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REVIEW

Assessment of lymph node involvement in colorectal cancer

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Abstract

Lymph node metastasis informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. It is core to all contemporary staging systems, including the widely used tumor node metastasis staging system. Patients with node-negative disease have 5-year survival rates of 70%-80%, implying a significant minority of patients with occult lymph node metastases will succumb to disease recurrence. Enhanced staging techniques may help to identify this subset of patients, who might benefit from further treatment. Obtaining adequate numbers of lymph nodes is essential for accurate staging. Lymph node yields are affected by numerous factors, many inherent to the patient and the tumour, but others related to surgical and histopathological practice. Good lymph node recovery relies on close collaboration between surgeon and pathologist. The optimal extent of surgical resection remains a subject of debate. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision are amongst the surgical techniques with plausible oncological bases, but which are not supported by the highest levels of evidence. With further development and refinement, intra-operative lymphatic mapping and sentinel lymph node biopsy may provide a guide to the optimum extent of lymphadenectomy, but in its present form, it is beset by false negatives, skip lesions and failures to identify a sentinel node. Once resected, histopathological assessment of the surgical specimen can be improved by thorough dissection techniques, step-sectioning of tissue blocks and immunohistochemistry. More recently, molecular methods have been employed. In this review, we consider the numerous factors that affect lymph node yields, including the impact of the surgical and histopathological techniques. Potential future strategies, including the use of evolving technologies, are also discussed.

Key words: Colorectal cancer; Lymphatic metastases; Lymph node metastasis; Neoplasm staging; Tumor node metastasis classification; Sentinel lymph node biopsy; Lymph node excision; Histopathological assessment; Surgery

Core tip: The number of lymph nodes in surgical resection specimens is influenced by numerous factors. Good practice by surgeons and pathologists is essential to maximize lymph node yields, but there are non-modifiable factors related to patient and tumour. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision, all increase lymph node yields, but a definite benefit in prognosis is not proven and the optimal extent of surgical resection remains contentious. Conversely, further development in sentinel lymph node biopsy techniques could allow selective lymphadenectomy, whilst providing appropriate information to guide adjuvant therapy.

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INTRODUCTION

Lymph node metastasis (LNM) informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. As such, lymph node metastasis has had a role in colorectal cancer staging from the earliest classification systems. Its importance in prognosis has been borne out by successive classification systems and is reflected in all contemporary staging systems, in particular the widely used tumor node metastasis (TNM) staging system, developed and maintained by the Union for International Cancer Control and American Joint Committee on Cancer (AJCC).

Patients with node-negative disease have 5-year survival rates of 70%-80% in contrast to 30%-60% in those with node-positive disease. Survival is improved in the latter group by adjuvant chemotherapy. The 20%-30% disease recurrence in apparently completely excised tumours without lymph node metastases is thought to be due to occult lymph node disease. If this subset could be identified by better lymph node staging, they might also benefit from adjuvant chemotherapy.

There are several prognostic factors other than lymph node disease status that also identify patients who might benefit from adjuvant treatment. These include venous invasion, peri-neural invasion, tumour perforation, serosal involvement and incomplete resection[1,2]. However, lymph node assessment remains a mainstay of deciding adjuvant chemotherapy. To achieve accurate staging, surgeons and pathologists must exercise due diligence in their respective practices. Most authorities recommend examination of a minimum of 12 lymph nodes, although the evidence base for this is weak. Behind this apparently simple number are numerous complex issues, many without clear solutions. In this review, we consider the factors that affect lymph node yields including the influence of surgical and histopathological techniques. Evolving concepts and technologies that are not in widespread use, such as sentinel lymph node evaluation, are also discussed.

FACTORS INFLUENCING LYMPH NODE ASSESSMENT

In order to identify and maximise the diagnostic information from lymph nodes within a specimen, it is important to understand the factors that influence the lymph node harvest (LNH). This relates to a range of different factors: The pathologist, the surgeon and factors inherent to the patient and tumour. While tumour and patient characteristics cannot be changed, the pathologist can employ various techniques to maximise both the LNH and gain additional diagnostic information from enhanced study of the lymph node. The surgeon can modify the surgical procedure to excise more tissue or use ancillary techniques to aid selection and examination of lymph nodes by the pathologist.

ROLE OF THE HISTOPATHOLOGIST

Contemporary lymph node staging

There are several tumour staging systems, of which the TNM staging system is the most widely used internationally. It seems self-evident that lymph node metastasis indicates the presence of tumour cells within a lymph node. However, precise definition of different types of burden is crucial. Metastatic disease is often sub-classified into isolated tumour cells (ITCs, < 0.2 mm), micrometastases (defined as > 0.2 mm but < 2 mm) and macrometastases (⩾ 2 mm). More recently, the concept of molecular positivity has been introduced. The classification of nodal disease (N-stage) under the current 7th edition of the TNM staging system (TNM7) is summarised in Table 1.

