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MINIREVIEWS

Digestive cancer surgery in the era of sentinel node and epithelial-mesenchymal transition

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Abstract

Lymph node involvement is one of the most important prognostic indicators of carcinoma of the digestive tract. Although the therapeutic impact of lymphadenectomy has not been proven and the number of retrieved nodes cannot be considered a measure of successful cancer surgery, an adequate lymph node count should be guaranteed to accurately assess the N-stage through the number of involved nodes, lymph node ratio, number of negative nodes, ratio of negative to positive nodes, and log odds, *i.e.*, the log of the ratio between the number of positive lymph nodes and the number of negative lymph nodes in digestive carcinomas. As lymphadenectomy is not without complications, sentinel node mapping has been used as the rational procedure to select patients with early digestive carcinoma in whom nodal dissection may be omitted or a more limited nodal dissection may be preferred. However, due to anatomical and technical issues, sentinel node mapping and nodal basin dissection are not yet the standard of care in early digestive cancer. Moreover, in light of the biological, prognostic and therapeutic impact of tumor budding and tumor deposits, two epithelial-mesenchymal transition-related phenomena that are involved in tumor progression, the role of staging and surgical procedures in digestive carcinomas could be redefined.

Key words: Lymph node count; Lymph node ratio; Sentinel node; Tumor budding; Tumor deposits

Core tip: We summarize the current knowledge on the assessment of nodal status and nodal staging in digestive carcinomas and highlight the prognostic impact of two epithelial-mesenchymal transition-related phenomena, tumor budding and tumor deposits, that are involved in tumor progression. In light of the biological, prognostic and therapeutic impact of these phenomena, the role of staging and surgical procedures in digestive carcinoma could be reevaluated and redefined.

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INTRODUCTION

Lymph node involvement is one of the most important prognostic indicators of carcinoma of the digestive tract. In contrast to Eastern countries, in Western countries lymph node involvement is not considered to be a prognostic "governor" and the therapeutic impact of lymphadenectomy is not acknowledged. Recent advances in minimally invasive treatment procedures for cancer have promoted their application for the assessment of lymph node status (positive/negative), *i.e.*, sentinel node mapping and biopsy. In addition, other prognostic factors related to epithelial-mesenchymal transition (EMT) that are involved in tumor progression, such as tumor budding and tumor deposits, have been gaining ground.

Here, we review the current knowledge on these issues and highlight the need for a redefinition of the role of surgical and staging procedures in digestive cancer surgery in light of recent advances in our understanding of the biology of tumor progression.

NUMBER OF EXAMINED NODES, LYMPH NODE RATIO, LOG ODDS

Several studies have shown an association between the number of excised nodes and overall survival, providing evidence that examination of an insufficient number of lymph nodes (LNs) may have a detrimental effect on survival in patients with gastrointestinal carcinoma[1,2]. However, much of this appears to be the effect of stage migration, which impacts the stage-specific survival without affecting overall survival[3]. Variations in patient demographics, tumor location and tumor biology raise questions regarding the evidence for a minimum LN harvest[1,4]. In gastric cancer, the stage migration effect is most striking when fewer than 10 LNs are assessed, but it is still present with a greater number of examined LNs[5,6]. Therefore, although current guidelines support the assessment of a minimum of 16 LNs, examination of more LNs is necessary to reduce the stage migration effect[1]. In colorectal cancer, the aim should be to collect as many LNs as possible to improve staging and increase survival. In fact, particularly following neo-adjuvant treatment for rectal cancer, downstaging with fewer LNs implies a positive treatment response and a more favorable prognosis[4].

