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Relative impact of earlier diagnosis and improved treatment on survival for colorectal cancer: A US database study among elderly patients

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ABSTRACT

Purposes: To estimate what proportion of improvement in relative survival was attributable to smaller stage/size due to early detection and what proportion was attributable to cancer chemotherapy in patients with colorectal cancer (CRC).
Methods: We studied 69,718 patients with CRC aged ≥66 years in 1992–2009 from Surveillance, Epidemiology, and End Results registries. Study periods were categorized into three periods according to the major changes or advances in screening and chemotherapy regimens: (1) Period-1 (1992–1995), during which there was no evidence-based recommendation for routine CRC screening and 5-fluorouracil was the mainstay for chemotherapy; (2) Period-2 (1996–2000), during which evidences and guidelines supported the use of fecal occult blood test (FOBT) and sigmoidoscopy for routine CRC screening; and (3) Period-3 (2001–2009), during which Medicare Program added the full coverage for colonoscopy screening to average-risk individuals, and several newly developed chemotherapy regimens were approved. Outcome variables included the likelihood of being diagnosed at an early stage or with a small tumor size, and improvement in relative survival.
Results: Compared to period-1, likelihood of being diagnosed with early stage CRC increased by 20% in period-2 (odds ratio = 1.2, 95%CI: 1.1–1.2) and 30% in period-3 (1.3, 1.2–1.4); and likelihood of being diagnosed with small-size CRC increased by 60% in period-2 and 110% in period-3. Similarly, 5-year overall relative survival increased from 51% in period-1 to 56% in period-2 and 60% in period-3. Increase in survival attributable to migration in stage/size was 9% in period-2 and 20% in period-3, while the remaining survival improvement during period-2 and period-3 were largely attributable to more effective chemotherapy regimens (≥71.6%) and other treatment factors (≤25%).
Conclusions: Improvements in CRC screening resulted in a migration of CRC toward earlier tumor stage and smaller size, which contributed to ≤20% of survival increase. Survival improvement over the past 2 decades was largely explained by more effective chemotherapy regimens (≥71.6%).

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer mortality in the United States (U.S.) [1,2]. About 70% of CRC patients were diagnosed at age 65 or older [2]. Several studies have shown that in the past two decades, the survival rate of CRC patients has increased substantially due to the improvements in early detection and chemotherapy regimens, largely in clinical trial settings [3–10]. However, it is unclear whether benefits from these improvements have been observed in community-based elderly patients.

Widespread use of screening and advances in screening strategies played a key role in CRC survival improvement. With the increasing evidence on the benefit of fecal occult blood test

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(FOBT) and sigmoidoscopy during 1990s, the U.S. Preventive Service Task Force for the first time in 1996 recommended the annual use of FOBT, periodic use of sigmoidoscopy, or routine use of both modalities for all persons aged 50 or older [11–13]. Because colonoscopy is able to detect lesions in the entire colon and has a high sensitivity for lesions ≥10 mm, Medicare began to cover colonoscopy since 2001 for individuals with average-risk of CRC [14–16]. The evolution in implementation of CRC screening strategies almost doubled the screening rate from 1987 to 2008 [17]. However, it is unclear whether improvements in early detection have had led to the diagnosis of CRC toward earlier stage and smaller size among elderly patients with CRC.

Advances in chemotherapy also played a key role in CRC survival improvement [18–24]. During 1950–1995, 5-fluorouracil (5-FU) was the mainstay of chemotherapy. In 1990, an U.S. National Institutes of Health expert panel recommended adjuvant chemotherapy due to the evidence of its benefit in reducing risk of recurrence and improving survival [18]. Since then several other chemotherapy regimens have been developed and approved for treating CRC patients: in 1996, irinotecan was approved for advanced colon cancer; in 2001–2004, capecitabine, an oral form of 5-FU, was approved by FDA for treating patients with stage IV colon cancer and later for treating patients with stage III colon cancer [19,20]; in 2002–2004, oxaliplatin was approved for treating patients with stages III or IV colon cancer; and in 2004–2008, a number of monoclonal antibodies such as bevacizumab and cetuximab were approved for advanced colon cancer [21–23]. Several studies have reported an improved survival due to a specific chemotherapy regimen among elderly CRC patients [9,10,24]. However, the overall impact of newly approved chemotherapy regimens on survival in population-based elderly patients remains unclear. It is also unknown what proportion of survival improvement was attributable to changes in tumor stage and size, and what proportion was attributable to more effective chemotherapy regimens. Hence, we studied a large nationwide and population-based cohort of elderly CRC patients to examine the changes in tumor stage and tumor size from 1992 to 2009, and to further quantify the effects of changes in stage/size and chemotherapy regimens on improved survival over the two decades.

