World Journal of Gastrointestinal Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4251/wjgo.v8.i5.466

World J Gastrointest Oncol 2016 May 15; 8(5): 466-473
ISSN 1948-5204 (online)

Non-surgical factors influencing lymph node yield in colon cancer

Patrick Wood, Colin Peirce, Jurgen Mulsow

Patrick Wood, Colin Peirce, Jurgen Mulsow, Department of Colorectal Surgery, Mater Misericordiae University Hospital, Dublin 7, Ireland

Author contributions: Wood P, Peirce C and Mulsow J contributed equally to this work; Wood P, Peirce C and Mulsow J analysed data; Wood P and Peirce C performed the research and wrote the paper; Peirce C and Mulsow J designed the research.

Conflict-of-interest statement: The authors of this paper have no conflicts of interest to declare.

Correspondence to: Jurgen Mulsow, Consultant Colorectal Surgeon, Department of Colorectal Surgery, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland. jmulsow@mater.ie
Telephone: +353-1-8545091
Fax: +353-1-8034023

Received: September 29, 2015
Peer-review started: October 1, 2015
First decision: November 13, 2015
Revised: December 15, 2015
Accepted: March 7, 2016
Article in press: March 9, 2016
Published online: May 15, 2016

Abstract

There are numerous factors which can affect the lymph node (LN) yield in colon cancer specimens. The aim of this paper was to identify both modifiable and non-modifiable factors that have been demonstrated to affect colonic resection specimen LN yield and to summarise the pertinent literature on these topics. A literature review of PubMed was performed to identify the potential factors which may influence the LN yield in colon cancer resection specimens. The terms used for the search were: LN, lymphadenectomy, LN yield, LN harvest, LN number, colon cancer and colorectal cancer. Both non-modifiable and modifiable factors were identified. The review identified fifteen non-surgical factors: (13 non-modifiable, 2 modifiable) which may influence LN yield. LN yield is frequently reduced in older, obese patients and those with male sex and increased in patients with right sided, large, and poorly differentiated tumours. Patient ethnicity and lower socioeconomic class may negatively influence LN yield. Pre-operative tumour tattooing appears to increase LN yield. There are many factors that potentially influence the LN yield, although the strength of the association between the two varies greatly. Perfecting oncological resection and pathological analysis remain the cornerstones to achieving good quality and quantity LN yields in patients with colon cancer.

Key words: Lymph node; Number; Factors; Yield; Colon cancer

Core tip: Surgeons, pathologists and patients alike must appreciate that there are many factors which influence lymph node (LN) yield in resected colon cancer specimens. Clinicians must strive for the perfect oncological operation and pathological analysis. However, clinicians should be aware that despite optimal surgery and pathological analysis, other factors may influence the LN yield following colonic resection for cancer.

Wood P, Peirce C, Mulsow J. Non-surgical factors influencing lymph node yield in colon cancer. *World J Gastrointest Oncol* 2016; 8(5): 466-473 Available from: URL: http://www.wjgnet.

com/1948-5204/full/v8/i5/466.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i5.466

INTRODUCTION

The American Joint Committee on Cancer/Union Internationale Contre le Cancer utilises the TNM system to stage colon cancer. The stage of disease is dependent on the depth of penetration into the intestinal wall (T1-T4), the presence of localized lymph node (LN) metastases (N0-N2) and the presence of distant metastases (M0-M1). This system potentially lends itself to "understaging" of disease since accurate staging is closely linked to both adequate and high quality LN evaluation. Indeed, numerous studies have demonstrated an association between the number of LNs examined and patient survival, with the consistent finding that an increased number of evaluated LNs leads to improved survival[1-9]. Furthermore, the decision to administer adjuvant chemotherapy is highly dependent on the presence or absence of LN metastases: When present, patients are classified as stage Ⅲ and typically receive chemotherapy while those with stage Ⅱ disease and no adverse features routinely undergo surveillance only.

The "gold" standard of at least a 12 LN examination following resection for colon cancer was initially proposed in 1990[10]. The National Institute of Clinical Excellence suggested that when more nodes are examined the tumour is significantly more likely to be classified as node positive. Conversely, when few nodes are examined, there is a substantial risk of understaging[11]. This standard has now been adopted in multiple guidelines for both colon and rectal cancer resection specimen analysis[12-14]. More recently, the analysis of ⩾ 12 LNs has been adopted as a standard quality indicator for colorectal resection specimens in the United States by the National Quality Forum[13,15], the National Comprehensive Cancer Network (NCCN), the American Association of Clinical Oncology and the American College of Surgeons[16-18]. However, the literature is variable on the subject with some groups suggesting that a harvest of 9 LNs is sufficient to stage node negative tumours[19], others agreeing that harvesting more than 12 LNs is adequate for staging colon cancer[4,6,20] and others still suggesting that there is no clear cut-off value and that as many LNs as possible should be harvested and analysed[2,8].

Irrespective of the agreed and accepted LN cut-off, it should be appreciated that multiple factors may be influence nodal yield. Undoubtedly, surgical technique and pathological analysis are the cornerstones for adequate LN examination, however other, principally patient factors may be of relevance and lead to reduced LN yield despite optimal surgery and specimen analysis. This study aimed to review both modifiable and non-modifiable non-surgical factors that have been shown to influence colonic resection specimen LN yield and to summarise the pertinent published literature.

LITERATURE REVIEW

A literature review of PubMed for the period 1991-2015 was performed to identify the potential factors which may influence the LN yield in colon cancer resection specimens. The terms used for the search were: LN, lymphadenectomy, LN yield, LN harvest, LN number, colon cancer and colorectal cancer. Both non-modifiable and modifiable factors were identified (Table 1) and the individual papers reviewed. Further relevant publications were identified by cross reference of the reviewed papers.