A universally agreed definition of what constitutes lymph node metastasis is important for communication between all parties involved in treating, diagnosing and researching colorectal cancer. It facilitates uniformity for the purposes of entry to clinical trials, subsequent applicability of the ensuing results and interpretation of historical trends. Any criteria should be objective, reproducible, evidence-based and met with broad agreement. However, significant changes to the criteria in successive editions of TNM have been criticised for lacking some of the above qualities.

Detailed analysis of the changes wrought by the two most recent TNM editions is presented elsewhere[3-5]. The main changes are summarised diagrammatically in Figure 1, but a few points warrant discussion. In the 6th edition (TNM6)[6] of the TNM staging system, isolated tumour cells became classed as N0 for the purposes of grouping tumours into AJCC stage Ⅰ to Ⅳ, in contrast to N1 in the 5th edition (TNM5)[7]. Secondly, extra-mural

Table 1 Nodal staging in the 7th edition of the tumor node metastasis staging system

N Stage	Description
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N0 (i-)	No regional lymph node metastases histologically, negative IHC
N0 (i+)	Isolated tumour cells, identified by H&E and/or IHC
N0 (mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
N0 (mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
N1mi	Micrometastases
N1	Metastasis in 1-3 regionl lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2b	N2b Metastasis in seven or more regional lymph nodes
N2a	N2a Metastasis in 4-6 regional lymph nodes

IHC: Immunohistochemistry. RT-PCR: Reverse transcription-polymerase chain reaction.

deposits are difficult to classify. In a study of 69 tumour deposits, step sections were performed on what were initially diagnosed as tumour deposits. A significant proportion were found to represent other patterns of tumour spread[8]. The "3 mm rule" stipulated in TNM5 was not based on published data, but had the advantage of being objective and reproducible[9], in contrast to the assessment of "contour" introduced in the 6th edition (TNM6)[10]. The "contour rule" was dropped in the 7th edition (TNM7), but explicit criteria were not provided to replace it. Left to the discretion of the pathologist, classification of extra-mural tumour is fraught with inter-observer variability[11]. Unsurprisingly, there has been stage migration as a result of these changes, making it difficult to compare historical data. Data from the Surveillance, Epidemiology and End Results population-based registries showed that 10% of colorectal cancer cases had "tumour deposits", of which 30%-40% occurred without concomitant lymph node metastases. Compared to TNM6, this represented up-staging of 2.5% of colon and 3.3% of rectal cases to N1c, a significant stage migration from stage Ⅰ to stage Ⅲ[12]. There have also been misgivings over the use of TNM7 following neoadjuvant treatment, where patchy tumour regression may give the false appearance of lymph node metastasis or discontinuous tumour deposit. Finally, the changes in definition tend to reduce lymph node counts[13], a concern where LNH is being used as a marker of "quality". It is hoped than the 8th of edition, due to published this year, will resolve some of these issues.

Dissection

In many pathology laboratories, macroscopic examination and dissection of colorectal cancer specimens is delegated to trainee pathologists, sometimes with limited experience and expertise. These large resection specimens tend to be left to the end of the "cut-up" session when time may be limited. Even in experienced hands, the detection of minute lymph nodes in mesenteric fat by palpation and dissection is painstaking and time-consuming. Marked variation in the assessment of colorectal cancer in the pathology laboratory, particularly in lymph node yields, is not a new issue[14,15], but there is now more awareness of the crucial role of dissection. Results from staff pathologists[16] and non-pathologist dissectors[17-19] may be superior, but it is likely that a major factor is not the expertise of the operator, but rather the time devoted to searching for lymph nodes. de Burlet *et al*[20] studied LNH in gastrointestinal tumour resection specimens. Twenty minutes was allocated to an initial lymph node search, followed by an extra 5 and 10 min, which increased yields by 12% and 20% respectively. Twenty additional minutes added a mean of 6 lymph nodes, albeit with a diminishing rate of lymph node discovery. The United Kingdom Royal College of Pathologists' Guidelines on Staffing and Workload allocates 8 points for cutting-up a colorectal resection, corresponding to an anticipated time spent of 31-50 min[21]. This would appear to underestimate the time required for a thorough job if de Burlet *et al*[20] findings are correct. Often little thought is given to the ergonomics around cut-up. To optimise lymph node yields, we recommend that large specimens should be dealt with first when the operator is still fresh.

Handling

Current practice in handling of lymph nodes is not uniform. The United Kingdom Royal College of Pathologist guidance recommends embedding each lymph node whole, if < 4 mm, and a central block through longest axis for larger nodes[22]. It is common practice to bisect or serially slice larger lymph nodes.

Typically, a single haematoxylin and eosin stained section is cut from each lymph node block, representing only a tiny volume of the lymph node in a single axis. Cutting more sections increases detection of lymph node metastases, including up-staging of several cases[23], but the workload implications for the laboratory and histopathologist makes routine application of this unfeasible. Similarly, identification of small deposits of tumour by immunohistochemistry increases detection, but once again, has significant cost and workload implications.

