Original research

Predictors of circumferential resection margin involvement in surgically resected rectal cancer: A retrospective review of 23,464 patients in the US National Cancer Database

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HIGHLIGHTS

- Nearly half of patients with CRM+ did not receive neoadjuvant therapy and nearly one-third did not receive any radiation.
- Factors predicting CRM+ included lack of insurance, higher grade, advanced stage, undergoing APR, and receiving radiation.
- CRM+ patients who did not receive neoadjuvant therapy had earlier disease than those who were CRM+ after neoadjuvant therapy.
- These findings suggest potential missed opportunities to achieve CRM− and indicate areas to improve rectal cancer care.

ARTICLE INFO

ABSTRACT

Introduction: The circumferential resection margin (CRM) is a key prognostic factor after rectal cancer resection. We sought to identify factors associated with CRM involvement (CRM+).
Methods: A retrospective review was performed of the National Cancer Database, 2004—2011. Patients with rectal cancer who underwent radical resection and had a recorded CRM were included. Multivariable analysis of the association between clinicopathologic characteristics and CRM was performed. Tumor <1 mm from the cut margin defined CRM+.
Results and discussion: Of 23,464 eligible patients, 13.3% were CRM+. Factors associated with CRM+ were diagnosis later in the study period, lack of insurance, advanced stage, higher grade, undergoing APR, and receiving radiation. Nearly half of CRM+ patients did not receive neoadjuvant therapy. CRM+ patients who did not receive neoadjuvant therapy were more likely to be female, older, with more comorbidities, smaller tumors, earlier clinical stage, advanced pathologic stage, and CEA-negative disease compared to those who received it.
Conclusions: Factors associated with CRM+ include features of advanced disease, undergoing APR, and lack of health insurance. Half of CRM+ patients did not receive neoadjuvant treatment. These represent cases where CRM status may be modifiable with appropriate pre-operative selection and multidisciplinary management.

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1. Introduction

The circumferential resection margin (CRM) is an important predictor of outcomes in rectal cancer surgery. An involved CRM is associated with increased local recurrence, distant metastasis and poorer overall survival [1—3]. Whether positive margin status is due to direct tumor or lymphatic spread beyond the mesorectum boundary or as a result of inadequate surgical technique, it continues to correlate with worse outcomes. While we continue to make progress on better clinical staging utilizing high definition imaging, such as pelvic MRI, it may also be beneficial to identify other factors that put patients at risk for a positive CRM.

The aim of this paper was to identify clinical and demographic variables associated with CRM involvement on a population level.

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2. Materials and methods

After approval from the institutional review board, the American College of Surgeons (ACS) a retrospective review of the National Cancer Database (NCDB) was performed to identify patients from 2004 to 2011 with a pathologic diagnosis of rectal adenocarcinoma who underwent radical surgery and had a documented CRM based on histology. This time period was selected because documentation of CRM status in the NCDB began in 2004. Patients were queried from the rectal cancer Participant User Files (PUF) of the NCDB. For adenocarcinoma, the following International Statistical Classification of Diseases (ICD O-3) codes were used: 8140—8148, 8200, 8260—8263, and 8480—8496. The sample size was determined by the inclusion of all eligible cases in the database within the specified study period.

Data was collected regarding patient, disease, and treatment variables. Patient variables included age, gender, race, geographic setting, insurance coverage, and comorbidities. Disease variables included year of diagnosis, grade, size, clinical TNM stage, pathological TNM stage, pre-operative CEA, presence of tumor deposits, and perineural invasion (PNI). Treatment variables included treating facility type, surgical procedure, chemotherapy, radiation, and treatment sequence (adjuvant/neoadjuvant).

The main outcome was a documented positive (involved) CRM, defined as tumor <1 mm from the cut specimen margin. The CRM was documented in some cases as a numeric distance (continuous) and in other cases as a categorical status (involved or clear). For the purpose of our analysis and to incorporate as much data as possible, the CRM was converted to a categorical variable for all patients (CRM+ or CRM−).

Patient, disease, and treatment characteristics were reported using the mean, median and range 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.

A multivariable analysis of the association between patient characteristics and CRM status was conducted using logistic regression. The variables for the model were obtained using the backward selection method (alpha exit = 0.05) and the final model was fit using Firth's method. From the estimated model, odd ratios and corresponding confidence intervals were obtained.

