Available online at www.sciencedirect.com

ScienceDirect

EJSO 40 (2014) 685–691

EJSO the Journal of Cancer Surgery

www.ejso.com

Is primary tumor resection associated with a longer survival in colon cancer and unresectable synchronous metastases? A 4-year multicentre experience

L. de Mestier [a], C. Neuzillet [b], A. Pozet [c], E. Desot [a], S. Deguelte-Lardière [d], J. Volet [a], M. Karoui [e], R. Kianmanesh [d], F. Bonnetain [c], O. Bouché [a,*]

[a] *Department of Hepato-Gastroenterology and Digestive Oncology, Robert-Debré University Hospital, Reims, France*
[b] *Department of Gastroenterology and Pancreatology, Beaujon University Hospital, Clichy, France*
[c] *Unit of Methodology and Quality of Life in Oncology, EA 3181, Saint-Jacques University Hospital, Besançon, France*
[d] *Department of Digestive and Endocrine Surgery, Robert-Debré University Hospital, Reims, France*
[e] *Department of Digestive Surgery, Pitié-Salpetrière University Hospital, Assistance Publique Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France*

Accepted 18 February 2014
Available online 28 February 2014

Abstract

Aim: To explore the survival impact of primary tumor resection (PTR) in patients with metastatic colon cancer (mCC) and unresectable metastases.
Methods: We retrospectively studied a multicenter cohort of consecutive mCC patients with unresectable metastases receiving first-line chemotherapy. A weighted Cox proportional regression model was used to balance for clinical variables associated with the probability of undergoing PTR, using inverse probability of treatment weighting (IPTW) based on a propensity score.
Results: Ninety-six patients were included. PTR was performed in 69 (72%). The rates of secondary resection of metastases ($p = 0.02$) and bevacizumab administration ($p = 0.02$) were higher in the PTR group. Raw median overall survival (OS) was 23.1 months (95%CI [14.6–27.8]) in the PTR group and 22.1 months (95%CI[12.3–23.7]) in the non-PTR group ($p = 0.11$). After adjustment on IPTW, OS was 23.1 months (95%CI[17.0–28.7]) in the PTR group and 17.2 months (95%CI[13.5–22.2]) in the non-PTR group (HR 0.68; 95%CI[0.50–0.93]; $p = 0.016$). This result remained significant on multivariate analysis (HR 0.71; 95%CI[0.50–1.00]; $p = 0.05$).
Conclusion: In mCC patients with unresectable metastases receiving chemotherapy, up-front PTR was independently associated with prolonged OS. Patients eligible for secondary metastases resection and/or bevacizumab may benefit the most from PTR. Randomized controlled trials are mandatory.

Keywords: Colon cancer; Metastases; Primary tumor; Resection; Palliative; Prognosis

Introduction

Colorectal cancer (CRC) stands as the third most frequent cancer and the first of gastrointestinal origin. In 2012, CRC incidence and mortality rates were 43.5/100,000 and 19.5/100,000 respectively, representing more than 214,000 deaths in Europe.[1,2] Between 20% and 30% of patients with newly diagnosed CRC have synchronous metastases, which are not resectable in 75–90% of cases.[3] In this

* Corresponding author. Department of Hepato-Gastroenterology and Digestive Oncology, Robert-Debré University Hospital, Avenue du Général Koenig, 51092 Reims Cedex, France. Tel.: +33 3 26 78 31 13.
E-mail addresses: louisdemestier@hotmail.com (L. de Mestier), obouche@chu-reims.fr (O. Bouché).

0748-7983/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2014.02.236

setting, the treatment is palliative and based on systemic chemotherapy, eventually associated with biotherapy, which was demonstrated to improve survival and quality of life.

