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ORIGINAL ARTICLE

Harvest of lymph nodes in colorectal cancer depends on demographic and clinical characteristics of the patients

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Abstract
Purpose This study aims to study the impact of clinical factors on the lymph node sampling in a large cohort of patients with colorectal cancer.
Methods A colorectal cancer database of 2298 patients in Queensland, Australia, was established. Zero-inflated regression method was used to model positive lymph node counts given the number of lymph nodes examined, with patient's demographic and clinical factors as covariates in the model. Sensitivity and survival analyses were performed to illustrate the applicability of the recommendation of the minimum number of lymph nodes need to be pathologically examined.
Results Younger patients with a larger sized tumour located at the left colon or rectum require fewer lymph nodes to be pathologically examined. Overall, 45.9% of the patients require eight or nine lymph nodes and 31.5% needs ten or 11 lymph nodes to be harvested for pathological examination. A simple formula could be used to obtain the minimum number of lymph node sampling required in patients with colorectal cancer based on patients' age as well as site and dimension of the cancer.
Conclusions The findings provide practical information about that the minimum number of lymph nodes that could be harvested at the time of collection of lymph nodes for pathological examination for patients with colorectal cancer. The minimum number of lymph nodes harvested depends on demographic (age) and clinical (location and dimension of cancer) characteristics of the patients with colorectal cancer.

Keywords Colorectal cancer · Lymph node · Adenocarcinoma · Harvest · Pathology

Introduction

The most important factor affecting the treatment plan and survival of patients with colorectal cancer is the pathological staging [1]. In patients without distant metastases, the pathological staging of the colorectal cancer depends on the presence or absence of lymph node (LN) metastases. Thus, it is imperative to obtain an appropriate number of LNs in pathological examination of colorectal cancer [2]. However, the number of LNs found in a resected specimen relies on the size of the mesentery resected, the care taken by the pathologist and surgeon, and the examination method adopted. The current guideline recommended that at least 12 LNs be examined in pathological examination of colorectal cancer [3]. In practice, not all specimens contain this number of LNs, especially for patients with rectal cancer who have received pre-operative chemo-radiotherapy [4]. A harvest of at least 12 LNs at the time of colorectal cancer resection could be difficult [2]. On the other hand, there were studies that suggested to examining > 12 LNs [5, 6] or as many as LNs that are available [7, 8].

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The objectives of this study were to investigate in depth the various clinical features that could affect the number of LNs collected in a large cohort of patients with colorectal cancer having long-term follow-up data.

Materials and methods

Patients

Patients with surgical resection of carcinoma in the large intestine were collected from the hospitals in Queensland, Australia. They were consecutive cases with no selection bias. Demographic, clinical, and pathological data were entered in a computerized database. Ethical approval of this study has been obtained from the Human Research Ethics Committee in the relevant institutes (Ref Nos. HREC/11/QRBW/93 and MED/05/06 HREC).

The size of the carcinoma was represented by the largest dimension of the cancer as measured in macroscopic examination. The cancers were staged according to the World Health Organization classification of gastrointestinal tumour [8]. The sites of the cancers were divided into either right or left side. Right-side cancers are defined as colon cancer in the caecum, ascending colon, and transverse colon. Left-side cancers are defined as rectal cancer or cancer in the descending colon and sigmoid colon.

Management of these patients was by a pre-agreed standardized multidisciplinary protocol. The follow-up period was defined as the interval between the date of surgery for colorectal carcinoma and the date of death or closing date of the study. The actuarial survival rate of the patients was calculated from the date of surgical resection of the colorectal carcinomas to the date of death or last follow-up. Only cancer-related death was counted as the end point in the statistical analysis.

