Advancing the multidisciplinary treatment of colorectal liver metastases

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Colorectal cancer (CRC) is the third most common cancer in the UK, with some 40,000 new cases each year [1]. It also remains the second most common cause of cancer death in the UK, despite advances in treatment [1].

Approximately 20–25% of CRC patients have liver metastases at presentation, and over 30% of the remainder go on to develop liver metastases [2]. The presence or absence of liver metastases is the primary determinant of survival [2]—their presence accounts for at least two thirds of all CRC deaths [3]. Indeed, in patients with liver-limited metastases, it is progression of the liver disease (rather than the primary CRC) that determines overall life expectancy [2].

For optimal management of liver metastases, it is important to involve all appropriate specialists in the multidisciplinary team (MDT) caring for patients with CRC. Guidelines for the management of CRC from the Association of Coloproctology of Great Britain and Ireland recommend that fit patients with resectable or potentially resectable liver metastases should be reviewed in the MDT with a hepatobiliary (HPB) surgeon and colorectal oncologist "to evaluate operability and to decide on a combined plan of management to optimise the chance of achieving complete resection of all metastatic disease" [4].

This article focuses on the rationale for advancing the multidisciplinary treatment of colorectal liver metastases, and on the improvements in outcomes that can be achieved. It is based on a meeting held at The Royal Marsden Hospital (Fulham) in February 2012, attended by more than 130 oncologists, HPB and gastrointestinal surgeons, clinical nurse specialists and other members of colorectal and HPB MDTs.

Liver resection: a potentially curative approach

An analysis of the 114,155 patients with CRC who underwent surgery in England between 1998 and 2004 reported an improvement in survival with liver resection [5]. Over that period, 3,116 patients (2.7%) underwent one or more hepatic resection. In line with expectations, 5-year survival of patients with unresected stage 4 CRC (i.e. mCRC) was considerably worse than for patients who underwent hepatic resection, 9% [95% CI 8.4-9.6] versus 44.2% [95% CI 42.4–46.1], respectively. Patients with stage 4 disease who underwent liver resection had 5-year survival rates comparable to those with stage 3 disease.

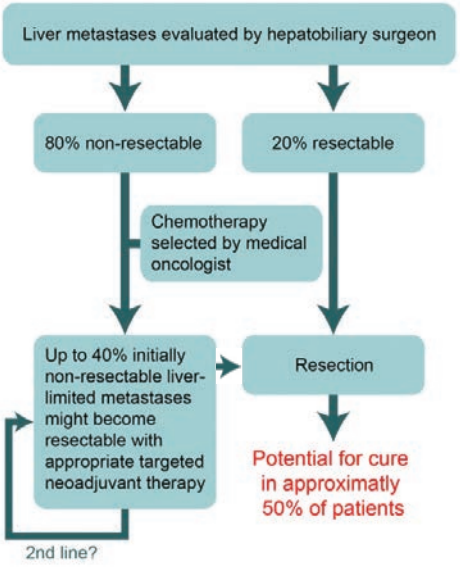

Figure 1: Resectability of liver metastases in CRC [Adapted from 7].
To achieve the best outcomes for patients, liver surgeons and medical oncologists must be involved from the outset in the multidisciplinary care of patients with colorectal liver metastases.

Because liver resection is a potentially curative approach to the management of colorectal liver metastases (Figure 1) [6], an increase in the proportion of patients eligible for such an intervention is an important goal. With approximately 85% of patients with colorectal liver metastases considered unresectable at presentation, the use of conversion therapy to shrink unresectable metastases may increase the proportion eligible for subsequent resection [7,8].

