Nodal Status, Number of Lymph Nodes Examined, and Lymph Node Ratio: What Defines Prognosis after Resection of Colon Adenocarcinoma?

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BACKGROUND: Lymph node ratio (LNR) has been proposed as an optimal staging variable for colorectal cancer. However, the interactive effect of total number of lymph nodes examined (TNLE) and the number of metastatic lymph nodes (NMLN) on survival has not been well characterized.

STUDY DESIGN: Patients operated on for colon cancer between 1998 and 2007 were identified from the Surveillance, Epidemiology, and End Results database (n = 154,208) and randomly divided into development (75%) and validation (25%) datasets. The association of the TNLE and NMLN on survival was assessed using the Cox proportional hazards model with terms for interaction and nonlinearity with restricted cubic spline functions. Findings were confirmed in the validation dataset.

RESULTS: Both TNLE and NMLN were nonlinearly associated with survival. Patients with no lymph node metastasis had a decrease in the risk of death for each lymph node examined up to approximately 25 lymph nodes, while the effect of TNLE was negligible after approximately 10 negative lymph nodes (NNLN) in those with lymph node metastasis. The hazard ratio varied considerably according to the TNLE for a given LNR when LNR $\geq$ 0.5, ranging from 2.88 to 7.16 in those with an LNR = 1. The independent effects of NMLN and NNLN on survival were summarized in a model-based score, the N score. When patients in the validation set were categorized according to the N stage, the LNR, and the N score, only the N score was unaffected by differences in the TNLE.

CONCLUSIONS: The effect of the TNLE on survival does not have a unique, strong threshold (ie, 12 lymph nodes). The combined effect of NMLN and TNLE is complex and is not appropriately represented by the LNR. The N score may be an alternative to the N stage for prognostication of patients with colon cancer because it accounts for differences in nodal samples. (J Am Coll Surg 2013;217:1090−1100. © 2013 by the American College of Surgeons)

Evaluation of an increasing number of lymph nodes (LN) has been shown to be associated with improved survival after resection of colon cancer.[1-3] Currently, it is generally accepted that at least 12 LN need to be evaluated in order to accurately assign the "true" nodal status of patients with colon cancer. This recommendation, initially made in 1991 by the working committee on staging for colorectal cancer of the World Congress of Gastroenterology, Digestive Endoscopy and Coloproctology,[4] was based on the recognition that a higher number of LNs examined resulted in a higher proportion of patients with LN metastasis.[5-7] The 12 LN recommendation has since been adopted by both the National Cancer Institute and the National Quality Forum.[8] Establishment of an LN "threshold" aims to prevent inadequate sampling and understaging, which are associated with worse survival due to stage migration and inappropriate omission of adjuvant chemotherapy.[9] Interestingly, more

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Abbreviations and Acronyms

AIC = Akaike's information criteria
HR = hazard ratio
LN = lymph node
LNR = lymph node ratio
NMLN = number of metastatic lymph nodes
NNLN = number of negative lymph nodes
TNLE = total number of lymph nodes examined

recently, several other studies have suggested that independent of LN metastatic status, a higher number of LNs examined is associated with survival—a finding that cannot be attributable to understaging.[10,11] Other mechanisms, such as differences in quality of care, patient characteristics, and tumor biology, have been suggested to explain these findings.[12,13]

Some investigators have questioned the use of 12 as an arbitrary cut-off value for the number of LNs examined. These authors have demonstrated an association between survival and the number of nodes examined ranging from 6 to 18.[3] However, the actual shape of this association and its interaction with the number of metastatic lymph nodes (NMLN), which could suggest a strong threshold effect and consequently the more appropriate cutoff, have not been characterized. More recently, other groups have proposed the use of lymph node ratio (LNR) as a better indicator of prognosis rather than simply the number of metastatic LNs.[14-18] Lymph node ratio is defined by the ratio of metastatic LNs relative to number of nodes examined. The assumption is that LNR accounts for both inadequate nodal sampling (ie, the denominator), as well as the fact that prognosis worsens with more metastatic LNs (ie, the numerator). In turn, higher weight is given to an LN metastasis in instances when fewer overall LNs are examined. Lymph node ratio also assumes that the risk of death is influenced the same way—albeit inversely—by the NMLN as by the total number of lymph nodes examined (TNLE). Although such an assumption may be reasonable, to our knowledge, this assumption has not been formally tested. The lack of methodologic data regarding the underpinnings of LNR and its true added prognostic value compared with LN status alone is important because LNR has been increasingly proposed as the optimal manner to stage patients with various malignancies.[19-21]

The purpose of this study was to define the association of the TNLE and survival among patients undergoing surgical resection of adenocarcinoma of the colon. We characterized graphically the nature of the association and, in turn, quantitatively delineated the relationship. In addition, we determined how the NMLN affects this association. Finally, we identified how the relationship between these variables affects the prognostic significance of the N stage and the LNR and suggest a new prognostic "N score" based on this observed relationship.

METHODS

Using data from the 1998 to 2007 Surveillance, Epidemiology, and End Results (SEER) database, patients with adenocarcinoma of the colon who underwent resection were identified. The SEER database collects data from 13 regional cancer registries covering 26% of the US population. Follow-up information is updated annually by each registry; data are de-identified before they become available for further analysis. Patients with a previous diagnosis of cancer, no information regarding the TNLE or NMLN, and those patients with distant metastatic disease were excluded from the analysis.

The patient data were randomly divided into a development (75%) and a validation (25%) dataset. The development dataset was used initially to determine the best model for the data and to define the shape of the association between NMLN and TNLE. Demographic and clinical variables for each sample were summarized and compared. Proportions were used to describe categorical variables. Mean and standard deviation were used for continuous variables that were normally distributed; median and range were computed otherwise. Univariate analysis of survival was performed using the Kaplan-Meier method.

Demographic and clinical variables including age, race, sex, tumor size, T category, site, and histologic differentiation were recorded. Differences in survival were compared with the log-rank test; multivariable analysis used the Cox proportional hazards model. Proportionality of hazards was verified for continuous variables divided into quartiles as well as for categorical variables. Restricted cubic spline functions were used to characterize the association between continuous variables and the risk of death. Splines are used when modeling a relationship between a continuous variable and an outcome that could be nonlinear. In brief, a spline is a smoothed polynomial function that is piecewise defined and where these "pieces" blend smoothly at the "knots" where the polynomial pieces connect. In order to determine the best model to describe the shape of the association between TNLE, NMLN, and survival, multiple models were compared. The first model (basic model) included clinic and demographic variables, as well as TNLE and NMLN as continuous (linear) variables. The second model included restricted cubic splines with 4 "knots" placed at 2, 10, 16, and 33 for TNLE, which corresponded to the 5th, 35th, 65th, and 95th percentiles, respectively; 3 "knots" were placed at 2, 8, and 12 for