Statistical methods

A probabilistic approach using zero-inflated negative-binomial (ZINB) regression models [9] was used to estimate the number of positive LNs, with adjustment for patient's characteristics, and the number of LNs examined was entered in the models as an exposure variable [10]. The number of examined LNs recommended was determined by the number of LNs with which the lower bound of the 99% CI for the estimated conditional mean of positive LNs was greater than 1 (note that a higher confidence level than a typical 95% was adopted). Two sensitivity analyses were performed to assess the "consistence" and the applicability of the new recommendation. PubMed database was searched to identify studies since 2000 on the number of LNs retrieved for patients with colorectal cancer. The performance of the refined guidelines compared to the current guideline of a minimum of 12 LNs to be examined was assessed using the Kaplan-Meier survival analyses.

Results

A total of 2298 patients (1283 men; 1015 women) having colorectal carcinomas with greater than or equal to one LN retrieved for pathological examination were considered (mean age 67 years; range 15–94 years; median 69 years). The average number of examined LNs was 14.5 (range 1–122; median 13). The average proportion of positive LNs was 0.13 (range 0.0–1.0). Patient's characteristics were provided in Supplementary Table S1.

Four patients with an extreme number of examined LNs (73, 79, 100, and 122) were excluded from the analyses, resulting in 2294 patients (99.8% of the data archive). Supplementary Table S2 displays the modelling results and the goodness-of-fit indicators; key demographic (age) and clinical (cancers' site and size) factors had a significant impact on the rate of positive LN metastases. Supplementary Table S3 shows the results of sensitivity analyses, demonstrating that the final ZINB model is consistent and the number of LNs recommended is applicable in various subpopulation structures.

Supplementary Figure S1 displays the minimum number of examined LNs for patients with distinct characteristics such that the estimated lower bound of the 99% CI for the covariate-adjusted mean number of positive LNs was greater than 1. Overall, the current guideline of a minimum of 12 recovered LNs may be more than sufficient in most instances (Figure S1). Younger patients with a larger cancer at the left colon or rectum could need fewer than 12 examined LNs harvested for pathological examination. Only 7.9% of the study samples require examination of > 12 LNs [6.5% (14 LNs); 1.4% (16 LNs)]; see Figure S1.

An Excel formula is displayed in Table 1 to obtain the minimum number of examined LNs needed for patients with specific categorical indicators. These include age groups (1 to 3 corresponding to ages < 60, 60–79, and ≥ 80 years), cancer site groups (1 and 2 corresponding to the right colon and left colon/rectum), and cancer size groups (1 to 3 corresponding to sizes < 30, 30–49, and ≥ 50 mm). The Excel formula for calculating the recommended minimum number of examined LNs is

$$\begin{aligned} &= IF(\text{age } group = 1, 12 + IF(size\ group = 3, 1, 0), IF(\text{age } group = 2, 14, 16)) \\ &\quad - IF(site\ group = 2, 1, 0) \times IF(\text{age } group = 1, 1, site\ group) \\ &\quad - IF(size\ group > 1, size\ group + IF(\text{age } group > 2, 2, 1), 0) \end{aligned} \quad (1)$$

where IF(, ,) is the Excel IF function for making logical comparisons in the form of IF(something is true, then do something; otherwise, do something else); see Table 1. For

Table 1 Recommended minimum number of examined lymph nodes

Age group	Site group	Size group	Recommended minimal number of lymph nodes to be examined
1 (< 60)	1 (right)	1 (< 30 mm)	12
1 (< 60)	1 (right)	2 (30–49 mm)	9
1 (< 60)	1 (right)	3 (≥ 50 mm)	9
1 (< 60)	2 (left)	1 (< 30 mm)	11
1 (< 60)	2 (left)	2 (30–49 mm)	8
1 (< 60)	2 (left)	3 (≥ 50 mm)	8
2 (60–79)	1 (right)	1 (< 30 mm)	14
2 (60–79)	1 (right)	2 (30–49 mm)	11
2 (60–79)	1 (right)	3 (≥ 50 mm)	10
2 (60–79)	2 (left)	1 (< 30 mm)	12
2 (60–79)	2 (left)	2 (30–49 mm)	9
2 (60–79)	2 (left)	3 (≥ 50 mm)	8
3 (≥ 80)	1 (right)	1 (< 30 mm)	16
3 (≥ 80)	1 (right)	2 (30–49 mm)	12
3 (≥ 80)	1 (right)	3 (≥ 50 mm)	11
3 (≥ 80)	2 (left)	1 (< 30 mm)	14
3 (≥ 80)	2 (left)	2 (30–49 mm)	10
3 (≥ 80)	2 (left)	3 (≥ 50 mm)	9

