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Original research

Lymphovascular and perineural invasion are associated with poor prognostic features and outcomes in colorectal cancer: A retrospective cohort study

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HIGHLIGHTS

- LVI/PNI are associated with several poor prognostic demographic and tumor variables.
- LVI/PNI are associated with lymph node positivity in colorectal cancer.
- PNI is associated with poorer overall survival (71% compared to 50% for no PNI).

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ABSTRACT

Background: Lymphovascular and perineural invasion (LVI and PNI) are associated with poor outcomes in several cancers. We sought to identify clinical variables associated with LVI and PNI in colorectal cancer (CRC) and to determine their impact on survival.

Methods: A retrospective review was performed of the National Cancer Data Base (NCDB), 2004–2011. Patients with CRC and a documented LVI or PNI status were included. Multivariate analysis was conducted to examine the associations between clinical variables and LVI/PNI, PNI and survival, and LVI/PNI and lymph node (LN) status in patients with T1 and T2 tumors.

Results: In total, 158,777 patients were included. LVI status was documented for 139,026 patients, 26.3% of whom were positive. PNI status was documented in 142,034 patients, 11.1% of whom were positive. The multivariable model identified a number of pathologic and clinical characteristics associated with the presence of LVI and PNI, including a number of features of advanced CRC. PNI was independently associated with reduced survival (HR 3.55, 95%CI 1.78–7.09). In T1 or T2 tumors, LVI and PNI were significantly associated with LN involvement.

Conclusions: LVI and PNI are associated with advanced CRC. PNI is an independent poor prognostic marker for survival in CRC. LVI and PNI are associated with LN involvement in T1 and T2 tumors. Documentation of LVI and PNI status on biopsy specimens may help in prognostication and decision-making in the management of these early tumors.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in the United States, accounting for an estimated 136,830 new cases and 50,310 deaths in 2014 [1]. Currently, the prognosis and treatment options are determined based on histopathological variables which have a direct relationship with survival and recurrence. The American Joint Committee on Cancer (AJCC) staging classification for CRC incorporates some of these variables (i.e. tumor depth, lymph node involvement, and the presence of metastatic disease) and considers other important variables simply as "prognostic factors" [2]. Thus, patients who fall

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within a single AJCC stage can have widely variable clinical courses and oncologic outcomes. As surgical and chemotherapy options expand, it becomes increasingly important to distinguish between low risk patients who will do well with minimal intervention and those who are at high risk of recurrence or progression who might benefit from radical surgery and adjuvant treatments.

Two tumor specific variables shown to be associated with survival in CRC are lymphovascular invasion and perineural invasion. Lymphovascular invasion (LVI) refers to the involvement of small lymphatic or blood (typically venous) vessels by tumor [3]. Perineural invasion (PNI) refers to the growth of tumor in, around, and through nerves and nerve sheaths [4,5]. Both LVI and PNI have been shown to be markers for poor survival in colorectal cancer, yet there is not universal agreement regarding their incorporation in staging and management decisions. The primary objective of this study was to identify clinical and pathological variables associated with LVI and PNI in colorectal cancer and to subsequently determine their impact on survival.

2. Methods

The American College of Surgeons National Cancer Data Base (NCDB) was searched to identify patients from 2004 to 2011 with a pathological diagnosis of appendix, colon, or rectal adenocarcinoma who had a documented LVI or PNI status (positive or negative) based on histological findings (surgery or biopsy specimen). Patients were queried from the colon, rectosigmoid and rectal Participant User Files (PUF) of the NCDB. This study was compliant with guidelines established by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) criteria [6].

Data collected included patient variables (age, sex, race, income, education level, geographic setting, insurance, distance from treating hospital, comorbidities), tumor variables (year of diagnosis, primary site, grade, size, clinical T/N/M stage, pathological T/N/M stage, preoperative CEA, microsatellite instability (MSI) status, KRAS status, loss of heterozygosity (LOH), resection margins) and treatment variables (treating facility location and type, surgical procedure, chemotherapy, radiation).

Education level is captured in the NCDB as the proportion of residents in a patient's zip code who did not graduate high school; for the purpose of our analysis, we divided this into four categories of educational attainment based on the proportion who did not graduate high school: lowest (>29%), low (20–28.9%), high (14.1–19.9%), and highest (<14%).