Lymphatic mapping, the process of injecting tracer at the tumour site and following lymphatic flow to identify lymph nodes, has been used to identify sentinel lymph nodes (SLN). These SLNs are then subject to more intensive histopathological scrutiny, so-called ultrastaging[24], typically consisting of additional levels and/or immunohistochemistry and in some cases molecular techniques[25]. The utility of SLN ultrastaging is hampered by the limitations of current

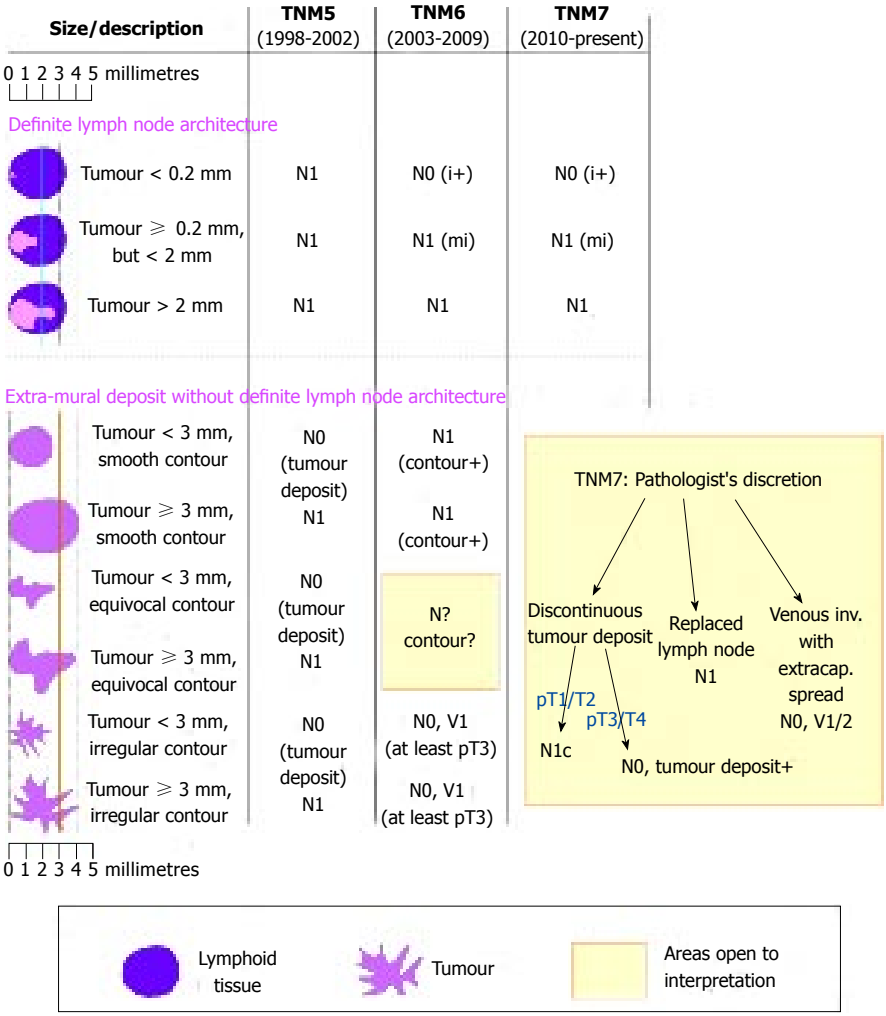

Figure 1 Changes in successive editions of the tumor node metastasis staging system. Top 3 rows: Size of deposit within definite lymph node. Under the 5th edition of the TNM staging system (TNM5)[7], the volume of tumour cells is immaterial, but from the 6th edition (TNM6) onwards[6], tumour burden is sub-classified by size; bottom 6 rows: Extra-mural deposits. TNM5 uses a 3 mm threshold; above this, the deposit is regarded as a lymph node metastases, below this, the deposit is regarded as a discontinuous extension of the main tumour. TNM6 relies on assessment of contour; smooth deposits are counted as nodes, whereas irregular contours are considered vascular invasion and upstaged in the T category. TNM7 leaves the decision to the judgement of pathologist with a wide range of outcomes.

SLN procedures, namely false negatives, skip lesions and failure to identify a SLN (see later section on SLN). The significance on prognosis of isolated tumour cells identified in this way is also contentious[25] and is discussed in the later section on the size of tumour deposits.

