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Qualitative and Quantitative Issues of Lymph Nodes as Prognostic Factor in Colon Cancer

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Key Words
Colon cancer · Lymph nodes · Sampling · Sentinel node · Quality · Surgery · Pathology · Volume · Molecular biology · Staging

Abstract
For patients undergoing curative resections for colon cancer, the nodal status represents the strongest prognostic factor, yet at the same time the most disputed issue as well. Consequently, the qualitative and quantitative aspects of lymph node evaluation are thus being scrutinized beyond the blunt distinction between 'node positive' (pN+) and 'node negative' (pN0) disease. Controversy ranges from a minimal or 'least-unit' strategy as exemplified by the 'sentinel node' to a maximally invasive or 'all inclusive' approach by extensive surgery. Ranging between these two extremes of node sampling strategies are factors of quantitative and qualitative value, which may be subject to modification. Qualitative issues may include aspects of lymph node harvest reflected by surgeon, pathologist and even hospital performance, which all may be subject to modification. However, patient's age, gender and genotype may be non-modifiable, yet influence node sample. Quantitative issues may reflect the balance between absolute numbers and models investigating the relationships of positive to negative nodes (lymph node ratio; log odds of positive lymph nodes). This review provides an updated overview of the current controversies and a state-of-the-art perspective on the qualitative and quantitative aspects of using lymph nodes as a prognostic marker in colon cancer.

Introduction

Colorectal cancer is a leading cause of cancer morbidity and mortality in the Western world. Progress in diagnosis and management has increased the expected long-term survival considerably over the past decades, now exceeding 60% for curatively resected patients [1, 2]. While considerable research efforts have been put into an increased understanding of the underlying disease mechanism at the genetic and molecular level [3], very few molecular features have made it into the clinical toolbox. Many genetic features have predictive or prognostic value [4], but molecular heterogeneity has prevented an overall applicable use of biomarkers for better

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staging so far. Still, stage based on tumor growth (T), nodal status (N) and distant metastasis status (M) remains the strongest predictor of survival. For patients undergoing curative resections, the node status represents the strongest prognostic factor [5]. Consequently, the qualitative and quantitative aspects of lymph node evaluation are thus being scrutinized beyond the simple and blunt distinction between 'node positive' (pN+) and 'node negative' (pN0) disease. Over the past decades, the principles of management of colon and rectal cancer have diverged [2, 6]. The contemporary standard of care for rectal cancers includes preoperative staging with magnetic resonance imaging, dedicated criteria for preoperative radiochemotherapy and standards of surgical technique as well as quality indicators including evaluation of the circumferential resection margin – now making rectal cancer prognosis superseding that of colon cancer patients [1]. For colon cancer, the 'lymph node' represents the single most evaluated, yet disputed, prognostic factor to the current date.

In this ongoing research area, there is considerable controversy ranging from a minimal or 'least-unit' strategy as exemplified by the 'sentinel node' (searching for the 'correct' node is better than finding all nodes) to a maximally invasive or 'all inclusive' approach by extensive surgery, dubbed D3 resection or 'complete mesocolic excision' (CME). Ranging between these two extremes of node sampling strategies are factors indicative of qualitative issues (i.e. lymph node harvest as an indicator of surgeon, pathologist and even hospital performance) and quantitative issues, i.e. the balance between absolute numbers and models investigating the relationships of positive to negative nodes (lymph node ratio; log odds of positive lymph nodes). This review provides an updated overview of the current controversies and a state-of-the-art perspective on the qualitative and quantitative aspects of using lymph nodes as a prognostic marker in colon cancer.

Methods

We searched the English PubMed indexed literature using combinations of the MeSH terms and/or the key words 'colon cancer', 'lymph node', 'sentinel node', 'node', 'lymph node ratio', and 'lymph node harvest' for the period 2000 until December 2012. Results including systematic reviews and meta-analyses (if available) and literature from the past 5 years (up to December 2012) were given priority for inclusion, as were large population-based studies, where available. Identified studies were scrutinized for further available studies by going through the reference lists.

