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Chemotherapy for resected colorectal cancer pulmonary metastases: Utilization and outcomes in routine clinical practice

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Abstract

Background: The role of chemotherapy in the setting of resected colorectal cancer pulmonary metastases (CRCPM) is not well defined. Here we describe utilization of peri-operative chemotherapy and outcomes among patients with resected CRCPM in the general population.
Methods: All cases of CRCPM who underwent resection from 2002 to 2009 were identified using the Ontario Cancer Registry (OCR). Electronic treatment records identified peri-operative chemotherapy delivered within 16 weeks before or after pulmonary metastasectomy (PM). Modified Poisson regression was used to evaluate factors associated with chemotherapy delivery. Cox proportional models were used to explore the association between post-operative chemotherapy and cancer-specific (CSS) and overall survival (OS).
Results: The study population included 420 patients. Thirty-six percent of patients (151/420) received peri-operative chemotherapy. Among these patients, 75% (113/151) received post-operative chemotherapy. Factors that were independently associated with use of post-operative chemotherapy included higher socioeconomic status (SES) and no prior adjuvant chemotherapy ($p < 0.01$). In adjusted analyses post-operative chemotherapy was not associated with improved CSS (HR 0.99, 95% CI 0.67–1.47) or OS (HR 0.93 95% CI 0.66–1.31). In exploratory analyses, among those patients who did not receive previous adjuvant therapy for the primary colorectal cancer, post-operative chemotherapy following lung metastasectomy was associated with HR 0.50 (95% CI 0.27–0.95) for OS and HR 0.59 (95% CI 0.27–1.27) for CSS.
Conclusion: One third of patients with resected CRCPM in routine practice receive peri-operative chemotherapy. A randomized controlled trial is warranted to evaluate whether chemotherapy following resection of CRCPM is associated with improved survival.

Keywords: Colon cancer; Metastasectomy; Adjuvant chemotherapy; Pulmonary metastases

Introduction

The lungs are the second most common site of metastases from colorectal cancer (CRC) with approximately 10–15% of patients developing pulmonary recurrence after curative resection.[1,2] Despite no randomized evidence to support it, the practice of pulmonary metastasectomy (PM) has become widespread based on data from retrospective studies that suggest that long-term survival is achieved for some patients. A recent meta-analysis reported that five-year survival for patients with resected colorectal cancer pulmonary metastases (CRCPM) is 27–68%.[3] A number of factors have been associated with poor survival including shorter disease-free interval, multiple lung metastases, involvement of mediastinal and hilar lymph nodes and

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elevated pre-operative carcinoembryonic antigen level (CEA).[4–6]

While guidelines recommend peri-operative chemotherapy for patients with resectable colorectal liver metastases (CRCLM),[7–9] little data support its use in resectable CRCPM. No randomized controlled trials have evaluated peri-operative chemotherapy versus surgery alone in this patient population. Some guidelines have extrapolated evidence for resectable CRCLM and recommend peri-operative chemotherapy for liver and/or lung metastases.[10,11] Most large retrospective studies describing management and outcome of patients with resected CRCPM have not evaluated the potential survival benefit of peri-operative chemotherapy. Two recent single institution studies of patients have reported conflicting results regarding the potential survival benefit of chemotherapy in this setting.[12,13] To address this gap in knowledge, we undertook a population-based study of patients with resected CRCPM to describe utilization and outcomes of peri-operative chemotherapy in routine practice.

Methods

Study design and population

We performed a population-based, retrospective cohort study to describe utilization of chemotherapy and outcome of resected CRCPM in the Canadian province of Ontario. Ontario has a population of approximately 13.5 million people and a single-payer universal health insurance program. The study cohort was defined using the Ontario Cancer Registry (OCR) to identify all incident cases of colorectal adenocarcinoma with pulmonary resection during 2002–2009. Electronic records of treatment were linked to the OCR. Extent of pulmonary metastases was not available in the existing data sources; therefore, we obtained surgical pathology reports for all cases. The study was approved by the Research Ethics Board of Queen's University.

Data sources and linkage

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario.[14] The OCR also provides information about vital status and cause of death. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical interventions and are known to be complete.[15] Provincial physician billing records from the Ontario Health Insurance Plan (OHIP), treatment records [Activity Level Reporting (ALR)] from regional cancer centers, and provincial records of chemotherapy delivery [New Drug Funding Program (NDFP) and Ontario Drug Benefits (ODB)] were used to identify chemotherapy utilization. These datasets were linked using unique encoded identifiers and analyzed at the Institute of Clinical and Evaluative Sciences (ICES). Surgical pathology reports were obtained from the OCR. A team of trained data abstractors reviewed the pathology reports and entered information about extent of disease and surgical procedure into an electronic database.

Measures and outcomes

Indicators of the socioeconomic status (SES) of the community in which patients resided at diagnosis were linked as described previously.[16] Quintiles (Q) of the median household income were based on the household income distribution for the full province of Ontario. Q1 represents the communities where the poorest 20% of the Ontario population resided. Geographic regions reflect the catchment areas for Ontario's regional cancer centers.[16] Co-morbidity was classified using the Charlson Index modified for administrative data.[17] Pre-operative chemotherapy was defined as chemotherapy given within 16 weeks before resection of CRCPM; post-operative chemotherapy was defined as treatment initiated within 16 weeks after surgery for CRCPM. Cancer-specific (CSS) and overall survival (OS) were measured from resection of CRCPM. To account for possible cause of death miscoding, CSS included death from any cancer. Complete information about vital status in the OCR was available up to December 31, 2012; cause of death was available up to December 31, 2010.

Analyses of factors associated with treatment and chemotherapy comparative effectiveness were restricted to patients who did not receive pre-operative chemotherapy. This was done for two reasons. First, administrative data sources do not distinguish between down staging chemotherapy for unresectable disease and peri-operative chemotherapy delivered to patients with resectable disease. Second, the extent of pulmonary metastases (i.e. size and number of lesions) would not be reliably known from surgical pathology reports among patients already treated with chemotherapy. Because these factors are known to be strongly associated with both chemotherapy utilization and outcome, subsequent analyses would be substantially limited by unmeasured confounding.

Because the survival measure began before the chemotherapy exposure window ended (i.e. at 16 weeks) our results were vulnerable to immortal person-time bias whereby patients dying during the exposure window have a lower chance of receiving treatment; this would artificially worsen survival of the no chemotherapy group. We therefore excluded patients dying within 16 weeks of surgery from survival analyses.

Statistical analysis

Comparisons of proportions between study groups were made using the chi-square test. CSS and OS were determined using the Kaplan–Meier method. Factors associated

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