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Original Research

Assessing the prognostic value of carcinoembryonic antigen levels in stage I and II colon cancer

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Abstract ***Background:*** Previous studies have shown that elevated preoperative carcinoembryonic antigen (CEA) levels are associated with worse prognosis in patients with colon cancer. These studies compared the prognosis of patients with elevated versus normal CEA levels. We sought to assess the prognostic role of increasing levels of CEA in stage I and II patients who did not receive adjuvant chemotherapy.
Methods: Using the National Cancer Database (2004–2014), we identified 45,449 individuals with stage I and II colon cancer who did not receive adjuvant chemotherapy and had preoperative CEA levels available. We estimated the optimal cut-point of CEA levels to predict survival using the Youden Index. Cox proportional hazards were used to compare individuals with CEA levels above and below the defined cut-point. In a secondary analysis, we examined the prognostic value of stage, age and tumour location.
Results: The optimal preoperative CEA cut-point to predict survival was 2.35 ng/mL. The adjusted HR for overall survival among individuals with preoperative CEA levels at or above

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compared with below 2.35 ng/mL was 1.56 (95% CI, 1.49–1.64). Individuals with CEA levels below 2.35 ng/mL had higher 3-year survival rates compared with those with CEA levels above 2.35 ng/mL (79.7% vs 64.5%, respectively).
Conclusions: Preoperative CEA levels at or above 2.35 ng/mL, found within the normal range, may be used to identify stage I and II colon cancer patients harbouring worse prognosis.

1. Introduction

Colorectal cancer is the third most common cancer and the second-leading cause of cancer-related deaths in men and women combined in the United States [1], with nearly 75% of patients diagnosed with non-metastatic and therefore potentially curable disease (i.e. stage I, II or III).

In colon cancer, following curative surgery, it is standard practice to administer adjuvant chemotherapy for stage III disease. For stage II disease, several risk factors for recurrence have been used to justify adjuvant chemotherapy, including T4 primary, tumour grade, inadequate lymph node sampling (<12), lymphovascular or perineural invasion, and clinical presentation with obstruction or perforation. However, the predictive function of those features has not been proven. Prior studies have estimated that approximately 20% of stage II colon cancer patients receive adjuvant chemotherapy [2]. Adjuvant therapy is generally not offered in stage II disease lacking high-risk features nor in stage I disease.

Carcinoembryonic antigen (CEA) is a complex glycoprotein involved in cell adhesion. CEA is secreted by a variety of solid tumours, including 90% of colorectal cancers [3]. Previous studies have shown that elevated preoperative CEA levels are associated with worse prognosis, including among patients with stage I and II disease [4–7]. These studies did not define a specific cut-point of CEA levels that could predict worse survival, but rather compared the prognosis of patients with elevated vs normal CEA levels. Of note, normal CEA levels vary among institutions, ranging between 3.0 and 5.0 ng/mL, and are not stage or disease specific.

The aim of the present study was to assess the prognostic role of increasing levels of CEA in stage I and II patients who did not receive adjuvant chemotherapy.

2. Methods

2.1. Data source and patient population

Our cohort was derived from the National Cancer Database (NCDB), a hospital-based cancer registry, from 2004 to 2014. The NCDB captures data on 70% of cancer diagnoses in the United States from >1400 hospitals with cancer programs accredited by the American College of Surgeons' Commission on Cancer and American Cancer Society [8]. All individuals with pathological stage I (T1-2N0M0) and stage II (T3-4N0M0) colon cancer who did not receive adjuvant chemotherapy were included in the analysis. Individuals with rectal cancer were excluded from the analysis, as perioperative treatment of rectal cancer differs from that of colon cancer.

2.2. Variables definition

Covariates included age, sex, race, patient comorbidities (Charlson-Deyo comorbidity condition, CDCC) [9,10], tumour location, tumour grade, and preoperative CEA levels. Race and ethnicity were used to create a composite variable categorised as white, African American or other/unknown. CDCC is defined as an index which predicts mortality for a patient who may have a range of comorbid conditions. Tumour location was defined either as proximal or distal. Proximal tumours included ICD-10 codes C18.0–18.3, and distal tumours included ICD-10 codes C18.5–18.7 and C19.9. Tumours located at the transverse colon were not designated as either proximal or distal. Tumour grade was defined as well differentiated, moderately differentiated, poorly differentiated or undifferentiated.

2.3. Outcomes definition

The primary outcomes were 3-year survival and overall survival, measured from the time of cancer diagnosis until death of any cause or last follow-up.

2.4. Statistical analysis

We estimated the optimal cut-point of CEA levels to predict survival using a mathematical method, the Youden Index, which is a frequently used summary measure of the receiver operating characteristic curve, that measures both the effectiveness of a diagnostic marker and enables the selection of an optimal cut-point [11,12]. Cox proportional hazards were used to compare individuals with CEA levels above and below the newly defined as well as the commonly used (5 ng/mL) cut-point. The Cox model was adjusted to all the above