Results

Quantitative Issues

There is no immediate and straightforward answer to the question what constitutes an adequate lymph node harvest after curative surgery for colon cancer. Most likely, the absolute number represents a continuum in terms of number of nodes needed for a proper node evaluation. However, to guide clinical practice and serve as a common reference, a general agreement has been reached, which is commonly referred to by most researchers. In 1990, a Working Party Report recommended to the World Congress of Gastroenterology in Sydney that at least 12 lymph nodes should be sampled to stage a patient with colorectal cancer [7, 8]. Since then, curative surgery of colorectal cancer has strived towards reaching ≥12 nodes, although an adequate yield is only achieved in about 60% of patients, even in the most recent series of both open and laparoscopic surgery [9]. Numerous publications about the optimal number of retrieved lymph nodes have been published. Several studies have investigated and found an association between an adequate node number and survival [10]. The 7th edition of the American Joint Committee on Cancer (AJCC) recommends obtaining at least 10–14 lymph nodes for adequate staging. Several population-based studies from Sweden [11] and the USA [12] have demonstrated an increase in node numbers with time. Also, an international multicenter study found a year-by-year increase in adequate lymph node yield after instituting requirements for adequate node harvest [13], although this was not followed by an increase in adjuvant chemotherapy.

Issues Concerning Upstaging

Among the prevailing arguments for a higher node harvest is the associated better staging (upstaging) of patients with pN+ who would otherwise be staged as pN0. One large study does not support this view. Although the number of harvested nodes steadily increased over 2 decades, the proportion of pN+ disease did not [12]. Furthermore, adequate lymph node evaluation for colon cancer was associated with lower mortality among all patients [14]. However, among 3-year survivors, the association between lymph node evaluation and lower hazard of death at 3 years was no longer significant at long-term follow-up, while postsurgical care – including adjuvant chemotherapy, surveillance colonoscopy, computed tomography (CT) scans, and carcinoembryonic antigen (CEA) testing – remained strongly associated

with lower long-term mortality, indicating that postsurgical care may partially explain the relationship between lymph node evaluation and mortality [14].

Quantitative Issues in the Mathematical Modeling of Lymph Node Evaluation

With the uncertainty around the absolute number of nodes harvested for proper staging, several investigators have explored other alternatives of relating the prognosis to the number of nodes found and their status as positive or negative. Among those suggested are [15–17]:

- total number of lymph nodes (LNT);
- number of positive lymph nodes (LNP);
- number of negative lymph nodes (LNN);
- ratio of positive lymph nodes (lymph node ratio = LNR), and
- log odds of positive lymph nodes (LODDS).

Among these, the LNR is probably the best investigated and particularly pertains to substaging of stage III disease [15, 18–26]. The LNR, defined as the ratio of the number of positive nodes over the total number of examined nodes, was proposed to stratify outcome in stage III patients. A recent systematic review of 16 studies including 33,984 patients summarized the role of LNR in stage III colon or rectal cancer. In all identified studies, the LNR was identified as an independent prognostic factor in patients with stage III cancer of the colon or rectum. The prognostic separation obtained by the LNR was superior to that of the number of positive nodes. The pooled hazard ratios for overall and disease-free survival were 2.4 and 3.7, respectively [15]. As such, the LNR allows superior prognostic stratification in stage III colorectal cancer but should be validated in prospective studies. Similar results were obtained in a series of almost 1,800 patients, where the LNR discerned groups of patients with divergent survival probabilities across all pN groups [18].