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Table 1. Doublet chemotherapy plus cetuximab in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	KRAS WT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Anti-EGFR agents								
CRYSTAL [16] (Phase III)	Unresectable mCRC	KRAS WT	FOLFIRI FOLFIRI + cetuximab	350 316	39.7 57.3	72 (21) 68 (22)	44.4 70.6	5.6 13.2
OPUS [16] (Phase II)	Unresectable mCRC	KRAS WT	FOLFOX FOLFOX + cetuximab	97 82	34.0 57.3	23 (24) 25 (31)	39.1 76.0	4.3 16.0
CELIM [18,19] (Phase II)	Unresectable CRC liver metastases	KRAS WT	FOLFOX/ FOLFIRI + cetuximab	67	70.0	67 (100)	70.0	33.0

CRC: Colorectal cancer; FOLFIRI: Irinotecan, leucovorin, fluorouracil; FOLFOX: Oxaliplatin, folinic acid, fluorouracil; mCRC: Metastatic colorectal cancer; ORR: Overall response rate; WT: Wild-type. Please refer to the publications for details of dose and schedule.

Who should be considered for liver resection?

The criteria for resection of CRC liver metastases have changed in recent years [9,10]. A meta-analysis has shown that seven factors traditionally associated with poor prognosis (poorly differentiated primary tumour, node-positive primary tumour, liver tumour >5 cm diameter, >1 liver metastases, positive resection margin, extrahepatic disease and raised carcinoembryonic antigen level) show a significant relationship with poor survival post-resection, but the effect is modest and does not necessarily preclude surgery [11].

While these prognostic factors may prove useful when considering therapeutic options, a new definition of resectability is required. It has been proposed that resection can be carried out if complete removal of all liver metastases will leave at least 30% of remnant liver [2]. Using this criterion, three categories of patients can be defined [12]:

- Easily resectable
  - Complete resection is likely with tumour-free margins
- Marginally resectable
  - Tumour-free margins unlikely
  - Small liver remnant
  - Concomitant resectable extrahepatic metastases
- Definitely unresectable
  - Widespread hepatic disease
  - Unresectable extrahepatic metastases
  - Multiple metastatic sites

Conversion therapy to increase resectability

Analysis of six studies of neoadjuvant treatment in patients with unresectable colorectal liver metastases has suggested a correlation between tumour response and subsequent resection rates [8]. Studies of neoadjuvant dual combination chemotherapy have found response rates of 48–60%, and R0 resection rates of 10–33% [8,13-15]. Efficacy can be improved when anti-epidermal growth factor (EGF) receptor therapy, cetuximab, is combined with the chemotherapy regimen (see Table 1) [16-19]. For example, compared with doublet chemotherapy alone, a combination of cetuximab and doublet chemotherapy resulted in improved response rates (70–76% vs 39–44%) and R0 resection rates (13–16% vs 4–6%) in subset analyses of patients with KRAS wild-type liver-limited disease [16].

A phase II study designed to explore the response and resection rates of cetuximab in combination with doublet chemotherapy in patients with unresectable colorectal liver metastases, reported response and R0 resection rates of 70% and 33%, respectively, in patients with KRAS wild-type disease [18,19]. The addition of cetuximab was not associated with increased peri-operative complications when compared with other studies reporting liver resection in this setting [18].

Studies of cetuximab-based neoadjuvant treatment were appraised in the development of guidance from the National Institute for Health and Clinical Excellence (NICE) on the first-line treatment of mCRC [17]. For patients considered fit enough to undergo resection of the primary tumour (and removal of liver metastases should they become resectable), NICE recommends treatment with cetuximab (within its licensed indication) in combination with FOLFOX (5-fluorouracil [5-FU], folinic acid and oxaliplatin) or FOLFIRI (5-FU, folinic acid and irinotecan). After a maximum of 16 weeks of neoadjuvant treatment, patients should be reassessed for potential liver resection.

