720 Szeged
Hungary
Tel: +363 04069859
Fax: +366 2545868
E-mail: kovari.bence.p@gmail.com

Introduction

According to the statistics of the GLOBOCAN project colorectal adenocarcinoma is the third most common malignant tumor (excluding skin cancers), with 1.36 million new cases annually worldwide, and causing the death of almost 0.7 million patients yearly [1]. The tumor stage based on the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) tumor node metastasis (TNM) system [2] is considered the most important prognostic factor.

The 5-year survival rate for patients with node-negative disease is 70-80% compared to the 30-60% for node-positive patients [3]. Clinical decision-making including the application of adjuvant chemotherapy is mainly based on the presence of lymph node metastasis, thus the method of pathological work-up by gross dissection and retrieval of lymph nodes for histological examination greatly influences treatment strategies of individual patients.

A long lasting debate with many controversies exists on how the colorectal cancer specimen should be dissected, how many if not all lymph nodes should be sampled and/or whether there is a minimum number of lymph node that need to be investigated. In addition, it is still largely unclear how the size of the lymph nodes is related to the risk of metastatic involvement and how important the tiny lymph nodes are.

Ideal number of lymph nodes to be sampled

Although the absolute number of pathologically evaluated lymph nodes depends on many factors (Table 1), it is essential to assess the lymph node status reliably for adequate prognostication and therapy planning.

To ensure that no metastatic lymph nodes will be missed due to undersampling, a minimum of 12 lymph nodes were recommended by the AJCC/UICC TNM system based on the paper by Fielding et al. [2,4]. Nevertheless, the evidence for this particular number is weak and it does not seem to hold much biological significance; furthermore other authors suggested other minimum lymph node numbers [5]. In the light of some studies the prognosis of colorectal cancer improves with the number of lymph nodes sampled even in node negative cases [6], a phenomenon which is not fully understood and is most likely due to immunological factors.

Based upon these data, it does not seem ideal to stop searching after the 12th lymph node is found, and in fact most guidelines recommend the histological examination of all grossly recognizable lymph nodes. Although audit of lymph node harvest can be a good tool for quality control, unfortunately the recommended number of harvested nodes is not reached in a significant number of cases, especially in left colectomy specimens, which can be as high as 80% in patients with rectal cancer after neoadjuvant therapy [7].

The extent of surgical lymph node sampling can be increased using certain procedures such as extended lymphadenectomy, high arterial ligation or total mesocolic excision (TME procedure), and it is important to note that the use of laparoscopic technique does not influence lymph node counts compared to open surgery [3].

Regarding the pathological work-up, many factors can influence the number of collected nodes: the applied national protocols, expertise and motivation of the dissector (e.g. non-pathologist, trainee or consultant), and most importantly the allocated time per specimen. According to the United Kingdom guidelines, 30-50 minutes of cut-

up time should be anticipated in the case of usual colorectal resection specimens [8]. Based on the work of de Burlet et al., if an initial 20 minutes long lymph node search is extended by an additional 5 or 10 minutes, the yield can be increased by 12 or 20%, respectively [9].

Over recent years several technical methods e.g. fat clearing, methylene blue injection, and acetone compression of adipose tissue [10] were developed to aid gross dissection and increase lymph node yield. These methods significantly increase the total number of examined lymph nodes, but according to some more recent publications these are not able to discover significantly more metastatic nodes [7,11].

Table 1 Parameters affecting the number of collected lymph nodes in colorectal cancer resection specimens

Factors affecting the number of lymph nodes pathologically examined for staging in colorectal cancer
Tumor-related factors • Tumor location • History of neoadjuvant treatment (in rectal cancer) • Tumor size (diameter) and depth of penetration (T classification) • Nodal status (N classification)
Procedure-related Factors • Extent and technique of surgical mesocolon/mesorectum removal • Skills and thoroughness of the pathologist (time per specimen), including adherence to gross dissection guidelines
Methods that may facilitate the recognition of lymph nodes: • Methylene blue injection • Fat clearing solution • Acetone compression

Relevance of lymph node ratio

Lymph node ratio is defined as the number of positive lymph nodes divided by the total number of evaluated nodes. Multiple studies demonstrated that the prognostic impact of the lymph node ratio is superior compared to the absolute number of metastatic nodes. Therefore, the lymph node ratio may improve the prognostic significance of the N-classification. It is of note that its prognostic impact may be related to the absolute number of retrieved nodes and may thus be related to the applied dissection technique. Optimal cut-off values for risk stratification still need to be defined [7].

