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Ramzi Amri, MD, PhD, Coen L. Klos, MD, Liliana Bordeianou, MD, MPH, David L. Berger, MD

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Ramzi Amri, MD, PhD, Coen L. Klos, MD, Liliana Bordeianou, MD, MPH, and David L. Berger, MD

1Division of General and Gastrointestinal Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.
2Section of Colon and Rectal Surgery, Department of Surgery, Washington University School of Medicine, Saint Louis, MO, United States.

*Correspondence to: David L. Berger, MD, Massachusetts General Hospital Division of General Surgery & Gastrointestinal Surgery, 15 Parkman Street 02114 Boston, MA
Fax: 617724-0067 E-mail: dberger@mgh.harvard.edu

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Running head: LNR and resection length in colon cancer

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Abstract: 175 words
Synopsis: This study assessed whether adjusting lymph node ratio (LNR) for resection length (RL) impacts its prognostic value in colon cancer. Provided that resections are performed following standard oncologic principles, our analysis shows that resection length does not significantly impact the prognostic value of LNR after colectomy for colon cancer. Based on these results, correcting LNR for resection length seems redundant and may even act as noise distorting LNR values in some cases.
**Background:** Lymph node ratio (LNR), the ratio of tumor-positive lymph nodes (+LN) to the total number of resected lymph nodes (rLN), predicts recurrence and survival in colon cancer. Variations in colonic resection length (RL) may influence rLN, +LN, or both, thereby potentially impacting LNR and its prognostic value in colon cancer.

**Methods:** All colon cancer patients treated surgically at our center from 2004 through 2011 were included in an IRB-approved data repository (n=1039).

**Results:** Larger RL was associated with increased rLN ($\rho=0.22$; $P<0.001$) but not with +LN ($P=0.21$). In node-positive patients (n=411) RL-adjusted LNR had weaker correlations with death ($\rho=0.338$ vs. 0.373, both $P<0.001$) or metastatic disease ($\rho=0.303$ vs. 0.345; both $P<0.001$) and a smaller area under the curve (death: 0.695 vs. 0.715, metastasis: 0.675 vs. 0.699). Findings were similar in segmental, extended segmental and total colectomy subgroups.

**Conclusions:** Provided that resections are performed following standard oncologic principles, our analysis shows that resection length does not significantly impact the prognostic value of LNR in colon cancer. Correcting LNR for RL seems redundant and may even act as noise distorting LNR values.
The prognosis after surgical resection of colon cancer in terms of recurrent disease and cancer-related survival is highly dependent on the histopathologic lymph node staging of the resected specimen. Pathology reports on colon cancer therefore routinely include the total lymph node yield (rLN) as well as the number of tumor-positive lymph nodes (+LN), since both reportedly are independent predictors for oncologic outcome: An increase in rLN may improve survival rates,\textsuperscript{1,2} while an increase in +LN significantly decreases survival.\textsuperscript{3} In the search for a lymph node staging system that may reflect prognosis after surgical resection of a primary cancer more accurately, both the effects on oncologic outcome of rLN and +LN can be captured in a single prognostic value: the lymph node ratio (LNR). LNR is calculated by dividing +LN by rLN and has been validated in large series of colon cancer patients as an independent prognostic factor.\textsuperscript{4-6}

Reflecting lymph node positivity as a fraction of the total number of resected lymph nodes may adjust for adequacy of resection when compared to evaluating lymph node positivity alone. Accordingly, LNR should be expected to predict recurrence and survival with more nuance than the N-stage of the American Joint Committee on Cancer’s (AJCC) TNM classification.\textsuperscript{7}

However, there is no specific protocol limiting the maximum length of the resected specimen (RL) when performing an oncologic resection of the colon. Therefore, there is considerable variation in RL from case to case depending on patient condition, margins applied, as well as tumor size; spread and site. RL has already been reported to significantly alter lymph node yields, with longer resections increasing overall lymph node yields.\textsuperscript{8} It may be important to consider the risk of understaging, as increased RL may result in a dilution of the fraction of positive nodes through a disproportionate increase in rLN, which impacts LNR in node-positive cases and may undermine its positive predictive value.