Several other ancillary techniques have been employed to aid the LNH. Modified lymphatic mapping can be achieved by injection of India ink at the time of surgery[26,27] and, similarly, *ex vivo* intra-arterial injection of methylene blue can accentuate lymph nodes[28,29]. Chemical fat clearance can be performed with a variety of chemical regimens, typically a mixture of fixatives and organic solvents, such as glacial acetic acid, xylene, acetone, and alcohol. With the fat partially removed, nodes are accentuated, facilitating manual dissection and increasing yields. The clearance techniques are not in universal usage due to the slight delay introduced in finalizing a report and safety issues related to the disposal of the volumes of hazardous chemicals generated. The entire mesentery can be embedded without fat clearance, so-called entire residual mesenteric tissue examination, which also increases yields[30]. There is no doubt that many of these techniques increase LNH, but there are not currently enough data to show that they result in significant up-staging[31].

Molecular techniques

The disadvantage of conventional ultrastaging is that it still relies on examination of a tiny volume of the lymph node. Lymph nodes harvested fresh can be processed to extract nucleic acids that can be analysed using reverse transcriptase and polymerase-based technologies. Some studies have used conventional polymerase chain reaction, but loop-mediated isothermal amplification, also known as one-step nucleic acid amplification (OSNA) can be performed in less than an hour and can be used intra-operatively. The results are quantitative and should reflect mRNA copy number. Thresholds are set to give grades of molecular lymph node involvement equivalent to conventional nodal staging, typically

⩾ 250 copies for micrometastases and ⩾ 5000 for macrometastases, although these figures are based on work done with breast cancer cases. Typical markers including carcinoembryonic antigen, cytokeratins 19/20 and guanylyl cyclase C. OSNA can be performed on the entire node[32-34] or half of the node in combination with conventional sections[35]. While up-staging was described in most series, there have been discrepancies not entirely explained by tissue allocation, suggesting conventional methods, albeit with ultrastaging-type protocols may have superior sensitivity and specificity. The data on how OSNA results correlates with the performance of single section histopathological analysis is sparse, particularly when isolated tumour cells are not included as a molecular category. Application of the OSNA technique to all lymph nodes harvested is not currently feasible outside of the research setting and practically-speaking, its main role is likely to be for the purposes of analysing sentinel lymph nodes.

Sentinel lymph node biopsy

The principle of sentinel lymph node biopsy (SLNB) is well established in melanoma and breast cancer, where the aim is to avoid unnecessary and potentially morbid lymphadenectomy. Unlike these two malignancies, where lymphadenectomy is a separate procedure, lymphadenectomy in elective colorectal cancer surgery is typically performed as part of a single surgical procedure. The lymphadenectomy component carries a low, but not entirely negligible morbidity. In a review of SLNB, Cahill questions the assumption that additional surgery carries no or minimal risk, particularly if radical lymphadenectomy is performed[36]. The effects of excising unnecessary tissue are difficult to quantify. However, if SLNB can readily and reliably determine lymph node status, permitting more conservative surgery, then reduced tissue dissection, shortened operative time and better bowel function are all desirable outcomes.

Another scenario where SLNB may be informative is in early T-stage colorectal cancers, particularly pT1 polyp cancers identified by bowel cancer screening programmes. Adequate local excision of these polyp cancers is often achieved by endoscopic resection, but there is uncertainty about whether segmental resection for lymphadenectomy is indicated, a particular dilemma in patients with significant co-morbidities. While certain tumour characteristics predict lymph node metastases[37-40], a SLNB should provide a definitive answer. SLNB can be performed laparoscopically[41,42] and potentially *via* other minimally invasive techniques, *e.g.,* a transcolonic approach using with natural orifice transluminal endoscopic surgery[43].

In this context, SLNB data specific to pT1/T2 tumours is of particular relevance, but many studies are small, typically include all T-stages or, in some studies, omit T-stage data. SLNB may have less of a role in pT3/T4 tumours as they are more likely to harbour lymph node metastases and therefore less likely to benefit from initial SLNB[44]. Additionally, an increased rate of false negatives has also been described in pT3/pT4 tumours[36].

Broader adoption of SLNB, however, is limited by the guarded results from existing studies. SLNB is beset by a number of problems: Failure to identify a SLN, false negatives and skip lesions[45-47]. Skip lesions have been hypothesised to be due to blocked lymphatic flow into involved lymph nodes, but this is not entirely explained by some data. It is unclear if the poor results are explained by technical problems, sub-optimal implementation of the technique or whether the concept is fundamentally flawed because of the inherently unpredictable pattern of lymph node involvement[36,48]. Further evaluation of these techniques is required to determine whether they should be generally adopted.

ADDITIONAL HISTOPATHOLOGICAL ASPECTS IN LYMPH NODE ASSESSMENT

The most obvious measurable parameter relating to lymph nodes is the total LNH. Sampling as many lymph nodes as possible is ideal, but the focus on absolute counts alone ignores the complex and sometimes interacting factors that influence LNH. A detailed analysis of lymph node counts is presented later in this review, but other characteristics related to lymph nodes are discussed here.

Size of tumour deposit and/or lymph node

There are two separate aspects to consider. Firstly, does lymph node size, irrespective of tumour involvement, have implications on LNH or prognosis? Secondly, if a lymph node is involved, is the size of the deposit within the lymph node significant?