NON-MODIFIABLE FACTORS

Ethnicity

There have been a number of studies which have assessed the influence of ethnicity on LN yield. The rationale as to why ethnicity would potentially affect the LN yield remains unclear.

In a large study Cone *et al*[21] interrogated the Surveillance Epidemiology and End Results (SEER)-Medicare database in the United States, evaluating all colonic cancer resections between the years 2000 and 2003. Their analysis included nearly 33000 patients, 62.5% of whom had less than 12 LNs in the resected specimen. Multivariate analysis showed that Hispanics were less likely than Caucasian patients to have ⩾ 12 LNs resected (OR = 0.61, 95%CI: 0.5-0.74). Hispanic patients were younger (although all patients in the analyses were older than 65 years), lived in more populated areas and had a lower income status than their Caucasian counterparts. The reduced LN yield did not confer a negative outcome with no significant difference in survival between the groups.

Other smaller single institution studies such as that by Valsecchi *et al*[22] failed to show an association between LN yield and ethnicity.

Age

Numerous studies have assessed the influence of patient age on LN yield in resected colon cancer, the hypothesis being that younger patients are more likely to have a more aggressive oncological procedure, or conversely that older patients frequently undergo less aggressive lymphadenectomy. A national United Kingdom study from 2006 reported that increasing age was associated with a significant reduction in the number of harvested LNs ($P < 0.001$)[23]. Moreover, for every 10 years increase in age in their cohort, there was an associated reduction in LN harvest by 0.9 nodes (95%CI: 0.7-1.1). The authors also noted that as the patient age increased there was also a significant increase in variability of LN harvest between the 79 participating centres ($P < 0.001$), which included both peripheral and tertiary referral centres. These findings were felt most likely to be due to a wider lymphadenectomy being performed in younger, medically fitter (and elective) patients as opposed to older patients with co-morbidities. An alternative

Table 1 Factors influencing lymph node yield in colon cancer resection specimens

Non-modifiable	Modifiable
Ethnicity	Tumour tattooing
Age	Neoadjuvant therapy
Gender	
Socioeconomic class	
Tumour location	
Tumour size	
Tumour histological subtype	
ASA grade	
Tumour classification and stage	
Tumour microsatellite instability	
Lymph node positivity/negativity	
Lymphovascular invasion	
Body mass index	

ASA: American Society of Anesthesiologists.

hypothesis is that LNs undergo a process of involution with increasing age[23].

Stocchi *et al*[24], in their study from the Cleveland Clinic, Ohio, also reported an association in 901 patients with stage Ⅱ colon cancer between increasing age and fewer examined LNs ($P < 0.001$)[24]. Patients younger than 65 years had a mean of 35.1 (range 15-44) nodes examined compared to a mean of 22.2 (range 12-28) nodes in patients older than 65 years.

Another population-based study by Chou *et al*[15] analysed 127927 patients who underwent resection for stages Ⅰ-Ⅲ colon cancer between 1994 and 2005 in the United States. Of note, in 4.6% of patients, no regional LNs were examined and thus, these individual patients were not staged. Once again, age was shown to be a consistently important determinant of LN yield and for every 10-year incremental increase in patient age, there was an associated average reduction of 9% in the number of harvested LNs ($P < 0.01$). It should be noted that over the timeframe of the study, there was not only an increase in the average LN yield, but also a decrease in the mean age at diagnosis for patients with colon cancer - from 70.3 years in 1994 to 68.8 years in 2005. The rationale for this significant association between age and LN yield in this paper was thought to be as a result of a "complex interplay of patient and surgeon factors". The authors explained this by hypothesising that older patients are likely to be considered higher-risk operative candidates and thus a suboptimal surgical dissection (with resultant inadequate lymphadenectomy) may be performed with a view to reducing operative time. Nathan and colleagues also interrogated the SEER database for patients operated with curative intent for stage Ⅰ-Ⅲ colon cancer between 1998 and 2005[25]. In the 27101 patients analysed, increasing patient age was again significantly associated with a decreased LN yield ($P < 0.001$). Finally, Baxter *et al*[26] also interrogated the SEER database, specifically focusing on patient who had undergone colonic resection for pT3 lesions. They identified 11044 patients and once again were able to show that older patients had fewer LNs examined ($P < 0.001$). Several other studies have mirrored these findings[22,27-34], however, 2 smaller studies of 341 and 223 patients respectively, failed to demonstrate an association between colonic LN yield and patient age[35,36].

Overall, it appears that increased patient age significantly influences LN yield in colon cancer.

Patient gender

A number of studies have shown a significant association between male sex and reduced LN yield[25,28,36]. The largest of these included over three hundred thousand patients in a United States population based study analysing factors influencing LN yield in patients with gastrointestinal cancer[28]. The reasons underlying this association are poorly understood. Dubecz *et al*[28] suggested that men are more likely to be uninsured and thus may be less likely to receive "state-of-the-art" treatment which might include adequate lymphadenectomy as performed in a high-volume colorectal centre.