The aim of this study is therefore to reveal the impact of resection length on rLN, +LN
and LNR, and assess whether LNR adjusted for resection length shows a more accurate and increased predictive value for long-term oncologic outcomes after curative resection for colon cancer.
Methods

Patients

A cohort including all surgically treated colon cancer patients at Massachusetts General Hospital (MGH) from 2004 through 2011 was extracted from the MGH cancer registry and included in a data repository after institutional review board approval, using prospective data from the Research Patient Data Repository, complemented by review of patient records. Our data repository was maintained prospectively starting 2011. Data on long-term outcomes is periodically updated by reviewing patient follow-up records and the social security death index. The last status review of survival and follow-up was on April 1st 2014. Data sources included postoperative pathology reports, with special interest to overall lymph node harvest, tumor positive lymph node harvest, resection length, and pathological TNM classification; surgery and clinical oncology clinical records and repositories for survival and recurrence rates, along with follow-up, disease-free survival and survival durations; and the national Social Security Death Index for overall survival information.

All patients that were treated for colon cancer with curative intent were included. The following cases were excluded: palliative resections (n=21), cases with a pathology report that does not detail a resection length of the specimen (n=11). The remaining 1039 out of 1071 patients were included for final analysis.

Definitions:

Lymph node ratio was calculated as conventionally defined, by dividing +LN by rLN. Resection length-adjusted LNR was defined as the ratio of positive lymph nodes to resected lymph nodes per centimeter of resected bowel +LN/rLN/RL, which can be simplified to
LNR/RL. In order to verify whether correction for resection length improved prognostic value, we measured the correlations between cancer outcomes and LNR, RL-adjusted LNR, as well as resection length alone. Subsequent analysis consisted of comparing measurements reflecting the sensitivity and specificity of these three measures for both recurrence and survival.

**Surgery and pathology**

Surgical resection of colon cancer is performed following the standards of National Guidelines Clearinghouse guideline NGC-7078. As such, lymphadenectomy happens en bloc with the segment involved with the primary tumor, along with all the mesentery containing the primary blood supply and the lymphatics of the involved colonic segment. Procedures aim to achieve distal and proximal margin clearance of at least 5 cm, a minimum of 12 resected nodes, and to include apical nodes when feasible. All surgical resection specimens were examined by the same group of gastrointestinal pathologists at our institution. Pathologic analysis was performed by standard protocol and reports included histologic type, description of resection margins, vascular and lymphovascular invasion, pathology stage (TNM), total number of regional lymph nodes present in the resected specimen, and number of tumor-positive lymph nodes. The pathologic dissection used to obtain lymph nodes is a relatively standardized procedure. There are dedicated pathology physician assistants who gross the specimen uniformly and a dedicated group of gastrointestinal pathologists reading the specimens. For the entire time span covered by this paper, the procedure for lymph node identification in colonic resection specimens was as follows: The mesenteric section of the resected specimen was cut from the colon. The specimen was then sectioned linearly in 0.2 cm strips. Each strip was carefully dissected for lymph nodes, with any encountered nodes being pulled out and fixed. Nodes >0.3 cm are bivalved, while nodes <0.3 cm are submitted whole. These nodes are put in paraffin and
sectioned. The resulting slides are then evaluated by one of six gastrointestinal pathologists. Cases are signed out after review. This process is regimented and subject to internal peer review.

Statistical analysis

Analysis was performed using the SPSS statistical software package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The boundary for statistical significance was set at a p-value below 0.05 (two-tailed) for all analyses. Distribution of baseline characteristics was evaluated through mean and range, as well as the medians and interquartile ranges (IQR), or the range from the first quartile (Q1) to the third quartile (Q3). Differences between continuous variables were assessed using a one-way analysis of variance (ANOVA). Correlation between LNR models and dichotomous outcomes was assessed using Spearman’s Rho coefficient (ρ), as we have no grounds to expect the relationship between LNR models and outcomes to be linear, as is assumed in the often used Pearson correlation. Lastly, a standard receiver operative characteristic (ROC) curve was used to estimate the specificity and sensitivity of LNR and its alternative RL-adjusted separate model in predicting long-term cancer related outcomes, as expressed by the area under the curve in node-positive patients.
Results