Chirieac *et al*[49] showed that nodal size significantly predicted overall survival in patients with node-negative colorectal cancer. They also speculated that high numbers of bulky negative lymph nodes were a product of an active host immune response, which ultimately contributed to improved patient prognosis and survival.

In some studies, LNM were more likely to be found in larger lymph nodes[50,51], perhaps because they are easily palpable and therefore preferentially sampled. In node-positive disease, the size of the lymph node (as opposed to the tumour deposit) appears to have no significance on outcome[52,53]. These studies and several others have demonstrated that many, if not the majority, of LNM occur in lymph nodes < 5 mm[51,54]. The relevance of this is that small LNs are harder or impossible to palpate and are therefore less likely to be sampled during pathological dissection. Secondly, it is hard to completely separate the size of the tumour deposit from the size of the lymph node as the deposit obviously cannot exceed the size of the node. According to TNM7 rules, a positive 1.9 mm lymph node will either be involved by isolated tumour cells or micrometastases, but never a macrometastases (Figure 1).

This leads to the next question: Is the size of LN tumour deposit significant? The size of the largest lymph node tumour deposit appears to be prognostic[55], but the overall volume of lymph node tumour burden appears to be less important than the number of involved lymph nodes[56].

There is also considerable debate about the significance of isolated tumour cells. The data shows a wide variation in the incidence of isolated tumour cells and micrometastases, ranging from 11% to 59%. Some demonstrate an adverse effect on survival[57-60], but others show no significance[61-64]. The discrepancy reflects the differences in study design such as method of detection, length of follow-up and whether other confounding factors were considered. As previously discussed, more thorough scrutiny of lymph nodes with ultrastaging and/or molecular methods may increase detection of tumour, but it is unclear what significance this has on prognosis as direct comparison of data difficult. A 2014 meta-analysis suggests micrometastases have an adverse prognosis whilst isolated tumour cells do not[65], but this distinction is not always straight-forward: The size cut-off of 0.2 mm is arbitrary and other definitions in terms of total cell numbers are hard to apply consistently.

Oncological practice in the United Kingdom continues to use the TNM5 definitions of lymph node metastasis, which defines the presence of any metastatic disease as N-positive, warranting adjuvant chemotherapy. Practice in other parts of the world differs, particularly in countries that have already adopted TNM7, which classifies isolated tumour cells as N0.

Extracapsular spread

Extracapsular extension is typically associated with more aggressive and infiltrative tumours. Heide *et al*[66] noted that extracapsular extension in rectal resections was connected with adverse local control and a higher rate of distant metastases. In another study, the survival rates and disease-free survival rates for patients with metastatic lymph nodes showing an extracapsular invasion pattern were significantly worse than cases showing no evidence of extracapsular extension[67].

Lymphoid hyperplasia/sinus histiocytosis

LNs negative for tumour may show reactive patterns such as follicular, parafollicular hyperplasia, as well as sinus histiocytosis. These have been regarded as indicators of active host immune response and are associated with an improved prognosis and 5-year survival rate[68]. A survival advantage has also been established in metastatic lymph nodes that also demonstrate a background of benign reactive inflammatory changes[69]. The host-response hypothesis may also explain why patients with lower lymph node yields are generally found to have a poorer prognosis, although reactive lymph nodes are more easily identified and may result in higher LNH and more accurate staging.

Ratio of involved lymph nodes

The use of the ratio of positive nodes to total LNH was first proposed by Berger *et al*[70] in 2005 as an additional prognostic factor. Several subsequent studies have corroborated the original findings[71-77], although what threshold to use is not clear. The results are not entirely consistent and there may also be differences between colonic and rectal tumour[78]. A minimum LNH is required to make the ratio valid. Conversely, large numbers of lymph nodes obtained through techniques such as fat clearing may increase the overall denominator, disproportionately reducing the ratio.

Mucin pools

LNM from tumours showing prominent mucinous differentiation may manifest as pauci-cellular mucin pools. Following neoadjuvant treatment, these may be rendered acellular. Further step levels are helpful to exclude viable tumour cells, but if no cells are found, these are regarded by most pathologists as lymph node negative[79,80].

ROLE OF THE SURGEON

The role of the surgeon is to excise the primary tumour and an appropriate amount of mesenteric tissue with clear margins, to allow adequate staging, whilst minimising potential complications. This raises the question of how much tissue should be removed to achieve optimal oncological outcomes.

Lymphadenectomy - therapeutic or prognostic?