Socioeconomic class

It has been suggested that patients with lower socioeconomic class may be less likely to be treated in specialised centres and to receive the most up to date management with the result that their LN yield following resection for colon cancer is lower. A population-based analysis of all patients with gastrointestinal (GI) adenocarcinomas treated surgically in the United States between 1998 and 2009 ($n = 326243$) was performed by Dubecz *et al*[28]. They aimed to evaluate time trends in lymphadenectomy for GI cancer and to identify factors associated with inadequate LN yield. Adequate lymphadenectomy was defined by the NCCN recommendations as a LN yield of > 12 in colon and rectal cancer. Throughout the study period it was found that the LN yield increased over time for all of the sub classifications of GI cancer. The median number of LNs retrieved for colon cancer increased from 9 in 1998 to 16 in 2009. However, only 49% of patients with a GI adenocarcinoma diagnosis underwent adequate lymphadenectomy. The rate of adequate evaluation was higher in colon cancer (77%) than in rectal cancer (42%). Patients living in areas with higher poverty rates were more likely to undergo inadequate lymphadenectomy. The socioeconomic data was based on county of residence which was linked to United States Census data. The first quartile, Q1 (most well off), had an adequate lymphadenectomy in 49% of cases, Q2 in 51% adequate while Q3 and Q4 (least well off) had adequate lymphadenectomy in 47% of cases. Patients of lower socioeconomic class were most likely to have an inadequate lymphadenectomy with the authors postulating that this finding most likely reflected a high proportion of uninsured patients who may be less likely to receive state of the art treatment. In a separate study, Rajput *et al*[29], also showed that insurance status was associated with LN yield across patients identified from the NCCN and SEER databases. On multivariate analysis, patients with Medicare and Medicaid plans had lower yields than patients covered by commercial plans ($P = 0.007$). The authors' belief was that this finding

was secondary to the age profile of the patients, with those in the Medicare population tending to be older than those with private insurance coupled with a demonstrable decrease in LN yield with increasing age across all patients in the study.

In summary, lower SE status may be associated with reduced LN yield following resection for colon cancer, however there are multiple factors that may underlie this association.

Tumour location

There is consistent evidence that the location within the colon of the primary is strongly associated with the number of LN examined by the pathologist, with the length of the specimen often implicated as the causative factor. Stocchi *et al*[24] reported that a 12 LN harvest was more likely with right sided as opposed to left sided carcinomas (85% *vs* 72%, $P < 0.001$). Similarly, in the study from Baxter *et al*[26], patients with a left sided colon cancer (and rectal cancer) were less likely to have an adequate LN evaluation compared with patients with right sided lesions. In a separate study, Wright *et al*[37] reported a median number of 12 LNs for right sided cancer and 9 LNs for left sided colonic tumours. Chou *et al*[15] also reported a similar trend: In a sub-analysis of right and left sided colon cancers, tumours located in the ascending colon and hepatic flexure had, on average, 34% more LNs retrieved than those in the sigmoid and rectosigmoid. However, the authors acknowledged that the SEER data on which their study was based did not record the length of the resected specimen and speculated that the observed differences in LN yield may in fact be due to longer specimen lengths following right sided resection. The association between specimen length and LN yield has been repeatedly demonstrated. Stocchi *et al*[24] showed that specimens less than 30 cm in length had a median LN harvest of 17 nodes whereas those longer than 30 cm had a median harvest of 24 nodes ($P < 0.001$)[24]. Shen *et al*[31] also reported variability in LN yield depending on both tumour site and specimen length. They studied 365 resected colon cancers and demonstrated an increased LN yield of 17.8 for caecal and ascending colon lesions *vs* 14.3 for sigmoid lesions ($P < 0.01$). Descending colon lesions were associated with the longest specimens at 29.2 cm and there was a clear association between the length of the specimen and LN yield, with an average of 11 LNs in specimens of 10 cm or less in length compared with 18.3 LNs when the specimens were over 30 cm in length. Numerous studies have shown similar patterns of decreased LN yield for left-sided *vs* right-sided colonic cancer[22,27,29,33,34,38-40]. Two smaller studies, analysing 137 and 48 colon specimens respectively, failed to show an association between LN yield and primary tumour site[41,42].

In summary, the published literature supports the hypothesis that tumour location influences LN yield in colon cancer.

Tumour size

It has previously been proposed that larger tumours elicit an intense antigenic response within the surrounding regional LN basin. This "response" may potentially make them more visible to pathologic examination and may thus lead to an increased LN yield[37]. In a study by Chou *et al*[15], for every 1 cm increase in tumour size, there was a corresponding average 2% increase in the number of examined LNs in colon cancer specimens. Tumour size was also shown to be a significant predictor of LN yield in univariate analysis in a study by Valsecchi *et al*[22] ($P < 0.01$). There have been 2 recent studies from the Memorial Sloan Kettering group, both reporting a strong association between tumour size and the nodal yield[27,43]. In the first study, tumour size of 4 cm or less resulted in a mean nodal harvest of 19.7 as compared to a mean nodal harvest of 23.3 when the tumour measured over 4 cm ($P = 0.02$)[27]. In the second and more recent study, analysis of 256 colectomy specimens demonstrated a linear relationship between tumour size and LN yield ($P < 0.0001$)[43]. Søreide *et al*[39] also showed that LN harvest is related to tumour size. Tumours greater than 5 cm had adequate LN yield in 50% of cases, compared to 24%, when tumour size were less than 5 cm.

Colon cancer histological subtype and tumour differentiation

Tekkis *et al*[23], in a study including more than 5000 patients, showed that the tumour differentiation was one of eight factors which had a significant influence on the number of LNs examined. Poorly differentiated tumours had significantly increased LN yield when compared to well or moderately differentiated lesions. In the same study, the tumour subtype was not shown to significantly influence nodal yield.

A number of other studies have reported an association between tumour differentiation subtype and LN yield, with the consensus being that the more poorly differentiated the tumour the greater the LN yield compared to well differentiated lesions[25,27,35,37].