Furthermore, in a large population-based study (n = 16,790), the investigators compared and analyzed the LNT, LNP, LNN, LNR, and LODDS for stage I–III disease [16]. Correlation analyses for patients with stage III disease showed that LNR and LODDS were highly correlated, as were LNT and LNN. LNT was prognostic of long-term survival in patients with stage II disease, while LNR and LNP were the most powerful prognosticators for patients with stage III disease [16]. Both the receiver operating characteristics curve analysis and area under the curve indicated that LNR had the best discriminating capability to predict 5-year survival, followed by LODDS. The overarching problem, though, is that for patients undergoing resection for colon cancer, all factors (LNR, LODDS, LNT, LNN, and LNP) have been proposed as a 'better' prognostic factor with no clear consistency between reports [15–17, 27–29].

The potential advantage of the 'ratio' approach is the potential for diminishing the role of the absolute number of nodes sampled. However, in one large study, the independent prognostic role of LNR was no longer present for patients with a sample count <10 nodes [30]. Further, a major problem with most of these 'mathematical' approaches is that the prognostic information only concerns patients with a metastatic lymph node present (i.e. stage III), and this information thus cannot be used to differentiate between the 'good' stage III cancers compared to the 'bad' stage II cancers, which often represents the clinical conundrum. That may be the cause for these methods not having reached a clinical implementation or use for clinical decision making as of yet.

Qualitative Issues

Examination of the surgical specimen after bowel resection constitutes the base for stratification of tumor stadium (pT_{1-4}) and the presence of lymph node metastases (pN status) as defined by the current criteria for staging. Careful evaluation of the specimen provides information on whether the primary tumor is confined to the bowel, or whether the tumor invades the pericolic fat (i.e. T_3) or adjacent organs (i.e. pT_4).

When distant metastases have been excluded, the presence of lymph node metastases (pN+) confirmed by histology, i.e. stage III disease, represents the most important prognostic factor after curative resection for colon cancer, and usually indicates that adjuvant chemotherapy should be offered. Thus, the nodal status of patients with colon cancer surgically treated with curative intent is of great importance both for further treatment decision making and for the prognosis.

A poor node harvest after surgery is associated with lower survival in many studies, and node yield has thus become the subject of quality measure in colon cancer care (fig. 1). Consequently, a fierce debate has ensued as to the responsible part for poor node harvest (= poor quality of care) [31–36]. The blame has been put on the surgeon (poor quality surgery), the pathologist (poor quality specimen handling), the hospital (low quality in low-volume hospitals) and also to patients (elderly fare worse, as do patients with emergency presentations) as well as tumor location (more nodes in the right colon) and possibly tumor biology (genetic determinants are related to higher node yields). Most likely, an interplay be-

