European Journal of Cancer 59 (2016) 13–21

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Management of liver metastases in colorectal cancer patients: A retrospective case-control study of systemic therapy versus liver resection

Jannemarie A.M. de Ridder [a,*], Eric P. van der Stok [b], Leonie J. Mekenkamp [c], Bastiaan Wiering [d], Miriam Koopman [e], Cornelis J.A. Punt [c], Cornelis Verhoef [b], Johannes H. de Wilt [a]

[a] *Department of Surgical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands*
[b] *Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands*
[c] *Department of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands*
[d] *Department of Surgery, Slingeland Hospital, Doetinchem, The Netherlands*
[e] *Department of Medical Oncology, University Medical Center Utrecht, The Netherlands*

Received 17 October 2015; received in revised form 26 January 2016; accepted 2 February 2016
Available online 16 March 2016

KEYWORDS
Colorectal liver metastases;
Survival;
Treatment;
Surgical treatment;
Liver resection;
Systemic therapy

Abstract ***Objective:*** To evaluate and compare the overall survival (OS) in case-matched patient groups treated either with systemic therapy or surgery for colorectal liver metastases (CRLM).

Methods: Patients with CRLM, without extra-hepatic disease, treated with chemotherapy with or without targeted therapy in two phase III studies ($n = 480$) were selected and case-matched to patients who underwent liver resection ($n = 632$). Matching criteria were sex, age, established prognostic factors for survival (clinical risk score). Available computed tomography (CT)-scans of patients treated with systemic therapies were reviewed by three independent liver surgeons for resectability. Survival was compared between patients with resectable CRLM (based on CT-scan review) who were treated with systemic therapy versus patients who underwent liver resection.

Results: A total of 96 patients treated with systemic therapy were included. Pre-treatment CT-scans of the liver were available for review in 56 of the systemically treated patients, and metastases were unanimously considered resectable in 36 patients (64.3%) (complex resectable: $n = 25$; 69%). These 36 patients were case-matched with 36 patients who underwent liver resection (wedge resection or segmentectomy: $n = 26$; 72%). Median OS in the patient group treated with systemic therapy was 26.5 months (range 0–81 months), which was significantly

* *Corresponding author*: Department of Surgery, Radboud University Medical Center, PO box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243617365; fax: +31 243540501.
E-mail address: jannemarie.deridder@radboudumc.nl (J.A.M. de Ridder).

http://dx.doi.org/10.1016/j.ejca.2016.02.003

lower than that in case-matched patients who underwent liver resection (median OS 56 months; range 6–116) ($p = 0.027$).

Conclusions: In this case-matched control study, surgery provided superior OS rates compared to systemic therapy for CRLM. Resection of CRLM should always be considered, preferably in a dedicated liver centre, since not all patients that qualify for resection are identified as such.

1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-death world-wide [1]. CRC patients develop metastases in 30–40%, depending on various factors such as T-stage, N-stage or histological subtype of the CRC (i.e. mucinous, signet ring cell or adenocarcinoma) [2]. Approximately 20% of patients present with synchronous distant metastases (stage IV disease) [3] and another 20% will develop metachronous metastases, predominantly located in the liver [4].

In terms of treatment, liver resection is considered the standard of care in patients with resectable colorectal liver metastases (CRLM), with 5-year survival rates ranging from 35–60% [5–7]. In recent years an increasing number of patients are considered eligible for surgical resection of CRLM due to improved treatment strategies, both surgical and non-surgical. These improvements include two-staged liver resections [8], portal vein embolisation [9] and pre-operative systemic therapy downsizing initially unresectable CRLM [10].

In order to predict prognosis of patients with CRLM considered for surgery, various groups have assessed risk factors [11,12] and multiple prognostic scoring systems have been developed [13–17]. The clinical risk score (CRS) by Fong et al. [18] is the most used scoring system, and its prognostic value has been validated by several independent investigators [19–21]. According to this CRS the following items are assigned one point: positive nodal status of the primary tumour, tumour size >50 mm, >1 metastases, CEA level >200 ng/ml and an interval between primary tumour and development of liver metastases <12 months. Patients with extra-hepatic disease are excluded. The total sum of the CRS divides patients into 'low risk' (0–2 points), and 'high risk' [3–5] of disease recurrence and overall survival (OS) after surgery [18].

Due to extra-hepatic disease and location, number or size of the liver metastases, only a minority of patients is, or will become, eligible for liver resection [13,22]. There are two issues that play an important role in the treatment of patients with CRLM. First, there is no consensus on the criteria for resectability. Blinded retrospective reviews on this topic illustrated great variability in the assessment of resectability, even between dedicated liver surgeons [10,23]. Second, chemotherapy regimens combining multiple drugs enriched with targeted agents, result in median OS of >30 months in patients with initially unresectable CRLM [24,25]. Despite these survival rates in patients treated with systemic therapy, there is little doubt that surgical resection of CRLM offers the best chance for long-term survival [26,27]. A randomised clinical trial on this topic is not considered to be ethical.

So, the challenge remains to identify all patients who may be candidates for radical surgery of CRLM. Although the majority of cancer patients are currently being assessed in multidisciplinary teams (MDT), specific expertise in liver surgery is often lacking in these teams.

Therefore, we investigated the baseline resectability status in the subgroup of patients with CRLM in two well-defined and prospectively established patient cohorts, who were considered to have unresectable CRLM and received systemic therapy within a clinical trial. The survival of patients who were considered resectable at baseline was compared to a matched control group of patients who underwent surgical resection of CRLM.

2. Methods

2.1. Patient population and data-collection

2.1.1. Patients treated with systemic therapy

We analysed patients with presumed unresectable CRLM at baseline who were included in two phase III randomised clinical trials from the Dutch Colorectal Cancer Group.

Starting in 2003, the CAIRO study randomised 820 metastatic CRC patients between first-line sequential and a combination treatment with capecitabine, irinotecan and oxaliplatin [28]. The CAIRO2 study included 755 metastatic CRC patients, who were randomly assigned to receive first-line treatment with capecitabine, oxaliplatin, and bevacizumab, or the same schedule with the addition of weekly cetuximab [29]. One of the inclusion criteria in both studies was that the metastases were unresectable. However a discussion of the individual patient in a multidisciplinary liver team was not mandatory for inclusion in both studies. Patients in the CAIRO study were required to have a World Health Organisation (WHO) performance status of 0–2, and in