Baseline characteristics

Of the 1039 included patients, 411 (39.6%) had tumor-positive lymph nodes identified in postoperative pathology. When comparing those with nodal disease to those without nodal disease, median total lymph node harvest (18±6 vs. 18±5.5; \( P=0.37 \)), and median resection length (21±6cm vs. 21±6.5cm; \( P=0.47 \)), did not differ significantly. In patients with tumor positive lymph nodes, the median number of positive nodes identified was 3 (IQR: 1-5) and the median LNR was 0.15 (IQR: 0.07 - 0.29). Segmental, extended segmental and total colectomies differed significantly in terms of median resection length: 20, 27, and 87 cm respectively (\( P<0.001 \)) and lymph node harvest: 17.5, 20 and 27 cm (\( P<0.001 \)), but not in LNR (\( P= 0.37 \)) or in the number of positive lymph nodes found (\( P=0.95 \)). For RL, a significant positive correlation with rLN (\( \rho=0.222; \ P<0.001 \)) was demonstrated, while there was no significant correlation between +LN and RL (\( \rho=0.039; \ P=0.21 \)). The baseline characteristics of our research population are displayed in further detail in Table 1.

Correlations between models and outcomes

The correlations of LNR and RL-adjusted LNR are shown in Table 2. The measured correlation coefficients were highly significant (\( P<0.001 \)) in most cases except for the substantially smaller total colectomies subset. Correlations of the outcomes with unadjusted LNR were stronger in nearly all cases, except for recurrence rates in the overall group and minute differences in disease-free survival and overall metastatic disease in total colectomies. In all cases, the differences in correlations were too small to be considered clinically relevant. Resection length did not demonstrate any significant correlations with any of the outcomes.
Sensitivity/specificity analysis by ROC curves:

All ROC curves are computed for node-positive patients, the population in which (RL-adjusted) LNR will have the largest potential value. Comparing ROC curves in the overall population, node-negative patients included, would be redundant since node-negative cases will yield a ratio of 0 in both LNR and RL-adjusted LNR. Figure 1 shows the ROC curves for death, metastatic recurrence and overall metastatic disease. The areas under the curve, for this population and all resection subsets are also displayed. In most cases, the predictive value expressed as area under the curve of LNR remains slightly superior to RL-adjusted LNR. In all cases, standard errors overlap, making any difference witnessed within margins of uncertainty. Resection length again fails to show any connection with any of the outcomes.
Discussion

Oncologists are constantly striving to expand, improve and fine-tune the tools available to assess both a patients' risk of recurrence and their chance of cure and survival. Efforts to stratify these risks in a standardized fashion often focus on pathological characteristics, as these can lead to risk assessments based on empirical data. In addition to important staging systems, like the AJCC/TNM and Dukes classification, the lymph node ratio was introduced as an adjunct lymph node staging system for malignant neoplasms of the breast,\textsuperscript{10} stomach,\textsuperscript{11} pancreas,\textsuperscript{12} rectum,\textsuperscript{13} gallbladder,\textsuperscript{14} melanoma,\textsuperscript{15} as well as colon cancer\textsuperscript{2,5,6}. The AJCC,\textsuperscript{16} the College of American Pathologists,\textsuperscript{17} and the National Cancer Institute\textsuperscript{18} unanimously recommend evaluation of as many lymph nodes as possible, with a minimum of at least twelve lymph nodes in total per specimen to warrant rigorous resections and prevent false negative specimens. The yield recommendation is motivated by the theory that increased nodal yields will decrease false negative results. However, in colon cancer, harvesting more nodes may simply occur by harvesting nodes from different basins, which may increase total nodal yield but with nodes that may not be relevant.

An important factor that may influence the total lymph node harvest is therefore the resection length of the specimen. There is often variability in the length of the resected colon segment and previous reports suggest that greater resection length is associated with higher overall lymph node harvests.\textsuperscript{8} We therefore hypothesized that resection length may need to be accounted for when using LNR to evaluate patient prognosis after oncologic resection for colon cancer.