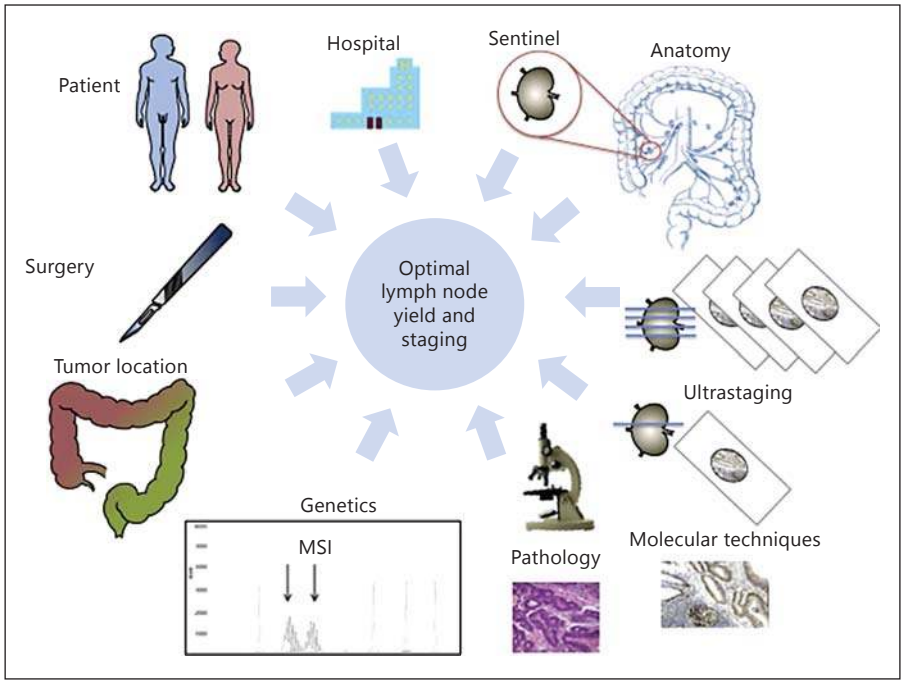

Fig. 1. Multiple factors may have an influence on the lymph node sampling in colon cancer.

tween these factors contributes to the actual number of nodes harvested in the individual patient. However, some issues deserve further attention in this regard.

Hospital Characteristics

Hospitals providing surgery for colon cancer may vary widely with regard to basic characteristics, such as caseload, teaching or non-teaching, rural or urban catchment area, primary hospital or referral center, with consequences for the selection of the patients treated at the various institutions. Several factors may influence the quality of treatment, and eventually treatment outcomes. The recommendation to evaluate ≥12 lymph nodes in the surgical specimen has been studied in a recent publication with regard to the influence of hospital volume and other characteristics [37]. The authors analyzed SEER data from 1996 to 2007 with regard to the ability to adhere to the ≥12 lymph node recommendation among 228 hospitals, which had treated about 25,000 patients curatively for colon cancer at different time periods. They found a clear trend of increased encounter of lymph node harvest ≥12 over the study period from 26.3% in 1996–1998 to 70.6% in the 2005–2007 time period. Interestingly, hospitals with initially insufficient lymph node harvest failed more frequently to improve the number of lymph nodes evaluated as compared to those hospitals which had a higher frequency of adequate lymph node harvest at the start of the study period [37]. Improvements were associated with several other hospital characteristics, such as teaching status or membership in professional surgical oncological associations among the surgical staff. While these factors lost statistical influence over time, hospital volume was still a significant predictor of lymph node harvest ≥12 at the end of the study period. A recent national cohort study from Norway showed that during 2007 and 2008 at least 12 lymph nodes had been evaluated in 69% of the patients [38]. Having an annual caseload of 25 colonic resections or less was found as an independent predictor of an insufficient lymph node harvest (set as ≤8 lymph nodes sampled). Hsieh et al. [39] demonstrated that lymph node harvest varied at different types of hospital, being higher at hospitals with cancer programs. Consequently, data reported from different registries [37–39] indicate that hospital caseload is of importance for adequate lymph node harvest. However, it appears that hospital volume per se is not the explanation, but may be rather an expression of higher standard of care at higher-volume hospitals. Higher-volume hospitals are better capable to prevent, detect and treat complications, in part because of their higher level of supportive care. The institution constitutes an independent prognostic factor, and both high-

er surgeon and hospital volumes are associated with lower mortality and better outcomes in colorectal cancer surgery [40].

Surgical Factors Influencing the Node Yield

Laparoscopic resections of colon cancer have been reported since the early 1990ies; however, implementation of laparoscopic surgery for curative treatment of patients with colon cancer has been slow, mostly due to the complexity of the procedure with a long learning curve, but also due to economic considerations. During the past decade, several randomized controlled trials have been performed with regard to the short- and long-term outcomes [41]. The number of lymph nodes harvested has been used as an outcome measure for the quality of the surgical specimen and showed that lymph node harvest was similar in both surgical approaches. A recent meta-analysis found no difference in the number of harvested nodes between laparoscopic and open surgery for colon cancer [42]. However, Mathis et al. [43] found a clear relationship between hospital caseload and lymph node harvest in laparoscopically resected specimens. At present, laparoscopic surgery is by many considered equal to open surgery. The US COST trial found no difference in lymph node sampling between open and laparoscopic surgery, nor was lymph node number prognostic for long-term survival [43]. The authors speculate that standardization, credentialing and monitoring may even out the prognostic impact of lymph node retrieval as found in this study [43].

