Primary Tumor Location and Survival in the General Population With Metastatic Colorectal Cancer

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Abstract

Recent evidence from clinical trials suggests that primary tumor location in patients with metastatic colorectal cancer correlates with differential outcomes. This large population-based cohort study involving 1947 patients confirms that primary tumor location is an independent prognostic variable regardless of age, performance status, and comorbid illness in the real-world patients with metastatic colorectal cancer. Patients with right-sided tumor have inferior survival compared with patients whose tumors originate in the left side of the large intestine.

Background: Recent evidence from clinical trials suggests that primary tumor location in patients with metastatic colorectal cancer correlates with differential outcomes, and patients with tumors originating in the right side of the colon have inferior survival. We conducted a large population-based cohort study using individual patient data to confirm the prognostic importance of primary tumor location in the general population with metastatic colorectal cancer. **Methods:** A cohort of 1947 patients who were diagnosed with metastatic colorectal cancer from 1992 to 2010 was studied. Ascending and transverse colon cancers were defined as right-sided tumors. Cox proportional multivariate analyses were done to determine prognostic significance of primary tumor location. **Results:** The median age was 70 years (interquartile range, 60-78 years), and the male to female ratio was 1.3:1. Twenty-nine percent had World Health Organization performance status of > 1. Seven-hundred and seventy (39%) patients had right-sided tumors, and 908 (47%) received chemotherapy. The median overall survival of patients with right-sided tumors was 14 months (95% confidence interval [CI], 12.7-15.3 months) compared with 20.5 months (95% CI, 18.5-22.5 months) of patients with left-sided tumors ($P < .001$). On multivariate analysis, right-sided tumors (hazard ratio [HR], 1.40; 95% CI, 1.20-1.60), no metastasectomy (HR, 2.40; 95% CI, 1.90-2.90), intact primary tumor (HR, 1.60; 95% CI, 1.32-1.90), an elevated carcinoembryonic antigen level (HR, 1.54; 95% CI, 1.30-1.90), lack of combination chemotherapy (HR, 1.52; 95% CI, 1.31-1.80), stage IVb disease (HR, 1.50; 95% CI, 1.17-1.86), leukocytosis (HR, 1.44; 95% CI, 1.28-1.73), and World Health Organization performance status > 1 (HR, 1.30; 95% CI, 1.10-1.55) were correlated with inferior survival. **Conclusions:** Our results confirm that individuals with metastatic colorectal cancer and right-sided tumors who received chemotherapy have inferior survival independent of other known prognostic variables. Future studies are required to understand the underlying pathophysiology.

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Introduction

Various clinical and pathologic markers and interventions are known to affect the outcomes of patients with metastatic colorectal cancer. Among them, the patient's age, performance status, and extent of the metastatic disease (for example, number of metastases sites) have been identified as important prognostic markers that

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correlate with survival.[1,2] Furthermore, molecular profiles of the tumors such as the presence of the BRAF mutation (noted in about 5% to 11% of metastatic colorectal cancer) are associated with differential outcomes.[3] Various interventions such as chemotherapy, biological agents, metastasectomy, and possibly primary tumor resection have contributed to prolonging the longevity of patients with metastatic colorectal cancer.[1] Emerging data suggests that that the primary tumor location may impact the outcomes of patients with metastatic colorectal cancer.[4-8] Several reports have shown that patients with tumors originating in the right side of the colon tend to have inferior survival.[5-8] For example, a retrospective analysis of a large randomized trial that evaluated cetuximab or bevacizumab as a first-line therapy in combination with chemotherapy, for patients with metastatic colorectal cancer, revealed that patients with KRAS wild-type right-sided primary tumors had a median overall survival (OS) of 19.4 months compared with an OS of 34.3 months of patients with left-sided tumors (hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.32-1.84).[5,9] Likewise, retrospective analyses of CRYSTAL (Cetuximab Combined with Irinotecan in First-line Therapy for Metastatic Colorectal Cancer) and FIRE-3 (FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab for metastatic colorectal cancer) trials that examined first-line cetuximab-based combination therapy showed that patients with right-sided tumors had inferior survival compared with the patients with left-sided metastatic disease.[6]

It is important to know that most emerging information about the prognostic significance of the location of the primary tumor came from retrospective analyses of first-line clinical trials in patients with metastatic colorectal cancer. There is limited information available about the prognostic significance of the primary tumor location in real-world patients. We conducted this large population-based cohort study using individual patient data to confirm the prognostic importance of the primary tumor location in the general population with metastatic colorectal cancer.

