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Colorectal cancer metastatic disease progression in Australia: A population-based analysis

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ABSTRACT

Background: No previous Australian population-based studies have described or quantified the progression of colorectal cancer (CRC) to metastatic disease. We describe patterns of progression to metastatic disease for an Australian cohort diagnosed with localised or regional CRC.
Methods: All localised and regional CRC cases in the New South Wales Cancer Registry diagnosed during 2000–2007 were followed to December 2011 for subsequent metastases (identified by subsequent disease episode notifications) or CRC death. Cox regression was used to identify factors associated with metastatic progression.
Results: After a median 5.3 years follow-up, 26.4% of the 12757 cases initially diagnosed with localised or regional colon cancer had developed metastatic disease, as had 29.5% of the 7154 rectal cancer cases. For both cancer sites, risk of metastatic progression was significantly higher for those initially diagnosed with regional disease (adjusted hazard ratio [aHR] 3.49 for colon, 2.66 for rectal cancer), and for older cases (e.g. aHR for >79 years vs <60 years: 1.38 for colon, 1.69 for rectal cancer). Risk of disease progression was significantly lower for females, and varied by histology type. For colon cancer, the risk of disease progression decreased over time. For rectal cancer, risk of metastatic progression was significantly higher for those living in more socioeconomically disadvantaged areas compared with those in the least disadvantaged area.
Conclusions: An understanding of the variation in risk of metastatic progression is useful for planning health service requirements, and can help inform decisions about treatment and follow-up for colorectal cancer patients.

1. Introduction

Recent estimates of cancer incidence and mortality in Australia show colorectal cancer (CRC) to be the second most commonly diagnosed cancer (excluding non-melanoma skin cancers) and the third most common cause of cancer death for the whole Australian population [1]. The main cause of cancer-related death is metastatic disease, so an understanding of the risk of developing metastatic CRC may be useful for informing decisions about the treatment and follow-up of patients, as well as the planning of future health service requirements. Previous population-based research on CRC disease progression has been relatively limited, although there have been a few international population-based studies published which reported the proportion of CRC cases who progressed to metastatic disease after receiving a single specified treatment [2–4]. Lord et al. described a method for estimating rates of metastatic progression for breast cancer using routinely collected population-based health data [5], and the method has also been used to report the patterns of metastatic progression for prostate cancer [6], The current study adapted the same method [6] to describe the patterns of progression to metastatic disease for localised and regional CRC cases and compare the risk of metastases by sociodemographic and disease characteristics in an Australian population.

2. Material and methods

This study was approved by the New South Wales (NSW) Population and Health Services Research Ethics Committee on 11 February 2016 (Reference: HREC/09/CIPHS/16).

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2.1. Data sources

Data for all primary localised and regional CRC cases (colon cancer: ICD-O-3 C18, rectal cancer: C19 and C20) [7] diagnosed during 2000–2007 were obtained from the population-based NSW Cancer Registry (NSWCR). The NSWCR must be notified if a patient presents for cancer treatment or a consultation at institutions in NSW [8]. There were 21930 localised and regional CRC cases identified, of whom we excluded 1077 cases who died within four months of diagnosis, 357 cases who were aged 90 years or older at diagnosis (due to the data on cause of death for very elderly patients being unreliable) and 585 cases with unknown country of birth. The remaining 19911 localised and regional CRC cases were followed to December 2011 for subsequent metastatic progression through episode notifications or death due to CRC.

2.2. Stage of disease

The stage of disease recorded in the NSWCR was based on staging information available from the cancer notifications the registry received. Stage at diagnosis was defined as the highest degree of spread recorded in the NSWCR within four months after the initial diagnosis, and subsequent metastatic disease was identified by cancer episode notifications dated more than four months after the initial diagnosis [6]. The NSWCR uses a modified summary classification [9] similar to that used by SEER [10]. This classification summarises stage of disease as localised – cancer is contained entirely in the tissue or organ of origin (equivalent to the American Joint Committee on Cancer [AJCC] stage I), regional – cancer has spread to adjacent organs or regional lymph nodes (equivalent to AJCC stages II and III), and distant – cancer has spread to distant sites (equivalent to AJCC stage IV) [9].