The key findings of this study were that an increased resection length correlates
significantly with lymph node yield, while the number of positive lymph nodes did not show a correlation with resection length. However, this discrepancy in correlations did not result in resection length being a confounder of the prognostic value of the lymph node ratio: Resection length was revealed to have no tangible association with cancer-related outcomes. Correspondingly, correcting lymph node ratio for resection length did not show a significant difference in correlation with oncologic outcomes in the overall population and patients with tumor-positive lymph nodes; nor did ROC curves show any significant improvement in sensitivity or specificity. Overall, the association strength of LNR with outcomes was most often decreased with adjustment for resection length in node-positive patients, bar a few exceptions where the difference was too small to quantify, and without statistical or clinical significance.

A limitation of our analysis is that the (sub)total colectomy portion of our population is underpowered due to its small sample size. Even though we found some statistically significant outcomes in this group, these results ought to be interpreted with caution, as they may not be representative for the subtotal colectomy population at large. Future research may focus on this (sub)total colectomy population, and those with tumor-positive lymph nodes in particular, to explore whether a length-adjusted lymph node ratio may provide a higher predictive value for oncologic outcome in these cases.

In colon cancer, increased total lymph node yields have frequently been linked to improved outcomes. As a result, resection length is being used as a surrogate marker for completeness of the oncologic resection. Although our data did show a significant positive correlation of resection length with an increase in total lymph node harvest, this correlation did not echo into a positive correlation between resection length alone and outcome. This may lead to the question of how accurately the total lymph node harvest actually reflects the quality of the
surgical oncologic resection and how extensive this resection should be. To address this issue, not only the length of the resected specimen may be an important factor, but also other dimensions adding to the complete specimen size may have to be considered.

The effect of resection length on lymph node staging has been reviewed in several studies by Hida et al. who advocate limiting resection margins and provided evidence that, depending on tumor distance from the primary feeding artery, distal and proximal margins as narrow as 3 cm (T1), 5 cm (T2) or 7 cm (T3 and 4) can be appropriate. Additionally, other Japanese studies have shown that longitudinal nodal spread of disease beyond a 10 cm margin is rare (0-4%). In Europe, several centers have explored the impact of standardized resection by complete mesocolic excision with central vascular ligation (CME with CVL) on outcomes using rLN as a surrogate marker for surgical quality, and as a prognostic tool that may limit the need for adjuvant chemotherapy. When the Erlangen team compared a series of colectomy specimens to those of a Japanese center practicing an alternative, but highly standardized fashion of resecting colon cancers, there were significant differences in length, total lymph node yield, as well as in the total surface of the resected mesentery per specimen. However, with all the aforementioned dimensions being significantly smaller in the Japanese cohort, the number of positive nodes per specimen was not significantly different and the oncologic outcomes of both cohorts were equally impressive. A prospective study comparing those who undergo resection with standardized margins, both longitudinal and at the level of the mesenteric resection, to those who undergo resection without standardized margins may provide more knowledge of how specimen size impacts lymph node yields and outcome accordingly.

It remains however essential not to view the presented evidence as arguments in favor of blindly striving for limitation of resection length or as a suggestion that “less is more” in all
situations. Indiscriminately aiming for the 12 lymph nodes a resection minimum has no intrinsic value if the resection length is inadequate. Resecting too little is inherently harmful to patients and any conservative approach to resections of malignant tumors should be following very clear guidelines.

Based on our results, the main conclusion to be drawn in the search for prognostic measures for surgically treated colon cancer patients appears to be that "more is not necessarily better": Correcting lymph node ratio values for resection length seems redundant; it adds little to nothing to the predictive value of LNR and unnecessarily complicates an otherwise simple and useful ratio. The increased lymph node yields resulting from greater longitudinal resection margins do not significantly skew the prognostic value of LNR in the overall and tumor-positive lymph node patient populations.
Disclosure

The authors report no conflicts of interest.