Size of the retrieved lymph nodes

As lymph node retrieval is dependent of lymph node size, the diameter of lymph nodes, which are ultimately relevant for prognostication of affected patients, is a frequent matter of debate. The size of the lymph node is related to the risk of metastatic involvement, with larger nodes being more commonly positive than smaller ones, but statistical analysis based on multiple series of lymph nodes so far failed to determine a reliable cut-off value to predict the presence of metastasis [12, 13, 14].

It is important to note that in a study carried out on a large series of lymph nodes almost half of the detected nodal metastases were in lymph nodes smaller than 5 mm [14]. Thorough specimen dissection and the identification of small (<2mm) lymph nodes can cause upstaging in up to 30% of the cases, but this does only rarely identify additional node positive patients [12].

How to deal with pericolic / extramural tumor deposits?

Pericolic tumor deposits (PTD) are tumorous foci embedded in the pericolic (or perirectal) fat, with no connection to the primary tumor, and should be differentiated from metastatic lymph nodes, vascular spread and perineural invasion [2]. The presence of PTD carries a worse prognosis with increased local recurrence rates, increased risk of distant metastases and decreased survival.

Several definitions of PTD have been used throughout the preceding editions of the AJCC/UICC TNM Staging Manual, illustrating how complex and arbitrary this category is. The definition of PTD and its distinction from metastatic lymph nodes (Figure 1) is crucial, but on the other hand probably the most difficult aspect of lymph node assessment, showing poor interobserver agreement even among experts [7]. The distinction should carefully be performed as it has direct impact on the N-classification and the metastatic as well as the absolute lymph node count.

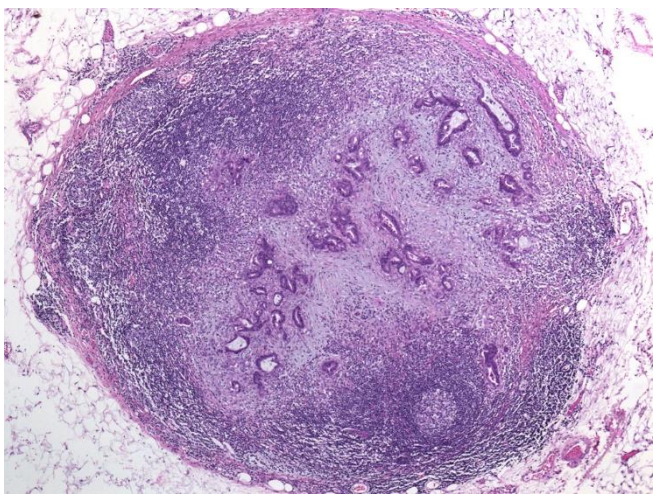

Figure 1a. Classical histological picture of lymph node metastasis of colorectal cancer and a typical pericolic tumor deposit

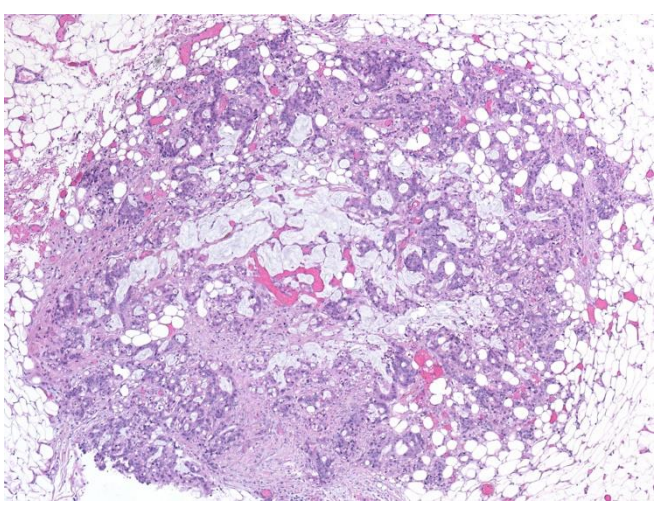

Figure 1b. [Hematoxylin and Eosin, initial magnification x100]