CME and Central Vascular Ligation

In a study comparing 'high tie' surgery with 'standard' surgery [44], the CME and central vascular ligation (CVL) surgery removed more tissue, had a longer length of large bowel and a higher measured area of mesentery – all indicative of a wider, and probably oncologically superior, resection. In addition, CME and CVL surgery was associated with more mesocolic plane resections and a greater lymph node yield, with a median number of nodes of 30 versus 18 for the 'standard' group.

Further, the Japanese D3 resection and the European CME with CVL are both based on similar oncologic principles [45]. A study comparing the two techniques [45] revealed that the 'European' extended longitudinal resection after CME with CVL increased the nodal yield (median 18 for Japanese D3 vs. 32 for European CME, $p < 0.001$) but did not increase the number of involved nodes (pN+). The proponents of CME state that the radical lymph node dissection in colon cancer is not associated with inferior outcomes for the patient [46]. No adverse effects were observed when the dissection is performed in embryonic planes preserving the autonomous nerves [45–47]. The complication rates were not increased compared to other studies, even to those with limited lymphatic dissection. In addition, radical lymph node dissection in colon cancer may improve survival. Reports also suggest CME is feasible with a laparoscopic approach [48, 49], which seems to offer specimens of similar quality to the open approach after CME-CVL surgery for colon cancer. Issues of completeness of excision from laparoscopy are raised for tumors located in the transverse colon. While the proponents of 'high tie' surgery point to improved survival and better oncological outcomes, this has yet to be replicated in systematic reviews and large data cohorts [50, 51]. In one study introducing CME surgery as a routine, the mean gain in lymph node was 2 (from 25 to 27) [47], which is unlikely to represent an oncological difference. Again, this points to other factors than surgery that may influence the lymph node yield. Some have also questioned the 'uniqueness' of the CME principle, as it may arguably already be performed at some standardized level in many institutions already [52, 53].

Pathology

Pathologic examination of the specimen, and the reporting that follows, influences the number of lymph nodes retrieved and the accuracy of the report. Several factors in pathology reporting may influence the lymph node assessment, of which the use of a structured template, the use of specific solutions to identify lymph nodes, and the time taken (either by the pathologist or a technical assistant) influence the number of nodes found in a specimen. Also, the specific evaluation of the lymph node per se may influence the detection rate of metastatic nodes, such as multiple slicing of a node, use of immunohistochemistry (IHC) or use of other molecular techniques to identify cancerous cells.

First, the use of synoptic reporting, a protocol or a template has been proven superior in ensuring that key parameters are reported [54–59]. These are parameters that are essential in planning further treatment and follow-up. At the same time, the use of a template in reporting has reduced the amount of time the pathologist spends on reporting. Also, technician or pathologist assistants have been demonstrated to achieve higher yield rates for lymph nodes in several studies, probably related to more time taken and a higher dedication to the work [32, 60–63].

Second, to increase the identification of lymph nodes in the specimen, several techniques have been tested [64–66]. An alternative to conventional fat clearing is the use

of a modified fixation method, usually applied as post-fixative agent. It involves using a mixture of glacial acetic acid, ethanol, water and formaldehyde (GEWF). The number of studies is fairly small and although a significant increase in lymph node number has been reported, the absolute yield is not reported consistently across studies [65–69]. The use of GEWF solution for 12–24 h increases the harvest from 9 to 15 lymph nodes for colon cancer and from 10 to 16 for rectal cancer without increasing the percentage of stage III cancer [66]. Pathologists in one hospital reported less time spent on the identification of lymph nodes when using the GEWF solution, but the increased number of lymph nodes will lead to more work for technicians and more time examining the lymph nodes on the microscope [65].