An Excel formula was used to obtain the recommended minimum number of examined lymph nodes for patients with distinct demographic and clinical characteristics. The categorical indicators were age group (1 to 3 corresponding to age < 60, 60–79, and ≥ 80), cancer site group (1: right colon, 2: left colon/rectum), and cancer size group (1 to 3 corresponding to size < 30, 30–49, and ≥ 50 mm). The recommended number of lymph nodes for 18 different combinations of age, cancer site, and size groups was listed. Formula = IF (age group = 1, 12 + IF (size group = 3, 1, 0), IF (age group = 2, 14, 16)) − IF (site group = 2, 1, 0) × IF (age group = 1, 1, site group) − IF (size group > 1, size group + IF (age group > 2, 2, 1), 0)

illustration, an example is highlighted in Table 1 for a patient aged ≥ 80 years (age group = 3) with a rectum cancer (site group = 2) of size ≥ 50 mm (size group = 3). Based on the above formula, the recommended minimum number of examined LNs is 9.

Supplementary Table S4 summarizes studies identified from the PubMed database, showing that the recommended numbers of examined LNs vary markedly among studies. There are 730 patients (31.8% of 2294) who had the number of examined LNs incompatible with the refined guidelines derived based on the above Excel formula. The Kaplan-Meier survival analyses showed that the performance of the refined guidelines is slightly better than the current guideline of a minimum of 12 LNs (Supplementary Figure S2).

Discussion

In some instances, pathologists were asked to re-examine the dissected specimen to find additional LNs to meet the *gold standard* of 12 LNs without considering the individual clinical condition. In this study, we noted that the minimum number of LNs to be harvested in pathological dissection depends on the distinct demographic (age) and clinical (location and size of cancer) characteristics.

To identify an appropriate number of examined LNs, Cox proportional hazard models [5], prediction modelling [6], logistic regression [7], and Kaplan-Meier method [8] have been considered. These studies found that the predictive probability of LN metastases increased with the number of examined LNs and the overall survival was improved with more examined LNs, suggesting either > 12 LNs or as many LNs should be pathologically examined as possible. Less-than-adequate node sampling should not be accepted as this has important prognostic implications. Sampling a greater number of LNs will increase the likelihood of proper staging. However, a LN yield of ≥ 12 was not associated with an increased probability of positive LNs [11]. Efforts to increase the LN harvest to > 12 per specimen did not upstage patients from TNM stage II to III, and the whole concept that more LNs are needed to stage patients correctly is contentious. Alternatively, da Costa et al. [12] suggested to determine the N-stage by the five largest LNs in the resected specimen of patients with colon cancer.

We adopted a ZINB model to estimate the number of positive LNs conditioned on patient's age, location, and size of cancer. There is very high 99% confidence that the true mean number of positive LNs will be at least one with the

recommended number of LNs to be examined pathologically. With reference to the literature search in Supplementary Table S4, our method offers the only guideline that makes recommendation on the basis of patient's demographic (age) and clinical (location and dimension of cancer) characteristics. While previous studies have supported the minimum of 12 examined LNs, we found that this recommended number of LNs may be more than sufficient in most instances. In our research, 45.9% of the study samples require only 8–9 LNs and 31.4% need 10–11 LNs to be pathologically examined. Only 7.9% of the study samples require examination of > 12 LNs (supplementary Figure S1).

The key strength of this study was the relatively large size of a cohort of patients with colorectal cancer, allowing the inclusion of patient's characteristics in the probabilistic model for estimating the minimum number of examined LNs. An increased validity and generalisability of our refined guidelines can be achieved.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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