ASA grade

The evidence to support an association between American Society of Anesthesiologists (ASA) grade and LN yield is limited. The rationale behind linking ASA grade and LN yield is similar to that for increasing age. Patients with higher ASA are often older and may undergo emergent surgery, which may lead to less radical dissection in order to complete the operation in a timelier manner. A national United Kingdom study published in 2004[23] did show that patients with higher ASA grade were less likely to have adequate LN harvesting when compared to patients with lower ASA grades: ASA Ⅲ *vs* Ⅰ ($P < 0.001$) and ASA Ⅳ-Ⅴ *vs* Ⅰ ($P = 0.036$).

LN positivity

The available literature shows conflicting findings with respect to the influence of LN positivity on LN yield. Any

association, positive or otherwise, should be interpreted with some caution due to the potential for underlying bias. An association between increased LN yield and nodal positivity, as shown by Tekkis *et al*[23] for example, may simply reflect a more comprehension search for nodes. On the other hand, a finding of multiple involved nodes may lead to a less thorough search for further nodes leading to a lower overall nodal yield. In a study by Nash *et al*[27], no correlation was demonstrable between the total number of LNs examined and the number of LNs with metastatic disease ($P = 0.32$). However, there was a trend towards finding one fewer LN in each specimen for every 2 metastatic LNs.

Lymphovascular invasion

Lymphovascular invasion (LVI) is a surrogate marker for tumour aggressiveness and is associated with a poorer outcome. The limited available data shows no association between LVI and LN yield. Gelos *et al*[35] performed a retrospective analysis of 341 patients who underwent colorectal cancer resection with curative intent between 2000 and 2005 and investigated the impact of a number of factors including LVI on LN yield. There was a median of 15.17 LNs retrieved per patient, with 82.8% of the 341 patients having a LN harvest greater than 12, however the presence of LVI did not influence tumour LN yield. In another smaller study (48 patients) with a mean LN count of 14.1, no statistically significant relationship existed between the number of LNs and the presence of LVI ($P = 0.64$)[42].

Microsatellite instability

An association between LN yield and microsatellite instability (MSI) has been put forward by a number of authors. MSI tumours are considered less aggressive than their microsatellite stable (MSS) counterparts and may demonstrate an enhanced host inflammatory reaction[44-47].

An association between a high rate of MSI and a high total LN count in colorectal cancer has been demonstrated in a number of small studies. Higher LN retrieval may in part explain the improved survival seen in patients with MSI. Søreide *et al*[39] studied 121 patients under the age of 75 with the aim of determining whether proximal tumour location and MSI improved LN yield. One thousand two hundred (1200) LNs were retrieved from 121 patients and of these, 96 were positive (0.8%). Median LN harvest was 10 and only 36% of patients had an adequate harvest (*i.e.*, 12 or more LN). MSI was found in 33 out of the 121 patients (27%) and this was associated with a greater median LN yield of 12 *vs* 9 in the MSS group. Fifty-four percent of patients with MSI had adequate LN harvest *vs* 29% in the MSS group and 36% in the study as a whole [OR = 2.9 (1.3-6.5), $P = 0.011$][39].

Eveno *et al*[48] reported a smaller series of 82 patients with stages Ⅰ and Ⅱ colon cancer and also showed a significantly increased LN yield in the MSI group (mean 23.6 *vs* 13.7 LN).

A separate study investigated the association between MSI and LN yield but did not show a significant association[49]. Of 168 patients with stage Ⅲ colon cancer the mean total LN yield for MSI and MSS tumours was 15.9 and 16.9 respectively ($P = 0.664$). The authors concluded that increased survival in the MSI group ($P = 0.026$) could not be explained by differences in LN yield.

Body mass index

Studies performed in patients with gastric and rectal cancers have shown an association between obesity and reduced LN yield[50,51]. Damadi *et al*[52] retrospectively reviewed 191 patients who underwent a resection for colon cancer between 1999-2006. They hypothesized that obese patients with a body mass index (BMI) > 30 kg/m^2 would have a smaller yield of LNs compared to non-obese patients with a BMI < 30 kg/m^2, however they found no significant difference between the groups (mean LN yield 12.7 in obese *vs* 12.4 in non-obese, $P > 0.2$).

Linebarger *et al*[53] performed a retrospective review of 401 patients, and stratified them into six groups based on BMI: Underweight (< 18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), stage Ⅰ obesity (30-34.9 kg/m^2), stage Ⅱ obesity (35-39.9 kg/m^2) and stage Ⅲ obesity (> 40 kg/m^2). They found no significant difference in the number of LNs harvested for each of the groups.

Kuo *et al*[54] retrospectively analysed 645 patients with stage Ⅲ colon cancer from Taiwan who underwent colectomy. Patients were again placed into four groups based on their BMI: Obese (BMI > 27 kg/m^2), overweight (BMI 24-27 kg/m^2), normal (BMI 18.5-24 kg/m^2) and underweight (BMI < 18.5 kg/m^2). The mean BMI of the patients in the study was 23 kg/m^2. The authors showed a significantly increased mean LN yield in the underweight patient group (28.1 *vs* 23 in the normal BMI group, 19.5 in the overweight group and 19.8 in obese patient group respectively). A 2010 study analysed a cohort of 718 NCCN patients with stage Ⅰ-Ⅲ colon cancer and found three factors were associated with not meeting the quality standard of a 12 LN evaluation: Left-sided tumours, stage Ⅰ disease and a BMI > 30 kg/m^2[28].

The impact of BMI on LN yield is overall unclear, with some studies pointing to a reduced in patients with a higher BMI.

