Available online at www.sciencedirect.com

ScienceDirect

EJSO the Journal of Cancer Surgery

EJSO xx (2016) 1–8 www.ejso.com

Chemotherapy delivery for resected colorectal cancer liver metastases: Management and outcomes in routine clinical practice

A. Krishnamurthy [a], J. Kankesan [b], X. Wei [a], S. Nanji [b,c], J.J. Biagi [b], C.M. Booth [a,b,d,*]

[a] *Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Queen's University, Kingston, Canada*

[b] *Department of Oncology, Queen's University, Kingston, Canada*

[c] *Department of Surgery, Queen's University, Kingston, Canada*

[d] *Department of Public Health Sciences, Queen's University, Kingston, Canada*

Accepted 25 August 2016

Available online ■ ■ ■

Abstract

Background: International guidelines recommend peri-operative chemotherapy for patients with resectable colorectal cancer liver metastases (CRCLM). Chemotherapy delivery in routine practice is not well described.

Methods: All cases of CRC who underwent resection of LM in 2002–2009 were identified using the population-based Ontario Cancer Registry. Electronic treatment records identified chemotherapy delivered within 16 weeks before or after hepatectomy. All pathology reports were reviewed to describe extent of LM. Modified Poisson regression was used to evaluate factors associated with chemotherapy delivery. Cox proportional hazards model and propensity score analysis were used to explore the association between post-operative chemotherapy and cancer-specific (CSS) and overall (OS) survival.

Results: We identified 1310 patients. Sixty-two percent of cases (815/1310) received peri-operative chemotherapy; 25% (200/815) pre-operative, 45% (366/815) post-operative, and 31% (249/815) pre- and post-operative. Utilization of chemotherapy increased over time from 51% in 2002 (57/112) to 73% in 2009 (157/216, $p < 0.001$). Fifty-four percent of patients received FOLFOX, 41% FOLFIRI, and 10% 5-FU monotherapy. Factors that were independently associated with greater utilization of post-operative chemotherapy included younger age ($p < 0.001$), female sex ($p = 0.050$), shorter disease-free interval ($p = 0.006$), and no prior adjuvant chemotherapy ($p < 0.001$). Utilization of chemotherapy varied substantially across geographic regions (from 24% to 71%, $p = 0.001$). Post-operative chemotherapy was associated with improved CSS (HR 0.58, 95%CI 0.44–0.76) and OS (HR 0.49, 95%CI 0.38–0.61); results were consistent in propensity score analysis.

Conclusion: Utilization of chemotherapy for resected CRCLM in routine practice has evolved with emerging evidence. Post-operative chemotherapy is associated with improved survival in the general population.

Keywords: Colon cancer; Chemotherapy; Surgery; Liver metastases; Quality of care; Outcomes research; Knowledge translation

Introduction

Surgical resection of colorectal cancer liver metastases (CRCLM) has become standard practice and is associated with long-term survival in ~30–50% of patients.[1–3] Chemotherapy for CRCLM can be given in three different settings: 1) downstaging chemotherapy to convert unresectable disease; 2) post-operative "pseudoadjuvant" chemotherapy; and 3) peri-operative chemotherapy given to patients with resectable disease before and after surgery. The evidence in support of chemotherapy comes from clinical trials that have shown improved progression-free

* Corresponding author. Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, 10 Stuart Street, Kingston, ON, K7L 3N6, Canada. Fax: +1 (613) 533 6794.

E-mail address: boothc@kgh.kari.net (C.M. Booth).

http://dx.doi.org/10.1016/j.ejso.2016.08.022

survival.[4–6] No Level I evidence has compared a peri-operative approach (i.e. before and after surgery) to a post-operative "pseudoadjuvant" approach.

While guidelines universally recommend chemotherapy for patients with resectable CRCLM[2,7–9] this is based on evidence from clinical trials that enrolled patients from high volume institutions. Chemotherapy delivery and effectiveness has not been described in routine practice. This is important as it known that results from clinical trials and high volume centres may not apply to the general population.[10,11] To address these gaps in knowledge we undertook a population-based study of patients with resected CRCLM to describe chemotherapy delivery and outcomes in routine practice.

Methods

Study design and population

This is a population-based, retrospective cohort study to describe utilization of chemotherapy and outcome of resected CRCLM 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 population included all patients with CRC who underwent liver resection during 2002–2009. To identify the study cohort we used the Ontario Cancer Registry to identify all incident cases of colorectal adenocarcinoma with liver resection during 2002–2009. Extent of liver metastases was not available in the existing data sources; for this reason 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 Ontario Cancer Registry (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.[12] 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; these records are known to be complete.[13] Provincial physician billing records from the Ontario Health Insurance Plan (OHIP), treatment records [Activity Level Reporting (ALR)] from regional cancer centres, 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 analysed 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.[14] 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 centres.[14] Co-morbidity was classified using the Charlson Index modified for administrative data.[15] Pre-operative chemotherapy was defined as chemotherapy given within 16 weeks before resection of CRCLM; post-operative chemotherapy was defined as treatment initiated within 16 weeks after surgery for CRCLM. Cancer-specific (CSS) and overall survival (OS) were measured from resection of CRCLM. 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 downstaging chemotherapy for unresectable disease and peri-operative chemotherapy delivered to patients with resectable disease. Second, the extent of liver metastases (i.e. size and number of lesions) would not be reliably known from surgical pathology reports. 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.[16] 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 with post-operative chemotherapy were evaluated using modified Poisson regression. Factors associated with CSS/OS were evaluated using the Cox proportional hazards regression model. To control for confounding variables when exploring the association between ACT and survival,

Please cite this article in press as: Krishnamurthy A, et al., Chemotherapy delivery for resected colorectal cancer liver metastases: Management and outcomes in routine clinical practice, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.08.022