Original Study

Stage-based Variation in the Effect of Primary Tumor Side on All Stages of Colorectal Cancer Recurrence and Survival

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Abstract

Although the predictive and prognostic effect of primary tumor side in metastatic colorectal cancer is now widely accepted, it is poorly defined for early-stage disease. In the present analysis of > 6500 patients, we found stage-by-stage differences in survival outcomes according to the primary tumor location, which was partially attributable to differences in survival after recurrence. However, the primary tumor location did not influence the benefit of adjuvant chemotherapy.

Background: Multiple studies have defined the prognostic and potential predictive significance of the primary tumor side in metastatic colorectal cancer (CRC). However, the currently available data for early-stage disease are limited and inconsistent. **Materials and Methods:** We explored the clinicopathologic, treatment, and outcome data from a multisite Australian CRC registry from 2003 to 2016. Tumors at and distal to the splenic flexure were considered a left primary (LP). **Results:** For the 6547 patients identified, the median age at diagnosis was 69 years, 55% were men, and most (63%) had a LP. Comparing the outcomes for right primary (RP) versus LP, time-to-recurrence was similar for stage I and III disease, but longer for those with a stage II RP (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.52-0.90; $P < .01$). Adjuvant chemotherapy provided a consistent benefit in stage III disease, regardless of the tumor side. Overall survival (OS) was similar for those with stage I and II disease between LP and RP patients; however, those with stage III RP disease had poorer OS (HR, 1.30; 95% CI, 1.04-1.62; $P < .05$) and cancer-specific survival (HR, 1.55; 95% CI, 1.19-2.03; $P < .01$). Patients with stage IV RP, whether de novo metastatic (HR, 1.15; 95% CI, 0.95-1.39) or relapsed post–early-stage disease (HR, 1.35; 95% CI, 1.11-1.65; $P < .01$), had poorer OS. **Conclusion:** In early-stage CRC, the association of tumor side and effect on the time-to-recurrence and OS varies by stage. In stage III patients with an RP, poorer OS and cancer-specific survival outcomes are, in part, driven by inferior survival after recurrence, and tumor side did not influence adjuvant chemotherapy benefit.

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Introduction

Multiple series have demonstrated the prognostic effect of the primary tumor side in patients with metastatic colorectal cancer (mCRC).[1-4] Although multiple clinical, pathologic, and molecular differences have been described when comparing right- versus left-sided cancers, the relative contribution of each to side-based differences in overall survival (OS) for patients with mCRC remains uncertain.

The effect of primary tumor side in early-stage CRC remains relatively underexplored. A recent meta-analysis of 66 studies found improved OS outcomes for early-stage disease patients with a left primary (LP) tumor (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.79-0.84; $P < .001$).[1] However, stages I, II, and III were combined in that analysis. Three large Surveillance, Epidemiology, and End Results (SEER) program data studies, a German study, and a Canadian population registry study have also evaluated the effect of primary tumor side in early-stage disease.[5-9] Although they mostly found poorer OS for stage III patients with a right primary (RP), conflicting results for those with stage II disease were reported according to primary tumor side, with either no difference or improved OS outcomes with RP disease. Furthermore, these series did not report the recurrence-free survival (RFS) outcomes.

The VICTOR and QUASAR2 studies evaluated the RFS outcomes in a combined analysis of stage II and III colon cancer patients. Although no difference was found in RFS according to primary tumor side, RP patients had inferior OS compared with those with a LP.[10] The investigators concluded that this difference resulted from the effect of the primary tumor side on postrecurrence survival (PRS).[10]

Patients with early-stage disease have multiple endpoints of interest, especially because the OS analysis can potentially be confounded by non–cancer-related deaths, the relative benefit of adjuvant therapy, and PRS. To fully understand the effect of tumor side in early-stage CRC, a by-stage analysis that examines the time-to-recurrence (TTR), RFS, PRS and OS is required. We conducted these analyses using a comprehensive clinical registry with prospectively collected data and additional detailed information on known prognostic factors and treatment administered in the adjuvant setting.

Materials and Methods

Source Data

Using the Australian Comprehensive Cancer Outcomes and Research Database (ACCORD),[11] consecutive patients with a diagnosis of all stages of colorectal cancer were identified across 6 Australian hospitals from January 2003 to December 2016. The ACCORD is a dedicated and comprehensive database of prospectively clinician-collected data on clinical characteristics, pathologic information, surgical procedures, systemic treatment where relevant, and long-term outcomes. Patients with multiple primary tumors, indeterminate primary location, appendiceal cancers, and rectal tumors who underwent neoadjuvant therapy were excluded from the analysis.

Statistical Analysis

A total of 8253 patients with a diagnosis of CRC were identified, of whom 6547 (79%) were eligible for the present study (Figure 1). Tumors at and distal to the splenic flexure were considered a LP.

The healthcare group at IBM Research Australia provided the data analysis. A targeted data export was undertaken from the ACCORD database using the Lifelines Python library[12] to build Cox proportional hazards regression models for different cohorts and survival outcomes. Fields were not normalized and an L2 penalizer of 0.01 was applied. Preprocessing was applied to the records to map all missing values to a standard value. In addition, specific distinctions were abandoned for the sake of comparability and ensuring adequate data volumes for categorical values.

We performed univariate analyses on the fields of interest known from the reported data to potentially affect survival outcomes. These factors included age, sex, primary tumor side, Australian Clinicopathological Staging system (converted to the American Joint Committee on Cancer staging system for the present report), tumor differentiation, lymphovascular invasion, year of diagnosis, T stage, N stage, and number of lymph nodes examined. If the fields were not subsumed by other fields, they were also included in the multivariate analysis. The multivariate analysis excluded patients with missing data. Significance was determined using the log-rank test.

We calculated the HRs for tumor side for different subgroups by repeating the multivariate Cox analyses using only data for the relevant subgroup. Adjusted survival curves were created by averaging the predicted survival functions of the relevant instances, in accordance with the report by Chang et al.[13]

Results

General Demographic Data

Of the 6547 eligible patients where initial stage was known, 1104 (17%) had stage I disease, 1916 (29%) had stage II, 1767 (27%) had stage III, and 1513 (23%) had de novo stage IV disease. Across all stages, 4111 (63%) had a LP and 2436 (37%) had an RP, with a significantly greater prevalence of RP tumors (43% vs. 33%; $P < .001$) among women. Patients with an RP also had a higher median age at diagnosis (72 vs. 67 years; $P < .001$; Table 1).

Figure 1 Patient Inclusion and Exclusion Algorithm