Deeper level sections of metastatic lymph nodes may show a morphology in keeping with the definition of PTD and vice versa. According to a meta-analysis 8% of patients with colorectal cancer have PTD without lymph node metastases,

in 18% a combination of lymph node metastases and PTD is found, in 28% only lymph node metastases were seen, whereas in 46% of cases no metastases were present [15]. The changing concept of PTD, which is still in progress, hampers its application in everyday routine practice.

Conclusions

Lymph node staging is the cornerstone of clinical decision making as well as therapy planning for patients with colorectal cancer. Many factors including the methods of pathological work-up can influence the number of examined lymph nodes, which can serve as a quality indicator. The adherence to current pathological guidelines and thorough specimen dissection with the allocation of sufficient time, are vital to produce reliable prognostic data. Although the evidence for the minimum number of harvested lymph nodes is week, the AJCC/UICC TNM Staging Manual recommends a minimal number of 12 nodes. As the examination of the lymph nodes smaller than 2mm can cause upstaging in the N-classification in around one third of cases, the investigation of small lymph nodes seems relevant, although it rarely identifies patients as node-positive. The incorporation of the lymph node ratio in the pathology report is encouraged. The ever-evolving concept of PTD still raises several problems that need to be solved in the future.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 16/01/2017.

2. Brierley JD, Gospodarowicz M, Wittekind C eds., TNM Classification of Malignant Tumours, 8th Edition, Wiley Blackwell; 2017

3. Ong ML, Schofield JB. Assessment of lymph node involvement in colorectal cancer. World J Gastrointest Surg. 2016;8:179-192.

4. Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, et al. Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT). J Gastroenterol Hepatol 1991; 6: 325-344

5. Cserni G, Vinh-Hung V, Burzykowski T. Is there a minimum number of lymph nodes that should be histologically assessed for a reliable nodal staging of T3N0M0 colorectal carcinomas? J Surg Oncol. 2002;81:63-69.

6. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst. 2007 21;99:433-441.

7. Resch A, Langner C. Lymph node staging in colorectal cancer: Old controversies and recent advances World J Gastroenterol. 2013 14;19:8515-8526.

8. Loughrey MB, Quirke P, Shepherd NA. Dataset for colorectal cancer histopathology reports. The Royal College of Pathologists; 2014

9. de Burlet KJ, van den Hout MF, Putter H, Smit VT, Hartgrink HH. Total number of lymph nodes in oncologic resections, is there more to be found? J Gastrointest Surg. 2015;19:943-948.

10. Gehoff A, Basten O, Sprenger T, Conradi LC, Bismarck C, Bandorski D, et al. Optimal lymph node harvest in rectal cancer (UICC stages II and III) after preoperative 5-FU-based radiochemotherapy. Acetone compression is a new and highly efficient method. Am J Surg Pathol 2012;36:202-213.

11. Märkl B, Schaller T, Krammer I, Cacchi C, Arnholdt HM, Schenkirsch G, et al. Methylene blue-assisted lymph node dissection technique is not associated with an increased detection of lymph node metastases in colorectal cancer. Mod Pathol 2013;26:1246-1254.

12. Rössler O, Betge J, Harbaum L, Mrak K, Tschmelitsch J, Langner C. Tumor size, tumor location, and antitumor inflammatory response are associated with lymph node size in colorectal cancer patients. Mod Pathol. [In press].

13. Cserni G. The influence of nodal size on the staging of colorectal carcinomas. J Clin Pathol. 2002;55:386-390.

14. Märkl B, Rößle J, Arnholdt HM, Schaller T, Krammer I, Cacchi C, et al. The clinical significance of lymph node size in colon cancer. Mod Pathol 2012;25:1413-1422.

15. Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. Histopathology. 2007;51:141-149.