Third, the definition of 'metastatic foci' influences the 'presence' of metastatic nodes. Ultrastaging, by means of IHC, may identify small lesions or clusters of cells not otherwise detected readily by the microscopic evaluation. Tumor cell deposits, defined between 0.2 and 2.0 mm, are referred to as occult metastasis (OM) or micro-metastases (pN1mi+) [70]. A number of adverse primary pathologic colon cancer characteristics, such as poor differentiation and lymphovascular invasion, correlate with the presence of OMs [71]. In patients with negative nodes on hematoxylin-eosin staining (HE) and stage T3/T4 colon cancer, lymphovascular invasion or high tumor grade, consideration should be given to performing IHC for cytokeratins (epithelial markers). The detection of OMs in this subset may influence decisions regarding adjuvant chemotherapy and risk stratification [71]. One area where the ultrastaging procedure has been used is for sentinel lymph nodes (SLNs). In one randomized study [72] comparing standard pathological evaluation with SLN, the SLN mapping, step sectioning, and IHC identified small-volume nodal disease and improved staging by about 10% in patients with resectable colon cancer. However, the clinical significance of colon cancer micrometastases in SLNs is not currently known. Recently, a novel diagnostic system, called one-step nucleic acid amplification (OSNA), has been designed to detect cytokeratin 19 (CK-19) mRNA as a surrogate for lymph node metastases. In one study [73], half of each lymph node was analyzed initially by HE followed by an intensive histologic workup (5 levels of HE and IHC analyses, the gold standard for the assessment of sensitivity/specificity of OSNA), and the other half was analyzed using OSNA. Compared with intensive histopathology, OSNA had 94.5% sensitivity, 97.6% specificity and a concordance rate of 97.1%. OSNA resulted in an upstaging of 2 of 13 patients (15.3%) with LNN colon cancer after standard HE examination [73]. However, this needs to be replicated and validated in other studies before clinical utility can be recommended.

SLN Technique

An area of interest to both surgeons and pathologists is the sentinel node principle. The concept of SLN, i.e. a lymph node highly representative for the remaining lymph nodes within the draining area of a certain anatomical area, has gained wide acceptance in surgery for breast cancer and malignant melanoma of the extremities [74, 75]. This approach has also been of interest in the field of surgery for colorectal cancer during the past decade. The main idea is that conventional pathologic lymph node examination is limited as mostly one or two slides of the lymph node identified in the specimen are examined, and thus microscopic lymph node metastases may be overlooked, leading to understaging of a subgroup of patients who should receive adjuvant chemotherapy. As extended examination of all harvested lymph nodes with multiple slides appeared not to be feasible in daily practice, extensive examination of SLNs might provide highly reliable information with regard to pN status of the surgical specimen. The concept of SLN diagnosis has been investigated widely with intraoperative in vivo or ex vivo sampling [70], and with various techniques such as IHC or molecular techniques, including polymerase chain reaction (PCR) [76]. Methodological challenges and the application of both an in vivo and an ex vivo approach make comparisons difficult. Radiocolloid technique is feasible [77], but labor intensive and not superior to the regular blue-dye technique currently used in most studies. In a recent systematic review [78], the pooled SLN identification rate was 90.7% (95% CI 88.2–93.3), with a significantly higher identification rate in studies including >100 patients or studies using the ex vivo SLN technique. The pooled sensitivity of the SLN procedure was 69.6% (95% CI 64.7–74.6), which increased to 80.2% (95% CI 4.7–10.7) when IHC findings were included. The authors concluded that there was an overall sensitivity of 70% in patients with colorectal cancer, and that the SLN procedure had an increased sensitivity and refined staging in early-stage colon cancer. The ex vivo SLN mapping, regarded as an easy technique, was considered most applicable in addition to conventional resection in colon cancer [78]. In a similar systematic review [79], analysis of data showed no significant difference in sensitivity between colon and rectal cancer. Also, there was no dependency of sensitivity on T stage for both colon and rectal cancer. The subgroup of eight studies with high methodological quality