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

This work has been reported in line with the STROBE criteria [4].

3. Results

A total of 152,543 cases of rectal adenocarcinoma were identified in the NCDB between 2004 and 2011. Of these, 89,189 patients underwent radical surgery. A CRM status was documented for 23,464 patients (26.3%) and these patients were included in the study. The characteristics of the study cohort are summarized in Table 1. Most patients were treated at community or academic comprehensive cancer programs in metropolitan settings. Median age was 63.0 years. The vast majority of patients were white, had few or no comorbidities, and had government or private health insurance. Tumors were predominantly moderately-differentiated and smaller than 5 cm in size. The majority of cases were clinical stage II or III disease, while distant metastases were present at diagnosis in 9.3% of cases. Neoadjuvant chemotherapy, radiation, and chemoradiation were administered to 3.5%, 5.0% and 45.4% of patients, respectively. Adjuvant radiation and chemoradiation were administered to 3.3% and 8.3% of patients, respectively (Table 2).

There were 3131 patients (13.3%) with a positive CRM (CRM+). Of these, 54.2% received neoadjuvant therapy in the form of chemotherapy (4.5%), radiation (2.5%), or both (47.2%). Adjuvant radiation and chemoradiation were administered in 2.8% and 12.2% of CRM+ patients, respectively (Table 2). Nearly one-third of CRM+ patients received no radiation as part of their treatment. The most common reasons given for not administering radiation among CRM+ patients were: it was not part of planned treatment (81.1%), it was contraindicated due to patient risk factors (6.9%), or it was refused by the patient or substitute decision-maker (5.8%).

On univariable analysis, factors associated with CRM+ were lack of health insurance, larger tumor size, higher tumor grade, more advanced pathologic TNM stage, lymph node involvement, elevated CEA, perineural invasion, presence of tumor deposits, undergoing abdominoperineal resection (APR), and receiving chemotherapy or radiation (Table 1).

On multivariable analysis, variables independently associated with CRM+ were lack of health insurance, diagnosis in the latter part of the study period, higher tumor grade, advanced disease stage, undergoing APR, and receiving radiation at any point during treatment (Table 3).

Compared to patients who were CRM+ after neoadjuvant therapy, CRM+ patients who did not receive neoadjuvant therapy were more likely to be female, older, with a greater number of comorbidities, earlier clinical stage, and CEA negative disease. They were also more likely to undergo partial proctectomy rather than a more extensive procedure. On final pathology, they were more likely to have T4, node positive, and PNI positive disease (Table 4).

4. Discussion

The pathologic CRM is known to be a critical factor in the prognosis of rectal cancer [1]. CRM involvement is an independent predictor of increased risk of both local and distant recurrence and decreased survival [2,3]. Despite its importance in prognostication and determining the need for adjuvant therapy after surgery, only a minority of rectal adenocarcinoma cases captured in the NCDB had a reported CRM since the start of item collection in 2004. The proportion of cases with documented CRM did increase in the latter part of the study period (which likely explains the increased frequency of CRM positivity in more recent years) but remained low overall at 26.3%.

CRM involvement is determined in large part by variables related to inherent tumor biology. We identified tumor TNM stage, higher tumor grade, and undergoing APR as factors independently associated with the risk of CRM involvement. Previous studies have also identified these factors [3,5—10] in addition to tumor size [6,8,11], distance above the anal verge [6], and the presence of lymphovascular or perineural invasion [6,7,9,10]. The potential to modify these variables is limited, but this does not imply that rates of CRM involvement cannot be reduced. The management of rectal cancer in the current era is complex, incorporating high quality imaging and multidisciplinary coordination of surgery, chemotherapy, and radiation. These components, in conjunction with correct total mesorectal excision (TME) technique, are critical to good outcomes. The increasing availability and utilization of high resolution imaging, particularly pelvic MRI, has allowed for evaluation of the tumor in relation to the mesorectal fascia (predicted CRM) [12]. This has enhanced the selection of patients who may benefit from strategies to achieve a negative CRM, including administration of neoadjuvant therapies and improved surgical planning [13]. Traditionally, efforts to downstage locally advanced rectal cancer have centered on the use of radiation in combination with 5-FU as a radiosensitizer. Increasingly, however, interest has turned to the use of full systemic chemotherapy with or without radiation [14—17]. Preliminary results of a multi-center randomized trial recently presented at the 2015 American Society of Clinical