How much tissue to remove is guided by the interpretation of the fundamental purpose of lymphadenectomy. There are divergent views on whether it is directly therapeutic or whether it provides mainly staging and prognostication[81]. The model espoused by Halsted at the end of the 19th century assumes sequential and step-wise spread of tumour outwards from the primary site. Radical surgery to remove all tumour not only provides staging information, but also potentially cures the tumour. In contrast, the Cady *et al*[82] paradigm assumes systemic spread may occur early in tumour growth and that improved outcomes derive from delivery of the optimum adjuvant treatment as determined by accurate staging. The Halsted radical mastectomy has been consigned to surgical history, but it is unclear if principles gleaned from breast cancer can be extrapolated to colorectal cancer.

Indirect evidence for a therapeutic effect has been inferred from studies looking at lymph node counts. The Intergroup Trial INT-0089 showed 5-year overall survival increased from 51% to 71% for N2 disease if > 35 lymph nodes were harvested compared to < 35[83]. Given this was N2 disease, better staging and stage migration cannot entirely explain the results which showed superior survival to that of published trials using optimal adjuvant chemotherapy, implying a curative component. Other explanations are possi-

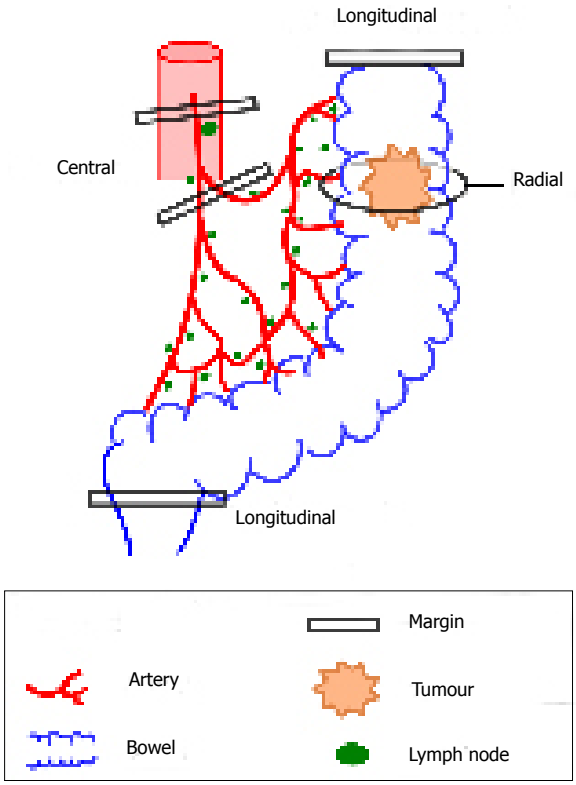

Figure 2 Anatomical extent of surgery. Schematic representation of the 3 anatomical boundaries of colorectal surgery.

ble, *e.g.,* high lymph node counts representing good host inflammatory response, but it is likely that lymphadenectomy is both prognostic and therapeutic, particularly in the rectum where total mesorectal excision (TME) achieves simultaneous local control and lymphadenectomy, with both components inherently inseparable. It is no surprise that when more mesenteric tissue is removed, LNH also increases. In theory, this leads to more accurate staging and potential therapeutic removal of involved lymph nodes. However, for many of the surgical techniques described below, the highest levels of evidence are lacking. It is therefore unclear whether the benefits of removing more tissue outweigh the increased operating time and potential morbidity associated with these procedures. A detailed review of surgical practice is beyond the scope of this review, but salient issues are considered below and readers are directed to other surgical guidelines[84-87].

What is adequate surgery?

Margins can be thought of as extending to 3 anatomical boundaries (Figure 2). Firstly, the longitudinal margin as determined by the axial extent of the bowel excised. Secondly, the extent of mesenteric tissue excised, in a centripetal direction towards the root of the supplying artery. Thirdly, radial margins, in the broadest sense, which may include *en bloc* excision of advanced local spread, *e.g.,* the abdominal wall or adjacent organs, but also encompasses the circumferential margin, or more accurately, the non-peritonealised margin. Frequently, these three margins cannot be manipulated independently of each other, but as a general rule, increasing the first two margins also increases lymph node yields.

Longitudinal margins

Typically, the segment of bowel containing the tumour is excised along with the mesentery delineated by its arterial supply. For colonic tumours, at least 5 cm of longitudinal clearance is advised to minimise anastomotic recurrence[88,89]. In the rectum, 5 cm proximal and 2 cm distal appears sufficient[90]. The Japanese Society for Cancer of the Colon and Rectum guidelines recommend at least 5 cm in the direction of lymph flow and 10 cm in opposite direction[91]. In practice, it is the vascular supply that dictates the extent of surgery. If the tumour straddles two arterial branches, both segments should be excised. Anatomical and functional considerations may also extend resection beyond oncological requirements. For instance, in left-sided tumours, many surgeons avoid anastomoses with the sigmoid colon as it is regarded as a "high pressure" segment and also receives no contribution from the marginal artery.