Acknowledgements

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References


Tables and Figures:

**TABLE 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Segmental</th>
<th>Extended Segmental</th>
<th>(sub)Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included (%)</td>
<td>1039</td>
<td>818 (78.7)</td>
<td>138 (13.8)</td>
<td>69 (6.6)</td>
</tr>
<tr>
<td>Age at surgery (mean, SD)</td>
<td>66.6 (13.9)</td>
<td>66.5 (13.8)</td>
<td>68.9 (13.8)</td>
<td>62.2 (14.6)</td>
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<tr>
<td>Gender (% male)</td>
<td>51.2</td>
<td>49.1</td>
<td>52.2</td>
<td>73.9</td>
</tr>
<tr>
<td>Resection length in cm mean (min-max)</td>
<td>26.6 (5-149)</td>
<td>20.8 (5-50)</td>
<td>31.4 (9-81)</td>
<td>85.9 (30-149)</td>
</tr>
<tr>
<td>Resection length in cm median (Q1-Q3)</td>
<td>21 (15.5-28)</td>
<td>20 (15-25)</td>
<td>27 (20-37)</td>
<td>87 (68–107)</td>
</tr>
<tr>
<td>LN harvest median (Q1-Q3)</td>
<td>18 (14-25)</td>
<td>17.5 (13-24)</td>
<td>20 (15-28)</td>
<td>27 (16-36.5)</td>
</tr>
<tr>
<td>Patients with at least one +LN (%)</td>
<td>411 (39.6)</td>
<td>326 (40.0)</td>
<td>51 (37.0)</td>
<td>27 (40.2)</td>
</tr>
<tr>
<td>Number of +LN median (Q1-Q3)*</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
<td>2 (1-5)</td>
<td>2 (2-5)</td>
</tr>
<tr>
<td>LNR median (Q1-Q3)*</td>
<td>0.15</td>
<td>0.15</td>
<td>0.11</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*In lymph-node positive patients
**TABLE 2** Correlation of Lymph Node Ratio models with outcomes

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>Node-positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNR</td>
<td>Resection Length</td>
</tr>
<tr>
<td>A. All resections (n=1039)</td>
<td>LNR&lt;sub&gt;RL&lt;/sub&gt; .354**</td>
<td>-.013&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Death</td>
<td>Recurrence</td>
<td>Overall metastatic disease</td>
</tr>
<tr>
<td>.158**</td>
<td>.168**</td>
<td>.003&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall metastatic disease</td>
<td>.484**</td>
<td>.033&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Survival duration</td>
<td>-.233**</td>
<td>-.044&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>-.368**</td>
<td>-.051&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>B. Segmental (n=818)</td>
<td>Death</td>
<td>.382**</td>
</tr>
<tr>
<td>Death</td>
<td>.379**</td>
<td>-.031&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall metastatic disease</td>
<td>.518**</td>
<td>.045&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Survival duration</td>
<td>-.244**</td>
<td>-.008&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>-.395**</td>
<td>-.046&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>C. Extended segmental (n=138)</td>
<td>Death</td>
<td>.226**</td>
</tr>
<tr>
<td>Death</td>
<td>.218*</td>
<td>-.112&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall metastatic disease</td>
<td>.319**</td>
<td>-.028&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Survival duration</td>
<td>-.157&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>-.064&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>-.211*</td>
<td>-.006&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>D. (sub)total (n=69)</td>
<td>Death</td>
<td>.339**</td>
</tr>
<tr>
<td>Death</td>
<td>.338**</td>
<td>.195&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall metastatic disease</td>
<td>-.086&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>.030&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Survival duration</td>
<td>-.277**</td>
<td>-.062&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>-.336**</td>
<td>-.046&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
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</table>

* P≤0.05  
** P≤0.01  
NS: non-significant, p-value>0.05
**Figure 1:** ROC curves for metastasis and death in node-positive patients

Receiver operating characteristic curves measuring sensitivity (y-axis) and specificity (displayed as 1-specificity on the x-axis) for death and metastasis in patients with tumor-positive lymph nodes in pathology in both models and resection length. A larger area formed by the model-specific line and the reference line, or area under the curve, denotes better average specificity and sensitivity.