An association between better postoperative long-term survival and a greater number of dissected nodes has also been reported in patients with several N0 digestive malignancies, including esophageal[7], gastric[8], colorectal[9], and pancreatic carcinomas[10,11]. This may be due to a not negligible rate of nodal micrometastasis, and the probability of missing a positive LN decreases as the number of examined LNs increases, *i.e.*, the Will Rogers phenomenon[7,9,12]. In patients with node-negative gastric cancer, a prophylactic D2 lymphadenectomy[8,13] with almost 16 LNs examined[12] seems to be effective, although retrieval of more than 25 nodes has been suggested[14]. The removal of at least 18 LNs during an esophagectomy with curative intent results in improved survival in esophageal cancer, particularly in patients with adenocarcinoma[7]. In N0 pancreatic carcinoma, examination of more than 10 LNs has been associated with improved survival[10]. In stage Ⅱ (T3-4N0) colorectal cancer, current guidelines consider a number of harvested LNs of less than 12 an indication to perform adjuvant chemotherapy; harvesting of less or more than 12 LNs allows a better prognostic stratification of stage Ⅱa (T3N0) patients for postoperative treatment[9,15]. On the basis of statistical considerations, the current recommended goal of 12-15 recovered lymph nodes without evidence of metastatic disease provides approximately 80% negative predictive value for colorectal carcinoma metastasis[16]. However, the clinical significance of micrometastasis [pN1(mi), *i.e.*, tumor cell clusters of > 0.2 mm but $\leqslant 2$ mm] and isolated tumor cells [pN0(i), *i.e.*, single tumor cells or small clusters of cells of $\leqslant 0.2$ mm at their greatest extent that can be detected by routine hematoxylin and eosin (HE) stains or immunohistochemistry (IHC) or clusters of $\leqslant 200$ cells in a single histological cross-section][17] in gastrointestinal carcinoma remains unclear[18]. In early and advanced pN0 gastric cancer, the occurrence of nodal micrometastasis was shown to have no impact on prognosis[19]; however, other studies showed that LN micrometastasis was one of the most important prognostic factors in multivariate survival analysis of pT1N0[20], and the prognosis was significantly poorer in patients with isolated tumor cells than in those without them[21]. A recent systematic review and meta-analysis reported that molecular detection of tumor cells (isolated tumor cells and/or micrometastasis) in regional lymph nodes is associated with an increased risk of disease recurrence and poor survival in patients with N0 colorectal cancer[22].

In N+ digestive carcinomas, lymph node ratio (LNR) is a better prognostic factor than number of metastatic nodes (pN), and it may minimize the stage migration effect[23-28] because it is assumed to be constant regardless of the number of examined nodes[29]. However, LNR stages can be more accurately differentiated with a large number (> 15) of examined nodes[11,30-32]. Negative node count has been proposed as a prognostic indicator in patients with gastric cancer based on the assumption that nodal metastasis and micrometastasis cannot be prevented without adequate negative node dissection[33,34]. A negative lymph node count has been associated with improved survival in colorectal cancer patients, independent of patient, pathologic and molecular characteristics; however, the beneficial effects of a negative count are stronger in stage Ⅰ-Ⅱ patients than in stage Ⅲ-Ⅳ patients[35]. Moreover, a straight ratio between negative and positive lymph nodes (RNPL), which provides direct information on nodal metastasis, micrometastasis, and the immune condition of the patient, could be more accurate than LNR for the prognostic evaluation of curatively resected gastric cancer[36]. At the same time, the log odds of positive lymph nodes (LODDS), *i.e.*, the log of the ratio between the number of positive LNs and the number of negative LNs, is superior to the pN+ and LNR classifications for prognostic assessment in gastric and colorectal carcinoma[37,38]. In effect, LODDS is a function of the number of negative LNs, whereas LNR is a function of the total number of LNs[39]. Moreover, LNR is not applicable to pN0 patients, whereas LODDS is a useful lymph node classification for pN0 patients because it can discriminate between subgroups with different survival rates[38]. With respect to the pN and LNR classifications, LODDS has shown more power for minimizing the stage migration phenomenon caused by an insufficient number of retrieved nodes[38,40].

The prognostic power of the number of involved nodes in patients with digestive carcinomas is limited.

Furthermore, although the therapeutic impact of lymphadenectomy has not been proven and the number of retrieved nodes cannot be considered a measure of successful cancer surgery, an adequate LN count should be guaranteed to accurately assess the N-stage through the number of involved nodes, LNR, number of negative nodes, ratio of negative to positive nodes, and LODDS in digestive carcinomas[4,41]. In fact, in Western countries, D2 lymphadenectomy is gradually becoming the recommended surgical approach for patients with resectable gastric cancer[11,42,43], and total mesorectal excision (TME) is the recommended procedure for extraperitoneal rectal carcinoma. However, because lymphadenectomy is not without complications and institutional screening programs leading to the detection of cancer at an early stage have increased the prevalence rate of clinical N0 tumors, sentinel node (SLN) mapping has been used as the rational procedure to select patients in whom nodal dissection may be omitted or a more limited nodal dissection may be preferred.