The length of bowel resected may be extended in several scenarios on the basis that spread of tumour beyond normal segmental boundaries has been described, a finding partially borne out by intra-operative lymphatic mapping. Extended lymphadenectomy can be achieved by performing an extended right hemicolectomy for proximal right-sided tumours[92,93]. Extended right hemicolectomy is also common performed for transverse colon and splenic flexure tumours, although there are no randomised, controlled trials to support this. Similarly, for left-sided tumours, one of the few randomised controlled trials in this area showed no benefit of left hemicolectomy over segmental resection[94]. The type of surgery employed, particularly the length of specimen, has a clear influence on LNH, but without lymphatic mapping, is not clear when extended surgery should be performed.

Central margins and extra-mesenteric lymphadenectomy

Classically, colonic tumour spreads along lymphatics in the distribution of the arterial supply[92,95,96]. Depending on their anatomical distribution, lymph nodes in the colon are described as pericolic, intermediate and apical/central/main, broadly corresponding to D1, D2 and D3 in the Japanese notation[87]. Lymphadenectomy can be performed up to and flush with the level of the origin of the artery[97], so-called complete vascular ligation, one of the key components of complete mesocolic excision (see below). This manoeuvre takes the apical node which is involved in about 3%-11% of tumours[93,97,98]. In tumours of the sigmoid colon and upper rectum, high ligation of the inferior mesenteric artery has been advocated as oncologically superior. This was first promulgated by Moynihan in 1908[99] and the debate on its value has continued for more than a

century. Despite good results in several, mainly cohort studies, other studies have shown no benefit (see systematic reviews in[100-103]). No benefit was seen in sigmoid tumours in a multicentre randomised controlled trial[94]. The issue, however, has not entirely been laid to rest and a randomised controlled trial of high ligation in the context of laparoscopic surgery is on-going[104].

Routine excision or sampling of lymph nodes outside the typical lymph node basin has also been advocated. Tumours around the hepatic flexure may spread to infra-pyloric nodes[97]. In the rectosigmoid region, the arterial supply is variable and spread to lateral (extra-mesorectal) pelvic lymph nodes may occur[96]. One paper describes lateral pelvic node involvement in up to 18%, rising to 36% in the sub-group of Dukes' C tumours[105]. Proponents of radical lymphadenectomy argue it is oncologically superior, both in achieving better staging but also therapeutically by removing all diseased lymph nodes. However, all of the above additions and modifications to "standard" lymphadenectomy may result in additional morbidity, particularly damage to neighbouring structures.

Depending on the anatomical site, this includes the duodenum, ureters and nerve plexuses[106]. Vascular compromise may occur from direct vascular damage or *via* reduction in collateral flow[107]. As extra-mesenteric and apical lymph node involvement is present only in a minority of cases, routine extended dissection represents unnecessary surgery for most patients. A selective approach has been advocated[98], but patients with the highest rates of aberrant lymph node involvement are those with high T-stage, the same group where lymphadenectomy is least likely to be curative due to the increased risk of systemic disease. The benefit of these procedures is unproven and potential morbidity may outweigh the benefits[108,109].

Radial margins

TME has been established as the optimal surgical technique for rectal tumours. Pioneered by Heald, introduction of the technique reduces local recurrence[110,111]. The same anatomical and oncological principles have been extrapolated to colonic tumours, so-called complete mesocolic excision (CME)[112]. Although a relatively new concept in the West, CME shares many features with D3 excisions that have been performed routinely in East Asia[113,114]. It is associated with better LNHs[115]. However, while it is supported by some compelling oncological and anatomical concepts, it encompasses many of the unproven surgical elements discussed above. The technique may prove itself in the fullness of time, but there is presently insufficient evidence to support it[116,117]. Furthermore, the unsuccessful attempts by European surgeons to adopt D3 lymphadenectomy for gastric cancer is a salutary reminder of how challenging it is to "import" purportedly superior surgical techniques from established centres[118].

Type of surgery

Laparoscopic and laparoscopic-assisted surgery is increasingly the default surgical approach to colorectal cancer resection. Superior peri-operative recovery and oncological equivalence has been demonstrated by several randomised controlled trials, including no significant difference in lymph node counts[119]. Many of techniques described above can be achieved laparoscopically, *e.g.,* CME[120-126], although randomised controlled trials are difficult to undertake. Laparoscopic CME therefore still lacks a convincing body of supportive evidence. The data on robotic surgery are promising[127], but at present only includes a single randomised-controlled trial.

INTRA-OPERATIVE PROCEDURES

A number of procedures can be performed intra-operatively to assist in lymph node staging. As previously discussed, lymphatic mapping entails injecting a tracer at the tumour site, which travels along lymphatics and facilitates identification of lymph nodes[24], including the sentinel lymph node. SLNs can be excised intra-operatively and for immediate results, can be subject to frozen section histological examination or OSNA[128]. Other technologies that provide immediate intra-operative results are the subject of on-going research, *e.g.,* optical coherence tomography and real time elastography[129].