showed a mean detection rate of 0.96 (95% CI 0.90–0.99) for colonic tumors and 0.95 (95% CI 0.75–0.99) for rectal tumors, and a mean sensitivity of 0.90 (95% CI 0.86–0.93) for colonic tumors and 0.82 (95% CI 0.60–0.93) for rectal tumors [78]. However, increased detection does not relate to improved survival or difference in survival in one study of SNLs characterized by molecular markers [76].

Nevertheless, from a clinical point of view, the introduction of SLN biopsy in colon cancer and its possible staging and prognostic impact remains a matter of controversy. One recent Swiss multicenter study found that the SLN procedure results in upstaging of >15% of node-negative patients [80]. Further, a Dutch study found better staging and improved survival from the SLN technique [70]. During follow-up, a lower recurrence rate was seen in N0 patients after SLN mapping compared with the conventional staging group (4 vs. 15.2%, p = 0.04). The SLN procedure [hazard ratio (HR) 4.1] was an independent predictor of disease recurrence [70]. In a systematic review, a total of 39 studies with 4,087 patients were included [81]. IHC, reverse transcriptase PCR, and both techniques were applied in 30, 7, and 2 studies, respectively. Thirteen studies were graded with low risk of bias. Meta-analyses revealed that molecular tumor cell detection in regional lymph nodes was associated with poor overall survival (HR 2.20; 95% CI 1.43–3.40), disease-specific survival (HR 3.37; 95% CI 2.31–4.93) and disease-free survival (HR 2.24; 95% CI 1.57–3.20). Subgroup analyses showed the prognostic significance of molecular tumor cell detection to be independent of the applied detection method, molecular target and number of retrieved lymph nodes. Molecular detection of occult disease in regional lymph nodes was associated with an increased risk of disease recurrence and poor survival in patients with node-negative colorectal cancer [81].

However, despite continued interest in SLN mapping and ultrastaging for colon cancer, to date, the results of SLN mapping for staging remain discordant and are not sufficiently accurate for identifying lymph node metastases, with a particular concern for the high rate of false-negative nodal staging [82, 83].

Patient Demographics, Tumor Biology and Genetic Factors

Age appears to be a determinant for lower lymph node yield [84]. Also, body mass index (BMI) has been suggested to be associated with the lymph node yield, but with diverse results [85, 86]. One study [85] demonstrated a decreased lymph node yield in patients being overweight (BMI >24), while a second study [86] found no difference in normal and overweight, but a higher lymph node yield in patients that were underweight (BMI <18). A third study did, however, not find any association among several investigated anthropometric features and lymph node harvest [87], so the influence on body composition, height and weight remains disputed and unsolved as of yet. Not surprisingly, the prognostic impact of anthropometric features and survival in colorectal cancer is also equivocally reported among studies [85–89].

The tumor location within the colon has been reported to be associated with differences in lymph node yield across several studies. Right-sided tumors have long been associated with a higher lymph node yield [11, 27, 60, 90, 91], and many have proposed this to be an effect of better and more adequate surgery, a larger specimen (and thus node harvest) with a right-sided hemicolectomy, and higher risk for lower-quality surgery and a smaller specimen length on the left side, in particular for left hemicolectomy, or sigmoid resections [38, 92].

In a population-based study that included over 153,000 patients, the investigators found that age, tumor location and tumor size were associated with lymph node yield [91]. Further, they found that for every decade increase in patients' age, there was a decrease of an average 9% in lymph node yield for both colon and rectal cancer [91]. Right-sided colon cancers had on average 34% higher lymph node yield than tumors in the descending or sigmoid colon. Whether this increased harvest can be associated with length of specimen could not be verified, since the SEER data do not document specimen length. Also tumor size was associated with the number of lymph nodes harvested; this association was stronger for colon cancer than for rectal cancer. Compared to T1 tumors, the percentage increase in lymph nodes for T2, T3 and T4 was 11, 24 and 18% for colon cancer, and 7, 20 and 16% for rectal cancer [91].