2. Patients and methods

2.1. Data sources

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset for cancer cases in 1992–2009, which covers 12 cancer registries and captures approximately 13.4% of the U.S. population [25–27]. It was reported that the SEER areas were excellent representation of all age groups and gender, but had higher socioeconomic status and were more urban than the remainder of the US populations [28]. The SEER data includes information on patients' demographics, year of diagnosis, tumor characteristics, initial treatment, causes of death, and follow up time [26]. Medicare data includes treatment information such as surgical, radiation, and chemotherapy, comorbidities and subsequent *follow-up for healthcare access in inpatient and outpatient services.*

2.2. Study population

We identified 69,718 Medicare beneficiaries aged 66 or older diagnosed with primary CRC. Patients were excluded if they (1) lacked continuous enrollment in Medicare Part A and B or participated in health maintenance organizations during 1992–2009 (n = 92,313) because claims for medical services from health maintenance organizations or for lack of Part B coverage may not be complete; (2) died within 6 months of cancer diagnosis or initiated chemotherapy after 6 months of cancer diagnosis (n = 34,115) because the study aimed to examine chemotherapy as adjuvant therapy following resection (for stage I–III) or as primary therapy for stage IV soon after the diagnosis (despite the uncertainty of the effectiveness of chemotherapy for stages I–II CRC, many patients with stage I–II CRC were found to receive chemotherapy and hence were included in the study [29,30]); or (3) had an unknown cause of death (n = 848) because the cancer-specific mortality cannot be determined without this information.

2.3. Study variables

2.3.1. Diagnostic time periods

Years of diagnosis were categorized into three periods according to the major changes or advances in screening and chemotherapy regimens: (1) Period-1 (1992–1995), during which there was no evidence-based recommendation for routine CRC screening and 5-FU was the mainstay for chemotherapy; (2) Period-2 (1996–2000), during which evidences and guidelines evolved to support the use of FOBT and sigmoidoscopy for routine CRC screening [11], and a new chemotherapy regimen, irinotecan was approved for treating patients with advanced CRC [17]; and (3) Period-3 (2001–2009), during which Medicare Program added the full coverage for colonoscopy screening to average-risk individuals [16], and FDA approved several newly developed chemotherapy regimens such as capecitabine, oxaliplatin, and bevacizumab for treating CRC [17].

2.3.2. Tumor stage and tumor size at diagnosis

We used SEER historic stage variable to categorize tumor stage [31], in which local stage was defined as a malignancy limited to the organ of origin that has spread no farther than the organ in which it started; regional stage was defined as tumor extension beyond the limits of the organ of origin; and distant stage was defined as tumor cells that have broken away from the primary tumor, have traveled to other parts of the body, and have begun to grow at the new location [31]. In this study, localized stage was considered as early stage, while both regional stage and distant stage were considered as late stage. Two different coding schemes EOD10-size (1988–2003) and CS tumor size (2004+) have been used to classify tumor size since 1992. Tumor size was recorded as the largest dimension of the primary tumor in mm [32,33]. We classified tumor size into six categories: ≤10 mm or microscopic foci, 11–20 mm, 21–30 mm, 31–40 mm, 41–50 mm, and >50 mm. For this study, tumor size ≤10 mm was considered as small tumor.

2.3.3. Overall survival and CRC-specific survival

Overall survival rate was defined as the proportion of those CRC patients who were still alive after the 5 years. CRC-specific survival was a net survival measure representing cancer survival in the absence of other causes of death [34], in which deaths from causes other than CRC were treated as censored observations. The causes of death were obtained using variable CODKM (coding: 14 and 24). Follow up time was calculated from the date of diagnosis to one of the following: date of death, date last known to be alive, or date of last follow-up (12/31/2009), whichever occurred first.

2.3.4. Patient and tumor characteristics

Covariates considered in this study included age at diagnosis (66–74, 75–85, >85), gender (female, male), race (African American, Caucasian, and Others), site of tumor (colon and rectum), tumor grade (I, II, III, and undetermined), and Charlson comorbidity index (0, 1, >1) which was created using both