Sentinel node mapping and biopsy

Recent meta-analyses have shown acceptable SLN detection rates and accurate determination of lymph node status in gastric cancer[44,45]. However, SLN mapping and nodal basin dissection are not yet the standard of care in early gastric cancer because of several unsolved anatomical (skip metastasis, multidirectional lymphatic drainage patterns) and technical (dye method, radio-colloid method or combination of the dye method and radio-colloid method) issues that may impact the detection rates and false negative rates. Moreover, there is another problem regarding the pathological diagnosis of SLN metastasis, including micrometastasis. Pathologic examination of SLNs has not been standardized in gastric cancers[46]. Serial sectioning results in a more accurate evaluation of metastases; however it is time-consuming. HE staining and IHC have been used in combination with serial sections of frozen and paraffin-embedded specimens for the detection of micrometastatic disease in SLNs[47]. Occult metastasis in SLN has been detected in 4% of pN0 gastric cancer patients using IHC in the 5-μm-thick serial step sections at 85-μm intervals of whole formalin-fixed paraffin-embedded tissues of all resected SLN[48]. The highly sensitive real-time reverse transcription polymerase chain reaction (RT-PCR) system, which enables rapid analysis to detect the mRNA of CK19, CK20 and carcinoembryonic antigen[49], and the one-step nucleic acid amplification (OSNA) assay[50] are promising tools for intraoperative diagnosis of SLN involvement in gastric cancer. In rectal carcinoma, the "*in vivo*" procedure of sentinel node mapping and biopsy entails breaking the mesorectal fascia intraoperatively to search for and dissect the SLNs. However, from a surgical point of view, the preservation of the integrity of the mesorectal fascia during rectal excision is necessary to minimize the risk of both residual tumor and relapses, and this assumption is the basis of the TME technique. The aim of the currently adopted SLN mapping procedure in colorectal carcinoma is not to avoid extended nodal dissection and therefore related morbidities, but rather to improve the sensitivity of the histopathological evaluation through the selective application of serial step sectioning, immunohistochemistry, and/or RT-PCR techniques, and "*ex vivo*" techniques of sentinel node mapping have been developed for this goal[51]. We observed that this *ex vivo* sentinel node procedure is an effective method for improving nodal staging in clinically node-negative colorectal carcinoma by immunohistochemical detection of micrometastasis in SLNs. However, it is not useful for the detection of satellites (*i.e.*, the presence of macroscopic or microscopic tumor deposits in pericolorectal adipose tissue), which should be assessed by TNM staging of colorectal cancers[52]. Moreover, the "*in vivo*" and "*ex vivo*" procedures are associated with a identification rate of 90% and a sensitivity of less than 70%[53]. Advances in imaging technologies could allow a more accurate preoperative detection of SLNs than the current dye- or radio-guided methods. Moreover, new dye-guided intraoperative technologies might revolutionize the SLN mapping procedure in gastrointestinal cancers. Indocyanine green (ICG) infrared or fluorescence imaging may identify a higher number of SLNs than radio-guided methods because the particle size of dyes is smaller than that of radioactive colloids. In gastric cancer, ICG infrared imaging is a useful tool in laparoscopic detection of SLNs. ICG fluorescence imaging is feasible even by preoperative ICG injection at, for instance, 1 or 3 d before surgery; it is also feasible in laparoscopy-assisted gastrectomy *via* a small laparotomy[47]. There is only limited experience with the application of ICG fluorescence-guided SLN mapping in colon cancer. The method has been shown as feasible and safe but further analyses in larger series are necessary to determine its definitive role in colon cancer patients[54].