Colorectal cancer comprises a heterogeneous group of patients both in terms of clinical presentation and clinicopathological features [93, 94], but also in the genetic make-up of the tumor itself [3, 4, 95]. An improved understanding of different genomic instability pathways of these tumors may provide prognostic information of clinical importance. For one, microsatellite instability (MSI) is associated with several characteristic clinicopathological features, including age (at both extremes) and highest prevalence of MSI associated with tumor location in the proximal colon [96]. Several recent studies have pointed to an association between MSI and increased number of lymph nodes in the specimen [90, 97–99]. Others have not found such an association [100], or did not find an independent role when including location [90].

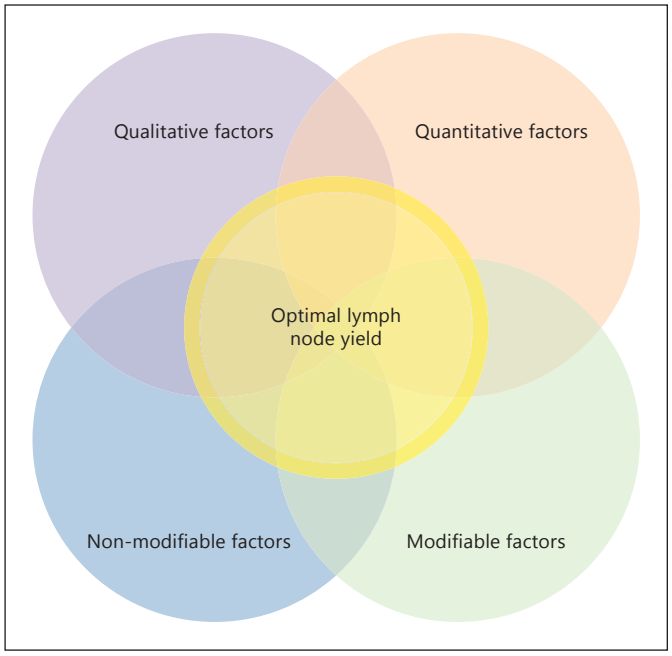

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Fig. 2. The optimal node sampling is dependent on quantitative and qualitative issues which may or may not be modified.

Conclusions and Future Strategies

As should be clear from the quantitative and qualitative factors studied above, there are a number of factors that may influence the sampling and evaluation of lymph nodes and consequently the accuracy of the staging of patients with colon cancer (fig. 1, 2). Most importantly, it should be recognized that several of the discussed aspects may be modified (e.g. type of surgery, quality of specimen evaluation, techniques for node identification and evaluation, hospital volume and overall quality), while others may not be modified through the nature of their existence (such as patient's age, gender, or inherited tumor biology) [60, 92, 101]. However, close collaboration between surgeons and pathologists is essential for proper lymph node harvest, evaluation and consequently staging. Future improvements in the understanding of cancer biology, but also combination of imaging techniques with biochemical tracers for investigating prognostic relevant factors may alter the mode and accuracy of staging, even for lymph nodes. Radioimmunoguided surgery has been entertained in sporadic reports over the last decade [102–107], also in combination with sentinel node biopsy or other technologies, yet it has not found its place in routine clinical practice with currently available technologies. Intraoperative fluorescence, using naturally fluorescent biomarkers or fluorescent tumor probes, probably offers the most practical means of intraoperative lymph node staging and may be facilitated by using nanotechnology [107]. Real-time elastography and optical coherence tomography may potentially provide an in vivo 'virtual biopsy'. While predicting the future is difficult, such novel molecular image-based techniques may be the next paradigm shift for staging in colorectal cancer surgery.

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