Colorectal Cancer Survival: An Analysis of Patients With Metastatic Disease Synchronous and Metachronous With the Primary Tumor

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Abstract

Using the population-based South Australian Clinical Registry for Metastatic Colorectal Cancer, we analyzed differences in survival between patients with metachronous and synchronous presentation of metastatic colorectal cancer. Patients with metachronous presentation have a longer overall survival than those with synchronous presentation, independent of treatment received. These results highlight the prognostic significance of metachronous vs. synchronous presentation.

Background: Whether metastatic colorectal cancer (mCRC) that presents synchronously with the primary lesion behaves differently from mCRC that appears metachronously to the primary disease is not clear. **Patients and Methods:** The South Australian Clinical Registry for mCRC collects data for patients diagnosed after February 2006. Data from 2502 patients, available on October 22, 2012, were analyzed according to stage at initial diagnosis (SAID) to compare outcomes between metachronous tumors (MTs) (stages I, II, III) and synchronous tumors (STs) (stage IV). Overall survival (OS) was calculated from the date of mCRC diagnosis. **Results:** Patients with ST had more liver-only metastases, and patients with MT had more lung-only, non-lung and non-liver, and non-lung metastases. The median time to recurrence differed significantly according to SAID: stage I, 49.3 mo (n = 29), stage II, 25.2 mo (n = 346) and stage III, 18.4 mo (n = 497). The median OS was longer for patients with MT than for those with ST (19.0 vs.14.9 mo, $P = .003$). For patients who received any treatment for mCRC, the OS was longer for patients with MT than for those with ST (19.2 vs. 15.3 mo, $P = .005$). In patients who received only chemotherapy for mCRC, the median OS was longer for patients with MT than for those with ST (15.2 vs. 9.9 mo, $P < .0001$). No difference in OS between the MT and ST groups for patients who did not receive treatment for mCRC (1.6 vs. 2.6 mo; $P = .95$). **Conclusion:** Patients with MT have a longer OS than those with ST, independent of treatment. Classification of patients according to whether they have metachronous or synchronous presentation of mCRC is prognostic. These results may add further support for population screening with the aim to reduce *de novo* metastatic disease.

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Introduction

Metastatic colorectal cancer (mCRC) is the fourth most common cause of cancer-related death worldwide, with the highest rates estimated in Australia and New Zealand, at 33.0 deaths per 100,000 persons.[1] The cancer stage at initial diagnosis (SAID) correlates with prognosis, with 5-year overall survival (OS) of 93.2%, 84.7%, 72.2%, 83.4%, 61.4%, 44.3%, and 8.1% for stages I, IIA, IIB, IIIA, IIIB, IIIC, and IV colorectal cancer (CRC), respectively.[2] Reported survival outcomes calculated from the date of initial diagnosis do not give insight into any effect

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resulting from CRC screening programs[3,4] for metachronous tumors (MTs), in other words, recurrent stage I, II, and III, compared with synchronous tumors (STs), in other words, metastatic disease is present at initial diagnosis.

Aside from potential early diagnosis and stage migration, differences in the biology based on SAID may also impact outcome. In early-stage CRC, stage II and III tumors appear to have different biology. Aside from lymph node status, stage II tumors are larger at diagnosis, independent of T-stage, compared with stage III tumors, particularly right-sided colon cancer (CC) with high microsatellite instability (MSI).[5] MSI due to somatic mutations in mismatch repair genes occur in 15% to 20% of CRCs, affecting 17% of stage II and 12% of stage III CRCs.[6] High MSI in stage II CRC is predictive of a better prognosis, with no additional benefit from 5-fluorouracil therapy,[7] whereas stage III CRCs still derive a benefit from adjuvant chemotherapy.[8] High MSI tumors are more proximal, poorly differentiated, mucinous, and show marked lymphocytic infiltration.[9]

Furthermore, there are differences in the efficacy of treatments according to SAID that may reflect this biological variation. Adjuvant chemotherapy for stage III CRC improves progression-free survival and OS[10]; however, its role in stage II CRC remains controversial,[11] and the survival benefit is limited to high-risk groups.[12] Also, drugs such as irinotecan,[13,14] bevacizumab,[15,16] and cetuximab[17,18] provide an OS benefit only for stage IV CRC. These differences in treatment efficacy speak to the underlying differences in tumor biology for the different SAIDs.