2.3. Study endpoints

The study endpoint was subsequent metastatic disease progression, which was identified by subsequent disease episode notifications (hereafter referred to as “episode notified” cases), or by notifications of CRC death (hereafter referred to as “CRC death notified” cases). Given that metastatic disease progression is considered to be on the pathway to death from CRC, patients who died from CRC were assumed to have a prior diagnosis of metastatic disease. As the NSWCR uses information up to four months after diagnosis to determine cancer stage at diagnosis, the time to metastatic disease notification was calculated from the date four months after initial CRC diagnosis to either the earliest date of subsequent metastatic notification, or to the date of CRC death. The NSWCR determined survival status and the cause of death to the end of 2011 by matching cancer cases against death records from the State Registry of Births, Deaths, and Marriages and the National Death Index. Cases with no record of metastatic progression were censored at the date of death from other causes or at 31 December 2011 if they were still alive.

2.4. Study variables

Sociodemographic variables used in this analysis included age and year of diagnosis, sex, country of birth, geographical location and socio-economic status (SES) based on the patient’s place of residence at diagnosis. Country of birth was grouped as Australia and major groups according to the Standard Australian Classification of Countries [11]. Geographical location of residence at diagnosis was classified as major cities, inner regional, and rural (including outer regional, remote and very remote areas) using the Australian Standard Geographic Classification Remoteness Structure, which is recognised as a nationally consistent measure of geographical remoteness, based on the physical road distance to the nearest town or service centre [12]. The Index of Relative Socio-Economic Disadvantage derived from the 2001 Census, was grouped into quintiles and used as a measure of area-level SES [13].

Disease characteristics used in this analysis included stage at diagnosis, primary tumour location and histology. Primary tumour location was defined based on ICD-O-3 [7]. For cancer, tumour histology is an important prognostic indicator and a determinant of responsiveness to specific cancer treatments [14]. In this study, cancer histology types with adequate numbers for analysis were classified into ten groups based on a slightly adapted version (by Stewart et al. [14]) of the morphology and topology codes in the ICD-O-3 [7]: unspecified adenocarcinoma (adenocarcinoma, not otherwise specified [NOS]) (AC-NOS), mucinous adenocarcinoma (MAC), mucin-producing adenocarcinoma (MPAC), signet ring cell carcinoma (SRCC), adenocarcinoma in villous adenoma (AVA), adenocarcinoma in tubulovillous adenoma (ATA), adenocarcinoma in adenomatous polyps (AAP), other specified adenocarcinoma, unspecified carcinoma (carcinoma, NOS), other specified carcinoma and all other types (Supplementary material 1).

2.5. Statistical analysis

All analyses were stratified by colon and rectal cancer. We used the Kaplan-Meier method and log-rank test to estimate the cumulative incidence for metastatic progression and test for differences in time to metastatic disease by initial stage at diagnosis. The annual hazard for metastatic CRC was calculated as the annual rate of failure by initial stage at diagnosis and was graphically represented using gauss kernel smoothing. We used Cox proportional hazards regression to identify risk factors associated with progression to metastatic CRC. The median survival after a subsequent metastatic notification was estimated to provide further information about the potential issue of cases living with metastatic CRC who were not notified to the NSWCR. We confirmed that the proportional hazards assumption was satisfied by testing the interaction of each of the study variables with survival time and by visual inspection of the Schoenfeld and scaled Schoenfeld residuals [15]. All analyses were performed using STATA (version 13.1) [16] and due to the number of factors under consideration, $p < 0.01$ was considered to denote statistical significance in the multivariable models.

3. Results

This study included 19911 patients diagnosed with localised or regional CRC during 2000–2007. Of these, 12757 were diagnosed with colon cancer (42.5% had localised disease and 57.5% had regional stage at diagnosis) and 7154 with rectal cancer (47.8% had localised disease and 52.2% had regional stage at diagnosis) (Table 1). The median age at diagnosis was 70 years for colon cancer and 67 years for rectal cancer. After a median of 5.3 years of follow-up (range: 0.1–11.7 years), 5485 (27.5%) cases initially diagnosed with localised or regional CRC had progressed to metastatic disease. Of these, 76.8% were notified within three years after initial diagnosis and 92.4% within 5 years, 77.5% were identified by episode notifications and 22.5% were identified by CRC death. The median survival after a notification of metastatic CRC was 8 months.

The overall cumulative metastatic CRC incidence was 26.5% at 5 years and 30.7% at 10 years. This was significantly higher (log-rank test $p < 0.0001$) for rectal cancer cases (28.2% at 5 years and 33.0% at 10 years) than for colon cancer cases (25.5% at 5 years and 29.3% at 10 years). For both colon and rectal cancer, cases with regional initial stage at diagnosis had significantly higher cumulative incidence of metastatic disease than those cases with localised