Methods

Study Population

The University of Saskatchewan's Research Ethics Board approved the study. Patients with newly diagnosed synchronous metastatic adenocarcinoma of the colon and rectum, from January 1992 to December 2010, living in the province of Saskatchewan, Canada, comprised the study cohort. Patients with neuroendocrine tumors, melanoma, lymphoma, gastrointestinal stromal tumors, and other histologic malignant diagnoses of colon and rectum were excluded. Ascending and transverse colonic tumors (up to the splenic flexure) were defined as right-sided tumors. All the other tumors arising from descending colon, sigmoid colon, and rectum were defined as left-sided tumors. The Saskatchewan Cancer Registry database, which is prospectively collected, was used to identify eligible patients. A trained research associate reviewed and recorded all individual patient data. The data entry was closed in June 2014. All patients were followed until the data entry closure date.

Statistical Analysis

Descriptive statistics were used to estimate baseline characteristics of the study cohort. The χ^2 and t tests were performed to compare the studied groups. The Kaplan-Meier method was used to calculate survival, and log-rank tests were performed to compare survival distribution of the studied groups. OS was defined as "time from the diagnosis of metastatic colorectal cancer to death from any cause." Patients who were either (1) alive at the data entry closure date or (2) were lost to follow up were censored at the last date that they were known to be alive. Multivariate analyses were performed to determine the prognostic significance of the primary tumor location in patients with metastatic colorectal cancer treated with chemotherapy. The Cox proportional hazard model was used, and the HRs and their 95% CIs were estimated. The following variables were examined with respect to their prognostic significance: age (< 70 vs. ≥ 70 years), gender, major comorbid illness as per Charlson Comorbidity Index, World Health Organization (WHO) performance status (< 2 vs. ≥ 2), active smoking, leukocytosis, elevated carcinoembryonic antigen (CEA) level (≥ 5 vs. < 5 mcg/L), site (right vs. left), grade (III vs. <III), extra-hepatic metastases, stage (stage IVa vs. IVb), mucinous tumor, combination chemotherapy, primary tumor resection, metastasectomy, radiation therapy, and time period ($\geq$ year 2006 vs. < year 2006). The log-log survival curves were used for the assessment of the proportional hazards assumption. All significant variables with $P < .05$ were examined, in a multivariate model, to assess their correlation with survival. During model building, the likelihood ratio test and t test were used to assess independent prognostic significance of the variable of interest. Testing for interactions with the disease site and the significant variables in univariate analyses was performed. A 2-sided P-value of $< .05$ was considered to be statistically significant. SPSS version 24.0 was used for statistical analysis (SPSS Inc, Chicago, IL).

Results

Demographic Information

A total of 1947 eligible patients were identified (Figure 1). Thirty-nine percent of patients had right-sided tumors, and 61% had left-sided tumors (Table 1). The median age was 70 years (interquartile range, 60-78 years), and the male to female ratio was 1.3:1. Twenty-nine percent of patients had WHO performance status of > 1, 37% had stage IVb disease, and 47% received chemotherapy. Fifty percent of women, compared with 38% of men, were diagnosed with a right-sided primary tumor ($P < .001$). In addition, a significant difference was noted between the 2 groups with respect to age, performance status, mucinous disease, liver metastases, and grade 3 tumors. Overall, 43% patients with right-sided tumor received chemotherapy compared with 49% of patients with left sided-tumors ($P < .05$).

Follow-up and Survival

The median follow-up period was 17.9 months (interquartile range, 9-33.7 months). The median OS of 908 patients with metastatic colorectal cancer who received any type of chemotherapy was 17.5 months (95% CI, 16.4-18.6 months). Patients with right-sided tumors had a median OS of 14.0 months (95% CI, 12.7-15.3 months) compared with 20.5 months (95% CI, 18.5-22.5 months) for patients with left-sided tumors ($P < .001$) (Figure 2A). The median OS of a subgroup of patients who were treated with bevacizumab-based chemotherapy for right-sided