With the establishment of population-based CRC screening programs, we expect to see more patients with earlier SAID.[3,4] Given the apparent biological differences, we may see a difference in survival between patients with MT and patients with ST that will be of prognostic significance. To evaluate this further, we used the data from the South Australian Clinical Registry (SACR) for mCRC.[16] Our primary analysis looked at OS between patients with MT and patients with ST. Secondary analyses reviewed any interactions between initial SAID and OS, time to recurrence (TTR), and patterns of metastases.

Patients and Methods

The SACR for mCRC is a statewide population-based database, established in February 2006, that collects information on patient, tumor, and treatment characteristics, as described by Neo et al.[16] For this analysis, data were collected between February 1, 2006, and October 22, 2012.

A total of 2502 patients were grouped by SAID to compare outcomes between MT and ST groups. All analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA). Disease-specific survival analysis was undertaken using conventional Kaplan-Meier product-limit estimates (differences in survival were tested using the log-rank test). OS was calculated from the date of diagnosis of mCRC to the date of death or the date of censoring of live cases on October 22, 2012, whichever came first. TTR was calculated from the date of diagnosis to the date of recurrence or date of censoring of live cases, whichever came first. All survival outcomes were analyzed using intervals of months.

Results

Patient Demographics

Data from 2502 patients were available for analysis on October 22, 2012. Patient demographics were stratified according to SAID (Table 1). The majority of patients had ST (64.3%), whereas the remainder had MT (1.2%, 13.8%, and 19.9% with stages I, II, and III CRC, respectively). The median age of patients was 70 years, balanced across the SAID. There was a male predominance (57%), balanced across the SAID. CC was the primary site in the majority of patients (68%). The dominant tumor grade was moderately differentiated (58%), with stage II/III CRC having more moderately differentiated tumors than stage I/IV CRC ($P < .0001$). Testing for the *KRAS* gene was performed infrequently at the time of this analysis (7%), but it was balanced across the SAID. Liver resection was performed in 35% of patients with liver-only metastases. For patients with liver-only disease, those with MT were more likely to have had liver resection than those with ST (56%, 61%, 59%, and 26% with stages I, II, III, and IV CRC, respectively; $P < .0001$). Lung resection was performed in 22% of patients with lung-only metastases. For patients with lung-only disease, those with MT were again more likely to have had lung resection than those with ST (25%, 32%, 26%, and 11% with stages I, II, III, and IV CRC, respectively; $P = .04$).

Patterns of Metastases

Patterns of metastases were evaluable in 2489 of 2502 patients (Table 2). Liver only was the most common site of metastatic disease (39%). For patients with MT, 29% had liver-only metastases, compared with 44% of patients with ST ($P < .0001$). For patients with MT, 13% had lung-only metastases, compared with 4% of patients with ST ($P < .0001$). For patients with MT, 28% had non-liver and non-lung metastases compared with 18% of patients with ST ($P < .0001$). Non-lung metastases were more common in patients with ST (13% vs. 7%, $P = .0001$), and non-liver metastases were more common in patients with MT (5% vs. 1%, $P < .0001$).

For liver-only and lung-only metastases, there was no difference between the MT and ST groups ($P = .30$). There was no difference in the proportion of patients with > 2 sites of metastases with regard to MT and ST ($P = .20$).

Patterns of Cancer Treatment

The patterns of care in the adjuvant setting for patients on the SACR for mCRC are collected retrospectively. The patterns of care in the metastatic setting are collected prospectively.

Patterns of Cancer Treatment for CC

Of the 552 patients diagnosed with metachronous CC, 545 provided data on patterns of care in the adjuvant setting (Table 3A). Surgery was performed in 91% of patients with metachronous CC (79%, 92%, and 92% for stages I, II, and III CC, respectively; $P = .20$). Adjuvant chemotherapy was given in 38% of patients with CC; of these patients, 14% were in stage II and 58% were in stage III CC ($P < .0001$). Of the stage II patients receiving adjuvant chemotherapy, 72% received single-agent fluoropyrimidines and 25% received oxaliplatin-based combination chemotherapy. Of the stage III patients receiving adjuvant chemotherapy, 60% received