Comorbidities are captured in NCDB as the Charlson/Deyo Comorbidity Score. This score is based on a number of reported ICD-9-CM secondary diagnosis codes and is reported as a single cumulative summary score. Each comorbid condition is assigned a weight based on adjusted risk of mortality or resource use; the sum of all weights results in a single comorbidity score for a patient. Because of the small proportion of cases with a Carlson/Deyo score greater than 2, the NCDB reports scores as 0, 1, or 2 (greater than 1).

The main outcome was the presence of LVI or PNI in the surgical or biopsy specimen. Secondary outcomes included overall survival in relation to PNI status and lymph node involvement in relation to LVI and PNI status specifically in T1 and T2 tumors. The inclusion of PNI and LVI status as variables in the NCDB began in 2004 and 2010, respectively, while vital status is available only for patients diagnosed before 2006. Thus, all cases with a known LVI status captured in the database were diagnosed in 2010 onward and survival analysis could not be performed in relation to LVI status for this reason.

Patient, tumor and treatment characteristics were reported using the mean, median and standard deviation for continuous variables and using frequencies and relative frequencies for categorical variables. Comparisons were made using the Kruskal-Wallis and chi-square tests for continuous and categorical variables, respectively.

The association between clinical and demographic characteristics and each of LVI and PNI status were evaluated using logistic regression models and presented as odds ratios with 95% confidence intervals. Multivariate logistic regression models were used to identify potential independent predictors of both LVI and PNI status. A multivariate Cox regression model was used to evaluate the association between PNI and overall survival while adjusting for confounding variables. Multivariate logistic regression models were used to evaluate the association between LVI and PNI status and lymph node status in T1 and T2 tumors while adjusting for confounding variables. The variables for the final models were obtained using the backward selection method (alpha exit = 0.05) and fit using Firth's penalized function.

All analyses were conducted in SAS v9.4 (Cary, NC) at a significance level of 0.05.

3. Results

There were 659,465 appendiceal, colon, rectosigmoid or rectal adenocarcinoma cases identified in the NCDB between 2004 and 2011. Of these, 158,777 patients (24.1%) had a documented LVI and/or PNI status (positive or negative). The characteristics of the study cohort are summarized in Table 1. In total, 158,777 patients were included. Most patients were treated at community or academic comprehensive cancer programs in metropolitan settings. Median age was 60.3 years. The vast majority of patients were white and had government or private health insurance. Tumors were predominantly well- or moderately-differentiated and larger than 5 cm in size; nearly one-fifth were located in the rectum. Disease stage was fairly evenly distributed among AJCC pathological stage groups I, II, and III, while distant metastases were present at diagnosis in 13.6% of cases. Surgery, chemotherapy, and radiation treatment were received by 89.2%, 40.4%, and 13.5% of patients, respectively.

LVI status was documented for 139,026 patients, 26.3% of whom were positive. PNI status was documented in 142,034 patients, 11.1% of whom were positive. Of 122,465 patients with both variables documented, 7.6% had both LVI and PNI present. LVI and PNI were significantly associated with one another ($p < 0.001$). LVI was present in 25.1%, 28.1%, 27.4% and 18.1% of tumors originating in the appendix, colon, rectosigmoid, and rectum, respectively. In comparison, PNI was less frequently identified at all sites: 11.1% in the colon, 13.1% in the rectosigmoid, and 10.2% in the rectum. PNI status was not available for appendiceal tumors.

On multivariate analysis, demographic variables associated with the presence of LVI were treatment at an academic center, treatment at a facility in the mid-Atlantic region, living in a less educated neighborhood, and living in a metropolitan area (Table 2). Black race predicted a lower likelihood of LVI. Clinical variables associated with LVI were higher tumor grade, size >4 cm, T3 or T4 tumors, LN involvement, and the presence of distant metastases. The presence of LVI was associated with a higher likelihood of receiving chemotherapy but a lower likelihood of receiving radiation therapy.

Demographic variables associated with the presence of PNI were treatment at an academic center, treatment at a facility in the mid-Atlantic region, male gender, and black or Asian race (Table 3). Clinical variables associated with PNI were primary site in the rectosigmoid or rectum, higher tumor grade, increasing T stage, LN involvement, and the presence of distant metastases. Tumors with PNI were more likely to have positive margins after resection and more likely to receive chemotherapy but less likely to receive radiation.