Whether patients may benefit from primary tumor resection (PTR) before chemotherapy administration has been a controversial issue for decades. Motivations for PTR are mainly prevention of complications related to the primary tumor (obstruction, perforation, hemorrhage) and quality of life improvement.[4] As PTR may lead to post-operative morbidity by itself, such a surgical procedure is questionable when the tumor is asymptomatic. However, emergency procedures to treat complications result in higher morbidity and mortality and may delay or even preclude chemotherapy administration.[5] Several authors have reported a benefit in overall survival (OS) and quality of life when PTR was performed, but there exists, to date, no consensus regarding the need to undergo PTR as the first step in the management of CRC patients with unresectable metastases. Above all, as no randomized study has been performed, only retrospective data are available, with many limiting selection biases. Finally, this issue may be answered differently between colon and rectal primary location, as natural history, complications and therapeutic options are different.

The aim of this study was to assess whether PTR may increase survival, in a series of consecutive patients with colon cancer and synchronous unresectable metastases treated with a first-line chemotherapy, in the routine practice. In this intent, a propensity score was performed to stratify on the likelihood to have undergone PTR.

Patients and methods

Study design

A multicentre retrospective study was conducted to evaluate the impact of PTR on overall survival (OS) in consecutive patients receiving a first-line chemotherapy for a colon cancer with synchronous unresectable metastases.

Patients

Clinical data from each consecutive patient receiving a first-line palliative chemotherapy for a metastatic colon cancer, from June 1, 2004 to June 1, 2008, in six digestive oncology units (Marne county, France), were retrospectively reviewed. Records were approved by the Institutional Review Board of Reims University Hospital. Final analysis was restricted to patients eligible for PTR with colon cancer and unresectable synchronous metastases, with WHO-PS 0-1 (World Health Organization – performance status). We compared patients who had undergone PTR before chemotherapy starting to patients who had not been operated on. Patients with rectal localization were not included. Unresectability of metastases was assessed in multidisciplinary meeting in all cases and was defined as the impossibility to achieve a complete and macroscopically curative resection of secondary tumors, because of multiple bilobar deposits, invasion of major liver pedicles precluding resection, and/or unresectable extrahepatic involvement.

Data collection

The following baseline data were retrospectively collected: demographic (age, gender), clinical (WHO-PS), institution type, tumor characteristics (metastases number and sites), biological (leucocytes, neutrophils, lymphocytes, hemoglobin, platelets and alkaline phosphatase). In addition to the PTR status, data were also obtained about therapies (number of chemotherapy lines, antiangiogenic biotherapy and inclusion in a clinical trial) and secondary treatment of metastases (surgery, radiofrequency thermoablation and hyperthermic intraperitoneal chemotherapy).

Endpoints

The primary endpoint was OS, defined as the time between the first injection of chemotherapy and death from any cause. Alive patients were censored at the last follow-up. Endpoint was set at October 1st 2010.

Description of the study population

The characteristics of the whole population are presented according to whether PTR was performed or not. Continuous variables were described as means (± SD) and compared using Student test or Kruskall–Wallis test in case of normal distribution or not, respectively. Qualitative variables were described as frequencies and percentages and compared using the χ^2 test.

Propensity score construction

A propensity score was calculated based on a multivariate logistic regression analysis and stood as the likelihood of undergoing PTR. The inverse probability treatment weight (IPTW) was used to balance clinical variables associated with PTR, in order to control for selection bias and allowing causal inference.[6] First, univariate logistic regression analysis was performed to explore which variables were associated with the likelihood of undergoing PTR. Then, all baseline variables were included in a multivariate logistic regression model. Age and neutrophil count were included as dichotomous variables, with the median values as cut-offs. To identify the optimal logistic regression multivariate model, calibration (Hosmer and Lemeshow goodness-of-fit test) and discrimination (area under the receiver-operating curve) tests were checked. Based on the final multivariate model, propensity score was calculated for each patient, using a coefficient of regression. Then, an inverse probability treatment weight (IPTW) was attributed to each patient following his treatment group (PTR or not). The weight allocated to patients undergoing