The rationale for performing SLN mapping and biopsy is to determine the N status in tumors in which the N status may impact the prognosis, thus potentially avoiding unnecessary lymphadenectomy. This is possible if the determination of N status is accurate, *i.e.*, when the SLN procedure has acceptable false-negative rates. Actually, in pN0 cases, a greater number of retrieved nodes have a beneficial impact on outcome, and a false-negative rate of SLN determination is common in gastrointestinal carcinomas. Moreover, apart from anatomical, technical, surgical and pathological issues, in light of the latest knowledge about the biology of tumor progression, determination of N status by the sentinel node mapping procedure, leaving out of consideration currently emerging progression-related phenomena, may not be sufficient for prognostic evaluation.

EPITHELIAL-MESENCHYMAL TRANSITION-RELATED PHENOMENA OF TUMOR PROGRESSION: TUMOR BUDDING AND TUMOR DEPOSITS

Two EMT-related phenomena involved in cancer progression have been recently shown to have prognostic impact: tumor budding (TB), which is the presence of de-differentiated, isolated single cells or small cell clusters (up to five cells) scattered in the stroma at the invasive front of the tumor[55]; and the formation of tumor deposits (TDs, satellites), which are macroscopic or microscopic nests or nodules found in the lymph drainage area of a primary carcinoma without evidence of residual lymph nodes in the nodule. TDs may represent discontinuous spread, venous invasion or a totally replaced lymph node[17].

The EMT process allows an epithelial cell to assume a more mesenchymal phenotype with increased migratory capacity, invasiveness, resistance to apoptosis and production of extracellular matrix molecules[56]. Loss of E-cadherin, a transmembrane glycoprotein localized in the adherens junction of epithelial cells, is a key event in EMT, enabling tumor cells to migrate, invade and metastasize[57]. Interestingly, the first step in a tumor bud's life seems to be its detachment from the main tumor body by loss of membranous expression of the adhesion molecule E-cadherin[58]. TB has been observed in gastrointestinal carcinomas including colorectal, esophageal, gastric, ampullary and pancreatic carcinomas[55,59-65]. Although the definition of "high-grade budding" (*i.e.*, 10 buds in a 25 × field) by Ueno *et al*[55] is the most widely applied, there are no well-defined, evidence-based criteria for quantitative (*i.e.*, optimal cut-off and field diameter) and qualitative assessment of TB[66]. In colorectal carcinoma, TB is an independent predictor of tumor progression and outcome, especially in stage Ⅱ (T1-3 N0) tumors, in which high TB may be used as a high-risk criterion to select patients for adjuvant therapy[66,67]. In pancreatic carcinoma, high grade TB has been identified as an independent and highly unfavorable prognostic factor. Moreover, TB is associated with more aggressive phenotypes such as advanced pT classification and lymphatic invasion[65]. In esophageal squamous cell carcinoma, TB is a significant prognostic factor for patients who have undergone surgery alone[61], and high grade TB has been reported to be the most important predictor of poor prognosis in patients who received chemotherapy followed by surgery[62]. Moreover, tumor buds could be used as a potential target for new therapeutic approaches[58,65].

TDs have been detected in various types of carcinomas other than colorectal carcinoma, including gastric, pancreatic, gallbladder and bile duct carcinomas[68]. The latest TNM classification of colorectal carcinoma has categorized TDs as N1c[17]. However, the nature of TDs as well as their histopathological definition and prognostic classification regarding primitive tumor (T), regional nodal (N), or distant metastasis (M) categories are debated[69-71]. Several authors support the inclusion of TDs in the staging of gastric cancer[70-72]. Snail and Twist are transcriptional repressors of E-cadherin and EMT inducers. In colorectal cancer, overexpression of Twist enhances TD formation, and upregulation of Snail expression contributes to lymph node metastasis through two different molecular pathways, both involving EMT, by repression of the membranous expression of E-cadherin: Twist-EMT-TDs and Snail-EMT-LN metastasis[73]. Overexpression of Snail and Twist has been shown in pancreatic carcinoma[74].

Therefore, the occurrence of TB and formation of TDs seem to be the result of different steps in tumor progression promoted by EMT. Although the precise involvement of the EMT process in tumor progression is not well understood, the existence of other progression-related phenomena with biological, prognostic and therapeutic impact between the T, N and M is undeniable. In digestive cancers, the role of staging and surgical procedures could be re-evaluated and redefined from the perspective of the biological, prognostic and therapeutic impact of these tumor progression-related phenomena.

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