MODIFIABLE FACTORS

Tumour tattooing

Endoscopic tattooing is frequently performed in order to facilitate tumour localisation during laparoscopic resection. Tumour tattooing may inadvertently map the sentinel node and associated draining nodes and thus make them more readily identifiable for pathological evaluation. A retrospective case controlled trial conducted between 2005 and 2009 aimed to determine if colonoscopic tumour tattooing could be utilised to increase staging accuracy by increasing the LN yield[55]. The

authors assessed two groups of patients: The first group contained a series of 95 consecutively tattooed patients and the second group a series of 210 non-tattooed patients. All patients underwent surgery for colorectal cancer within the same time period. There was a higher LN yield in patients with pre-operative tattooing compared to the non-tattooed control group (median LN yield of 15 *vs* 12 nodes, $P = 0.014$). Multivariate analysis showed that the presence of carbon-containing LNs (with a detection rate of 71%) was an independent predictor for an increased LN yield ($P = 0.002$), although the reason for the lack of a predictive characteristic for the group in which tattooing did not result in carbon containing LNs was not clear.

The potential role of preoperative tattooing was also reported by Nash *et al*[27]. Their study was designed to develop a predictive model of LN yield in colon cancer. One hundred and fifty-two specimens from patients who had undergone resection for colon cancer were used, with detailed anatomical and surgical technique documentation on each specimen. A linear regression analysis was performed and this identified both predictors and confounders of the quantity of the LN harvest. Of the 15 variables analysed, it was found that tumour size, tumour location, number of resected pedicles and use of pre-operative tattoo had significant linear/quadratic relationships on the LN yield. When controlling for the 14 other variables, patients who underwent endoscopic tattooing had 3.1 more LNs harvested. This data further suggests that endoscopic tattooing may be used pre-operatively to maximise LN yield and increase the accuracy of disease staging. The authors acknowledged that as they did not record the proportion of LNs which harboured grossly apparent dye at the time of LN identification, they could not make a definitive conclusion as to the mechanism by which preoperative colonic cancer tattooing might increase LN yield Dawson *et al*[56] also hypothesised that pre-operative tattooing with India ink might increase the subsequent LN yield from the resected specimens. Their retrospective study included 174 patients who underwent surgery for colon cancer between 2006 and 2009. Sixty-two patients had pre-operative tattooing. The mean number of LNs harvested in the tattooed group was 23 compared to 19 in the non-tattooed group ($P = 0.03$). In the tattooed colon cancer group a 12 LN minimum was achieved in 87.1% patients *vs* 72.3% in the non-tattooed group. These results were mirrored in a separate analysis, within the same study, of 35 patients with rectal cancer. Once again, the results from this study suggest the routine utilisation of pre-operative colonoscopic tattooing may increase the LN yield in resected colonic malignancy.

Neoadjuvant chemotherapy

The role of neoadjuvant therapy in the setting of colon cancer remains in evolution. Data from studies performed in patients with rectal cancer has shown that neoadjuvant therapy may result in a decreased LN yield, however this is in the context of both radiotherapy and chemotherapy. The initial data from the United Kingdom based FOxTROT trial reported on 150 patients in 35 centres[57]. All patients had either T3 (with > 5 mm invasion into the muscularis propria) or T4 colon tumours and were randomised to either preoperative and postoperative chemotherapy or standard postoperative chemotherapy alone (2:1 randomisation). Overall, the authors reported that preoperative chemotherapy was a viable option with acceptable toxicity in this cohort. When the LN data were examined, 85 of 98 patients (87%) and 43 of 50 patients (86%) had 12 or more LNs examined in the combined preoperative and postoperative chemotherapy and postoperative chemotherapy groups respectively. Indeed, 46% and 54% of patients in both groups had greater than 20 LNs examined with median values of 21 and 22 nodes respectively ($P = 0.2$). The apical node was positive in 1 of 98 patients in the combined group (1%) and 10 of 50 patients in the postoperative chemotherapy only group (20%). Thus, in this study neoadjuvant chemotherapy did not result in a lower LN yield however more data is needed before definitive conclusions can be made.

CONCLUSION

There are many factors that can potentially influence the LN yield following resection for colon cancer and the relationship between these factors remains poorly understood. High quality oncological surgery and pathological analysis are the most important factors in ensuring optimal LN yield. However, the current review has highlighted a number of additional modifiable and non-modifiable factors that may also influence the number of LNs harvested. Older age, obesity, and male sex may be associated with reduced LN yield. Similarly, studies have shown an association between ethnicity and lower socioeconomic class and reduced LN harvest. Rather than being true associations, however, it is likely that these findings reflect, at least in part, external modifiable factors such as the surgeon's attitude to older patients undergoing surgery or the quality of care received by patients in lower SE groups. LN yield appears to be increased in patients with right-sided cancer, bulky tumours, or poor tumour differentiation. Again, these associations may reflect other factors known to influence nodal yield such as the length of the resection specimen. Nonetheless, these variables should be taken into consideration when evaluating the completeness of the LN harvest for individual patients.