Outside these techniques, the default histological analysis is performed on sections cut after formalin-fixation and paraffin embedding of the SLN. The results are therefore not available to influence immediate operative management. The exception is where the lymphatic mapping process identifies tracer in "aberrant" lymph node territory. The surgeon can choose to sample the abnormal lymph nodes or perform more radical lymphadenectomy. In 2 studies, *in vivo* lymphatic mapping changed the procedure in 9% and 22% of cases respectively[129,130]. In the latter study, nodal positivity was higher in patients undergoing a change of procedure.

THE INFLUENCE OF PATIENT AND TUMOUR CHARACTERSTICS

Patient

Several patient characteristics have been identified that influence LNHs[131]. However, factors identified in some studies are not corroborated by others. Fewer lymph nodes are generally obtained from specimens from older patients[132-134]. Gender seems to have no effect, while low counts have an inconsistent association with obesity, as measured by body mass index[135,136].

Tumour characteristics

Several histological characteristics of the primary

tumour have been shown to be associated with an increased risk of LNM. One meta-analysis identified 42 different factors. Only 15 were reported in 2 or more studies and not all are routinely analysed during standard reporting procedures[137]. Factors that are easily assessed during routine histological reporting include tumour site[133,134,138], stage[133] and differentiation. Higher counts are seen in tumours with microsatellite instability[139]. While not an exhaustive list, many of these features lack reproducibility, sensitivity and/or specificity. It is therefore uncertain whether any single feature in isolation is reliable enough to influence decisions on adjuvant treatment. Neoadjuvant chemotherapy and/or radiotherapy typically reduces the numbers of nodes sampled[133,140].

Predictive factors in submucosal (pT1) tumours are of particular interest as these are typically resected endoscopically and may require segmental resection for lymphadenectomy. Adverse factors in this group include poor tumour differentiation, depth of invasion and lymphovascular invasion[37-40]. If sentinel lymph node biopsy techniques can be refined, this would greatly aid decision-making in this group on whether additional surgery is appropriate.

LYMPH NODE YIELDS AS A MEASURE OF QUALITY

Many of the surgical and histopathological techniques discussed are based on the presumption that increased lymph node yields invariably leads to more accurate stage. This assumption warrants critical appraisal. Many organizations such as the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the United Kingdom Royal College of Pathologists have guidance stipulating a minimum lymph node yield of 12 lymph nodes per case. The choice of 12 was proposed in 1990 by the Working Party Report to the World Congress of Gastroenterology in Sydney[141], partly supported by subsequent studies, but has a poor evidence base.

Others have suggested alternative minimum numbers depending on the T-stage of tumour[142], with more numbers required for low T-stage disease. While it has been clearly demonstrated in numerous studies that prognosis improves with the number of lymph nodes sampled[143-146], this association does not prove causation. Furthermore, the association of lymph node counts and survival applies even in node-negative disease[147] which lends support to the alternative explanation that high lymph node yields are a surrogate marker of a vigorous host immune response to tumour. Conversely, low lymph node counts are associated with a worse survival and may, in itself, be an indication for adjuvant treatment. Much of the existing evidence is based on studies where LNs were harvested without recourse to special techniques and it is unclear if the same survival associations apply when additional or special techniques "inflate" the number of lymph nodes sampled. Not all studies have demonstrated a beneficial effect of higher lymph node yields[148]. Yet others have observed a trend of increased lymph node yields over several years, most likely reflecting better surgical and histopathological practice, but without a corresponding increase in the detection rate of LNM[149,150]. Similarly, the use of special techniques fares no better[151]. At the risk of repetition, we need to clearly distinguish the principle of association from causality. Increased lymph node yields show an association with survival, but do not cause it. Various techniques may increase the lymph node count, but may not change the underlying nature of the disease. It is established that lymph node yields are multifactorial, influenced by a combination of patient, tumour, surgical and pathological factors[131,152].

Clearly, there must be minimum standards in both surgical and histopathological practice. Surgery that fails to remove enough mesentery for staging and a cursory, hurried dissection by a pathologist, sampling only a handful of lymph nodes are likely, in combination, to lead to under-staging. However, for the majority of practitioners, the message about the importance of achieving accurate lymph node staging has been heard and implemented. Audit of LNHs is good practice, but the unthinking pursuit of ever higher lymph node yields should be resisted. In particular, it is unreasonable to link lymph node yields with quality payments, particularly when it is established that many factors influencing lymph node yields are outside the control of both surgeon and pathologist.

CONCLUSION

The importance of colorectal cancer lymph node staging cannot be over-emphasised. We have discussed many of the controversies associated with this challenging area and provided guidance about the rational application of additional techniques. TNM7 has not been universally adopted internationally[22], but publication of TNM8 is anticipated in this year. The authors anticipate that this will address some of the issues and lead to a consensus approach. The variable contribution of surgical, pathological, patient and tumour related factors means that this remains a contentious subject. This complex area continues to evolve with new developments, surgically and pathologically, providing novel methods to evaluate nodal disease.

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