

Liver resection rate following downsizing chemotherapy  
with cetuximab in metastatic colorectal cancer: UK  
retrospective observational study



H. Malik<sup>a</sup>, A.Z. Khan<sup>b</sup>, D.P. Berry<sup>c</sup>, I.C. Cameron<sup>d</sup>, I. Pope<sup>e</sup>,  
D. Sherlock<sup>f</sup>, S. Helmy<sup>g</sup>, B. Byrne<sup>h</sup>, M. Thompson<sup>i</sup>, A. Pulfer<sup>j,\*</sup>,  
B. Davidson<sup>g</sup>

<sup>a</sup> University Hospital Aintree, Liverpool, UK

<sup>b</sup> Royal Marsden Hospital, London, UK

<sup>c</sup> University Hospital of Wales, Cardiff, UK

<sup>d</sup> Nottingham University Hospitals, Nottingham, UK

<sup>e</sup> University Hospitals Bristol NHS Trust, Bristol, UK

<sup>f</sup> Pennine Acute NHS Trust, Manchester, UK

<sup>g</sup> Royal Free London NHS Foundation Trust, London, UK

<sup>h</sup> Merck Serono Ltd., Feltham, UK

<sup>i</sup> Formerly of Merck Serono Ltd., Feltham, UK

<sup>j</sup> pH Associates Ltd., Marlow, Bucks, UK

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**Abstract**

**Aims:** The high objective response rate to cetuximab along with chemotherapy in patients with colorectal liver metastases makes it an effective downsizing protocol to facilitate surgery in those with initially unresectable disease. Adoption of this strategy has been variable in the UK. A retrospective observational study was conducted in 7 UK specialist liver surgical centres to describe the liver resection rate following a downsizing protocol of cetuximab and chemotherapy and to evaluate the quality and efficiency of processes by which the treatment was provided.

**Methods:** Data were collected in 2012 by reviewing medical records of patients with colorectal metastases confined to the liver, defined as unresectable without downsizing therapy at first review by a specialist Multi Disciplinary Team (MDT).

**Results:** Sixty patients were included; 29 (48%) underwent liver resection following cetuximab and chemotherapy. Of the 29, 17 (59% or 28% of all patients) achieved R<sub>0</sub> resection and 7 (24% or 12% of all patients) R<sub>1</sub> resection. All treated patients were KRAS wild-type.

**Conclusion:** In specialist liver surgical centres, where patients are evaluated for liver resection, optimal management by MDT using KRAS testing, cetuximab and chemotherapy results in a 28% R<sub>0</sub> resection rate in patients with initially unresectable colorectal cancer liver metastases.

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**Keywords:** Cetuximab; Downsizing chemotherapy; Liver resection; Colorectal cancer

**Synopsis**

A retrospective observational study of liver resection rates and health care processes associated with the management of patients with previously unresectable metastatic colorectal cancer treated with downsizing chemotherapy and cetuximab. Optimal outcomes are achieved with appropriate specialist management.

\* Corresponding author. pH Associates Ltd., Derwent House, Dedmere Road, Marlow, Bucks SL7 1PG, UK. Tel.: +44 1628 401720; fax: +44 1628 486029.

E-mail address: [amandapulfer@phassociates.com](mailto:amandapulfer@phassociates.com) (A. Pulfer).

## Introduction

Downsizing chemotherapy to facilitate resection of otherwise unresectable liver metastases from colorectal cancer has been widely studied and is a safe and effective strategy to improve the prognosis of patients with colorectal metastases confined to the liver.<sup>1,2</sup>

The addition of targeted biological agents such as cetuximab to chemotherapy regimens is a promising recent development in the available therapeutic options.<sup>3</sup> UK Technology Appraisal bodies have recommended cetuximab for use in the National Health Service (NHS) along with chemotherapy as a downsizing treatment for patients with KRAS wild-type (wt) metastatic colorectal cancer (mCRC) and otherwise unresectable liver metastases.<sup>4,5</sup> Subsequent to this study being conducted, in Dec 2013 the licence for cetuximab was updated to exclude patients that harbor additional KRAS and NRAS mutations (exons 2, 3 and 4 of KRAS and NRAS) which are negative predictors of outcome to cetuximab. Cetuximab is now indicated in patients with RAS wt metastatic colorectal cancer.<sup>6</sup>