REFERENCES

1 **Chang GJ**, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007; **99**: 433-441 [PMID: 17374833 DOI: 10.1093/jnci/djk092]

2 **Goldstein NS**. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol* 2002; **26**: 179-189 [PMID: 11812939]

3 **Le Voyer TE**, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003; **21**: 2912-2919 [PMID: 12885809 DOI: 10.1200/JCO.2003.05.062]

4 **Swanson RS**, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol* 2003; **10**: 65-71 [PMID: 12513963 DOI: 10.1245/ASO.2003.03.058]

5 **Prandi M**, Lionetto R, Bini A, Francioni G, Accarpio G, Anfossi A, Ballario E, Becchi G, Bonilauri S, Carobbi A, Cavaliere P, Garcea D, Giuliani L, Morziani E, Mosca F, Mussa A, Pasqualini M, Poddie D, Tonetti F, Zardo L, Rosso R. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. *Ann Surg* 2002; **235**: 458-463 [PMID: 11923600 DOI: 10.1097/0000065 8-200204000-00002]

6 **Wong JH**, Bowles BJ, Bueno R, Shimizu D. Impact of the number of negative nodes on disease-free survival in colorectal cancer patients. *Dis Colon Rectum* 2002; **45**: 1341-1348 [PMID: 12394433]

7 **Chen SL**, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 2006; **244**: 602-610 [PMID: 16998369 DOI: 10.1097/01.sla.0000237655.11717.50]

8 **Cserni G**, Vinh-Hung V, Burzykowski T. Is there a minimum number of lymph nodes that should be histologically assessed for a reliable nodal staging of T3N0M0 colorectal carcinomas? *J Surg Oncol* 2002; **81**: 63-69 [PMID: 12355405 DOI: 10.1002/jso.10140]

9 **Sarli L**, Bader G, Iusco D, Salvemini C, Mauro DD, Mazzeo A, Regina G, Roncoroni L. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *Eur J Cancer* 2005; **41**: 272-279 [PMID: 15661553 DOI: 10.1016/j.ejca.2004.10.010]

10 **Fielding LP**, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, Hermanek P, Jass JR, Newland RC. Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT). *J Gastroenterol Hepatol* 1991; **6**: 325-344 [PMID: 1912440 DOI: 10.1111/j.1440-1746.1991.tb00867.x]

11 Guidance on Cancer Services. Improving Outcomes in Colorectal Cancers. Manual Update. London: National Institute for Clinical Excellence, 2004

12 **Otchy D**, Hyman NH, Simmang C, Anthony T, Buie WD, Cataldo P, Church J, Cohen J, Dentsman F, Ellis CN, Kilkenny JW, Ko C, Moore R, Orsay C, Place R, Rafferty J, Rakinic J, Savoca P, Tjandra J, Whiteford M. Practice parameters for colon cancer. *Dis Colon Rectum* 2004; **47**: 1269-1284 [PMID: 15484340 DOI: 10.1007/s10350-004-0598-8]

13 **Nelson H**, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D, Sargent D. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001; **93**: 583-596 [PMID: 11309435 DOI: 10.1093/jnci/93.8.583]

14 **Sobin LH**. TNM classification: clarification of number of regional lymph nodes for pN0. *Br J Cancer* 2001; **85**: 780 [PMID: 11531267 DOI: 10.1054/bjoc.2001.1996]

15 **Chou JF**, Row D, Gonen M, Liu YH, Schrag D, Weiser MR. Clinical and pathologic factors that predict lymph node yield from surgical specimens in colorectal cancer: a population-based study. *Cancer* 2010; **116**: 2560-2570 [PMID: 20499400 DOI: 10.1002/cncr.25032]

16 **The National Comprehensive Cancer Network.** Quality Measures. [accessed 2008 Mar 25]. Available from: URL: http://www.nccn.org/professionals/quality_measures/PDF/ç.pdf

17 **Fellow of the American College of Surgeons**. CoC Quality of Care Measures. [accessed 2008 Sept 22]. Available from: URL: http://www.facs.org/cancer/qualitymeasures.html

18 **National Quality Forum.** Appendix A: Specifications of the National Voluntary Consensus Standards for Breast and Colon Cancer. [accessed 2008 Jun 27]. Available from: URL: http://www.qualityforum.org/pdf/cancer/txbreast-colonAppA-Specsvoting01-18-07

19 **Cianchi F**, Palomba A, Boddi V, Messerini L, Pucciani F, Perigli G, Bechi P, Cortesini C. Lymph node recovery from colorectal tumor specimens: recommendation for a minimum number of lymph nodes to be examined. *World J Surg* 2002; **26**: 384-389 [PMID: 11865379 DOI: 10.1007/s00268-001-0236-8]

20 **Goldstein NS**, Sanford W, Coffey M, Layfield LJ. Lymph node recovery from colorectal resection specimens removed for adenocarcinoma. Trends over time and a recommendation for a minimum number of lymph nodes to be recovered. *Am J Clin Pathol* 1996; **106**: 209-216 [PMID: 8712176]

21 **Cone MM**, Shoop KM, Rea JD, Lu KC, Herzig DO. Ethnicity influences lymph node resection in colon cancer. *J Gastrointest Surg* 2010; **14**: 1752-1757 [PMID: 20714936 DOI: 10.1007/s11605-010-1296-6]

22 **Valsecchi ME**, Leighton J, Tester W. Modifiable factors that influence colon cancer lymph node sampling and examination. *Clin Colorectal Cancer* 2010; **9**: 162-167 [PMID: 20643621 DOI: 10.3816/CCC.2010.n.022]

23 **Tekkis PP**, Smith JJ, Heriot AG, Darzi AW, Thompson MR, Stamatakis JD. A national study on lymph node retrieval in resectional surgery for colorectal cancer. *Dis Colon Rectum* 2006; **49**: 1673-1683 [PMID: 17019656 DOI: 10.1007/s10350-006-0691-2]

24 **Stocchi L**, Fazio VW, Lavery I, Hammel J. Individual surgeon, pathologist, and other factors affecting lymph node harvest in stage II colon carcinoma. is a minimum of 12 examined lymph nodes sufficient? *Ann Surg Oncol* 2011; **18**: 405-412 [PMID: 20839064 DOI: 10.1245/s10434-010-1308-5]