The technology appraisals of cetuximab for downsizing unresectable liver metastases were based on evidence from the CELIM study<sup>7</sup> which showed that cetuximab added to either FOLFOX or FOLFIRI regimens yielded high resection rates (34% achieved R<sub>0</sub> resection) and improved response rates in relation to historical controls. More recently, Ye et al. have shown improved resectability (26% R<sub>0</sub> resection rate), response rates and survival with the addition of cetuximab to conventional chemotherapy in a study directly comparing cetuximab plus chemotherapy with chemotherapy alone in patients with unresectable liver metastases of colorectal cancer.<sup>8</sup>

While robust randomized clinical trial data remains the essential basis of all evidence-based medicine, it is becoming increasingly important to supplement these studies with more broadly inclusive, contextualized ‘real world’ observational studies.<sup>9</sup> These take into account the preferences of patients and oncologists and withdrawal from chemotherapy in patients with significant side effects. Expert opinion has suggested that if provided in the usual UK context of management by multidisciplinary teams (MDTs) involving highly specialised liver surgical services, resection rates following downsizing chemotherapy combined with cetuximab could even exceed those seen in clinical trials.<sup>4</sup>

To date there have been no observational studies of the outcomes achieved with downsizing chemotherapy and cetuximab for colorectal liver metastases in UK clinical practice. It has been acknowledged that liver resection rate is a key outcome measure for this treatment and also recommended that patients receiving it should be managed only by MDTs that involve highly specialised liver surgical services.<sup>4</sup> Hence, this multi-centre retrospective observational study was conducted in 7 UK NHS specialist liver surgical centres with a primary objective of estimating the

proportion of patients with unresectable liver metastases who underwent liver resection following downsizing treatment with chemotherapy plus cetuximab. A secondary objective was to evaluate the health care process by which the treatment was provided in normal UK practice.

## Methods

Prior to commencement of the study at each centre, local NHS Trust Research and Development (R&D) management approval was obtained. Approval from an Independent Ethics Committee (IEC) was not required due to new Governance Arrangements for UK Department of Health Research Ethics Committees, effective from September 2011.<sup>10</sup> These allow studies involving the use of anonymised data collected by clinicians who already have access to identifiable records without IEC review or explicit patient consent.<sup>11</sup>

All patients meeting the inclusion/exclusion criteria were selected for inclusion in the study, by clinicians involved in their care within each centre, from clinical records and databases. There was no random sampling of subjects. Patients were included if: they had mCRC with metastases confined to the liver, defined as unresectable at first review by the specialist MDT; the specialist MDT review was after publication of NICE TA176 in August 2009 and they received downsizing chemotherapy and cetuximab, starting cetuximab between Oct 2009–Apr 2012. Patients were excluded if they had been enrolled in a clinical trial or had received privately funded healthcare, as these patients would not represent normal clinical practice in the NHS.

Data on patient and disease characteristics, resection rates, concomitant chemotherapy and response rates were collected retrospectively from medical records and hospital databases at each participating hospital. Where necessary, missing data were requested from other healthcare providers, most commonly referral centres and satellite centres providing chemotherapy administration, for details of chemotherapy and cetuximab prescribing.

For the evaluation of the health care process by which downsizing chemotherapy with cetuximab was managed, the participating centres were each asked to provide a service profile to describe the MDT structure, including specialist representation and workload.

Data collection was undertaken by members of the clinical team at each centre from February to November 2012. Prospective follow-up is ongoing to determine 5 year survival.

## Results

### Study centres

Service profiles were provided by all seven centres. Six described their MDT structure as hepatobiliary or hepatopancreatobiliary; three held hepatobiliary MDT meetings

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