25 **Nathan H**, Shore AD, Anders RA, Wick EC, Gearhart SL, Pawlik TM. Variation in lymph node assessment after colon cancer resection: patient, surgeon, pathologist, or hospital? *J Gastrointest Surg* 2011; **15**: 471-479 [PMID: 21174232 DOI: 10.1007/s11605-010-1410-9]

26 **Baxter NN**, Ricciardi R, Simunovic M, Urbach DR, Virnig BA. An evaluation of the relationship between lymph node number and staging in pT3 colon cancer using population-based data. *Dis Colon Rectum* 2010; **53**: 65-70 [PMID: 20010353 DOI: 10.1007/DCR.0b013e3181c70425]

27 **Nash GM**, Row D, Weiss A, Shia J, Guillem JG, Paty PB, Gonen M, Weiser MR, Temple LK, Fitzmaurice G, Wong WD. A predictive model for lymph node yield in colon cancer resection specimens. *Ann Surg* 2011; **253**: 318-322 [PMID: 21169808 DOI: 10.1097/SLA.0b013e318204e637]

28 **Dubecz A**, Solymosi N, Schweigert M, Stadlhuber RJ, Peters JH, Ofner D, Stein HJ. Time trends and disparities in lymphadenectomy for gastrointestinal cancer in the United States: a population-based analysis of 326,243 patients. *J Gastrointest Surg* 2013; **17**: 611-618; discussion 618-619 [PMID: 23340992 DOI: 10.1007/s11605-013-2146-0]

29 **Rajput A**, Romanus D, Weiser MR, ter Veer A, Niland J, Wilson J, Skibber JM, Wong YN, Benson A, Earle CC, Schrag D. Meeting the 12 lymph node (LN) benchmark in colon cancer. *J Surg Oncol* 2010; **102**: 3-9 [PMID: 20578172 DOI: 10.1002/jso.21532]

30 **Bilimoria KY**, Stewart AK, Palis BE, Bentrem DJ, Talamonti MS, Ko CY. Adequacy and importance of lymph node evaluation for colon cancer in the elderly. *J Am Coll Surg* 2008; **206**: 247-254 [PMID: 18222376 DOI: 10.1016/j.jamcollsurg.2007.07.044]

31 **Shen SS**, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. *Arch Pathol Lab Med* 2009; **133**: 781-786 [PMID: 19415953 DOI: 10.1043/1543-2165-133.5.781]

32 **Jakub JW**, Russell G, Tillman CL, Lariscy C. Colon cancer and low lymph node count: who is to blame? *Arch Surg* 2009; **144**: 1115-1120 [PMID: 20026828 DOI: 10.1001/archsurg.2009.210]

33 **Nedrebø BS**, Søreide K, Nesbakken A, Eriksen MT, Søreide JA, Kørner H. Risk factors associated with poor lymph node harvest after colon cancer surgery in a national cohort. *Colorectal Dis* 2013; **15**: e301-e308 [PMID: 23582027 DOI: 10.1111/codi.12245]

34 **Gonsalves WI**, Kanuri S, Tashi T, Aldoss I, Sama A, Al-Howaidi I, Ganta A, Kalaiah M, Thota R, Krishnamurthy J, Fang X, Townley P, Ganti AK, Subbiah S, Silberstein PT. Clinicopathologic factors associated with lymph node retrieval in resectable colon cancer:

a Veterans' Affairs Central Cancer Registry (VACCR) database analysis. *J Surg Oncol* 2011; **104**: 667-671 [PMID: 21337344 DOI: 10.1002/jso.21886]
35 **Gelos M**, Gelhaus J, Mehnert P, Bonhag G, Sand M, Philippou S, Mann B. Factors influencing lymph node harvest in colorectal surgery. *Int J Colorectal Dis* 2008; **23**: 53-59 [PMID: 17823805 DOI: 10.1007/s00384-007-0378-8]
36 **Sinan H**, Demirbas S, Ersoz N, Ozerhan IH, Yagci G, Akyol M, Cetiner S. Who is responsible for inadequate lymph node retrieval after colorectal surgery: surgeon or pathologist? *Acta Chir Belg* 2012; **112**: 200-208 [PMID: 22808760]
37 **Wright FC**, Law CH, Last L, Khalifa M, Arnaout A, Naseer Z, Klar N, Gallinger S, Smith AJ. Lymph node retrieval and assessment in stage II colorectal cancer: a population-based study. *Ann Surg Oncol* 2003; **10**: 903-909 [PMID: 14527909 DOI: 10.1245/ASO.2003.01.012]
38 **Scabini S**, Rimini E, Romairone E, Scordamaglia R, Pertile D, Testino G, Ferrando V. Factors that influence 12 or more harvested lymph nodes in resective R0 colorectal cancer. *Hepatogastroenterology* 2010; **57**: 728-733 [PMID: 21033218]
39 **Søreide K**, Nedrebø BS, Søreide JA, Slewa A, Kørner H. Lymph node harvest in colon cancer: influence of microsatellite instability and proximal tumor location. *World J Surg* 2009; **33**: 2695-2703 [PMID: 19823901 DOI: 10.1007/s00268-009-0255-4]
40 **Pappas AV**, Lagoudianakis EE, Dallianoudis IG, Kotzadimitriou KT, Koronakis NE, Chrysikos ID, Koukoutsi ID, Markogiannakis HE, Antonakis PT, Manouras AJ. Differences in colorectal cancer patterns between right and left sided colorectal cancer lesions. *J BUON* 2010; **15**: 509-513 [PMID: 20941819]
41 **Bamboat ZM**, Deperalta D, Dursun A, Berger DL, Bordeianou L. Factors affecting lymph node yield from patients undergoing colectomy for cancer. *Int J Colorectal Dis* 2011; **26**: 1163-1168 [PMID: 21573900 DOI: 10.1007/s00384-011-1240-6]
42 **McPartland S**, Hyman N, Blaszyk H, Osler T. The number of lymph nodes in colon cancer specimens: what do the numbers really mean? *Colorectal Dis* 2010; **12**: 770-775 [PMID: 19508534]
43 **Samdani T**, Schultheis M, Stadler Z, Shia J, Fancher T, Misholy J, Weiser MR, Nash GM. Lymph node yield after colectomy for cancer: is absence of mismatch repair a factor? *Dis Colon Rectum* 2015; **58**: 288-293 [PMID: 25664706 DOI: 10.1097/DCR.0000000000000262]
44 **Guidoboni M**, Gafà R, Viel A, Doglioni C, Russo A, Santini A, Del Tin L, Macrì E, Lanza G, Boiocchi M, Dolcetti R. Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. *Am J Pathol* 2001; **159**: 297-304 [PMID: 11438476 DOI: 10.1016/S0002-9440(10)61695-1]
45 **Michael-Robinson JM**, Biemer-Hüttmann A, Purdie DM, Walsh MD, Simms LA, Biden KG, Young JP, Leggett BA, Jass JR, Radford-Smith GL. Tumor infiltrating lymphocytes and apoptosis are independent features in colorectal cancer stratified according to microsatellite instability status. *Gut* 2001; **48**: 360-366 [PMID: 11171826 DOI: 10.1136/gut.48.3.360]
46 **Michael-Robinson JM**, Reid LE, Purdie DM, Biemer-Hüttmann AE, Walsh MD, Pandeya N, Simms LA, Young JP, Leggett BA, Jass JR, Radford-Smith GL. Proliferation, apoptosis, and survival in high-level microsatellite instability sporadic colorectal cancer. *Clin Cancer Res* 2001; **7**: 2347-2356 [PMID: 11489812]
47 **Nash GM**, Gimbel M, Cohen AM, Zeng ZS, Ndubuisi MI, Nathanson DR, Ott J, Barany F, Paty PB. KRAS mutation and microsatellite instability: two genetic markers of early tumor development that influence the prognosis of colorectal cancer. *Ann Surg Oncol* 2010; **17**: 416-424 [PMID: 19813061 DOI: 10.1245/s10434-009-0713-0]
48 **Eveno C**, Nemeth J, Soliman H, Praz F, de The H, Valleur P, Talbot IC, Pocard M. Association between a high number of isolated lymph nodes in T1 to T4 N0M0 colorectal cancer and the microsatellite instability phenotype. *Arch Surg* 2010; **145**: 12-17 [PMID: 20083749 DOI: 10.1001/archsurg.2009.224]
49 **MacQuarrie E**, Arnason T, Gruchy J, Yan S, Drucker A, Huang WY. Microsatellite instability status does not predict total lymph node or negative lymph node retrieval in stage III colon cancer. *Hum Pathol* 2012; **43**: 1258-1264 [PMID: 22305240 DOI: 10.1016/j.humpath.2011.10.002]
50 **Dhar DK**, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, Kohno H, Nagasue N. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. *Oncology* 2000; **59**: 18-23 [PMID: 10895061 DOI: 10.1159/000012131]
51 **Görög D**, Nagy P, Péter A, Perner F. Influence of obesity on lymph node recovery from rectal resection specimens. *Pathol Oncol Res* 2003; **9**: 180-183 [PMID: 14530812 DOI: 10.1007/BF03033734]
52 **Damadi AA**, Julien L, Arrangoiz R, Raiji M, Weise D, Saxe AW. Does obesity influence lymph node harvest among patients undergoing colectomy for colon cancer? *Am Surg* 2008; **74**: 1073-1077 [PMID: 19062664]
53 **Linebarger JH**, Mathiason MA, Kallies KJ, Shapiro SB. Does obesity impact lymph node retrieval in colon cancer surgery? *Am J Surg* 2010; **200**: 478-482 [PMID: 20887841 DOI: 10.1016/j.amjsurg.2009.12.012]
54 **Kuo YH**, Lee KF, Chin CC, Huang WS, Yeh CH, Wang JY. Does body mass index impact the number of LNs harvested and influence long-term survival rate in patients with stage III colon cancer? *Int J Colorectal Dis* 2012; **27**: 1625-1635 [PMID: 22622602 DOI: 10.1007/s00384-012-1496-5]
55 **Bartels SA**, van der Zaag ES, Dekker E, Buskens CJ, Bemelman WA. The effect of colonoscopic tattooing on lymph node retrieval and sentinel lymph node mapping. *Gastrointest Endosc* 2012; **76**: 793-800 [PMID: 22835497 DOI: 10.1016/j.gie.2012.05.005]
56 **Dawson K**, Wiebusch A, Thirlby RC. Preoperative tattooing and improved lymph node retrieval rates from colectomy specimens in patients with colorectal cancers. *Arch Surg* 2010; **145**: 826-830 [PMID: 20855751 DOI: 10.1001/archsurg.2010.180]
57 **Foxtrot Collaborative Group**. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012; **13**: 1152-1160 [PMID: 23017669 DOI: 10.1016/s1470-2045(12)70348-0]

P- Reviewer: Bordas JM, De Nardi P
S- Editor: Wang JL **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com