The addition of anti-vascular endothelial growth factor (VEGF) therapy, bevacizumab, to doublet chemotherapy in a randomised controlled trial setting has not shown an increase in response

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Table 2. Doublet chemotherapy plus bevacizumab in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	ITT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Anti-VEGF agents								
NO16966 [20,21] (Phase III)	Unresectable mCRC	No	FOLFOX/ XELOX + placebo	701	38*	207 (29.5)	NA	11.6
			FOLFOX/ XELOX + bevacizumab	699	38*	211 (30)	NA	12.3
BOXER [22] (Phase II)	Poor risk CRC liver metastases	No	CAPOX + bevacizumab	45	78	30 (65)	NA	10

*Independently assessed. CRC: Colorectal cancer; CAPOX/XELOX: Oxaliplatin, capecitabine; FOLFOX: Oxaliplatin, folinic acid, fluorouracil; ITT: Intention to treat; mCRC: Metastatic colorectal cancer; NA: Not available; ORR: Overall response rate. Please refer to the publications for details of dose and schedule.

rates with a corresponding increase in resection rates (Table 2) [20,21]. A phase II, single arm study has explored the use of bevacizumab in combination with CAPOX (capecitabine, oxaliplatin) in patients with unresectable colorectal liver metastases (n=30) or upfront resectable liver metastases with a synchronous primary (n=15). A total of 3 patients with unresectable liver metastases underwent an R0 resection [22].

Triplet chemotherapy has been shown to achieve response rates of 71% [24] and R0 resection rates of 26-36% in patients with colorectal liver metastases initially considered to be unresectable [23, 24]. Single arm studies have investigated the addition of either cetuximab [25] or bevacizumab [26] to triplet chemotherapy producing response rates and R0 resection rates in the range of 79-80% and 40-60%, respectively (Table 3). Trials are on-going evaluating triplet therapy plus a targeted antibody in this setting to improve on response and resection rates further.

Importance of the liver MDT

Despite the importance of potentially curative hepatic resection for patients with colorectal liver metastases, analysis of resection rates in the UK has shown wide geographical variation [5]. Across cancer networks, there was a four-fold difference (1.1–4.3%), with a ten-fold difference between individual hospitals (0.7–6.8%). While some variation may reflect differences in patient populations, there may also be disparities in clinical practice and service organisation.

A cancer network has examined the issue of variability in care delivery in an audit of patients with mCRC who survived resection of primary CRC, and were treated with palliative chemotherapy and not liver resection [27]. Of 110 patients in this category during 2009, 37 were discussed at a HPB MDT and 73 patients were not, i.e. the decision to move to palliative care did not involve an HPB surgeon. Of the 73 patients not seen by the HPB MDT, 20 had multisite disease and the decision to offer palliative care was considered appropriate. However, there were 53 patients with liver-limited disease, for whom the guidelines recommend discussion by the HPB MDT [1,4].

After independently reviewing radiology reports and imaging for these 53 patients, six HPB surgeons scored the resectability of the liver metastases [27]. One patient was excluded because all the reviewers reported the imaging to be of insufficient quality. The reviews of the remaining 52 patients showed consistency in evaluation between the surgeons (kappa score 0.577). In 33 of the 52 cases (63%), the majority of reviewers considered that resection was possible.

Examination of liver resection rates in various studies highlights the role of HPB surgeons in the MDT caring for patients undergoing conversion treatment for unresectable colorectal liver metastases. Despite similar response rates to cetuximab plus chemotherapy for KRAS wild-type, unresectable, liver-limited disease (70–79%), there was marked variability in the liver resection rate (13–60%) reported in clinical studies [16,18-19,25]. Where the decision on initial and subsequent resectability was determined without the involvement of an HPB surgeon, the rate of liver resection after neoadjuvant treatment was 13–16% [16]. Where the decision rested with an MDT involving an HPB surgeon, the liver resection rate was 33–60% [18-19,25].

Conclusion

Liver metastases are common in patients with CRC [2], and the leading cause of mortality [3]. Hepatic resection is potentially curative [6], so increasing the proportion of patients eligible for surgical treatment is key to improving outcomes. Multidisciplinary treatment, including

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Table 3. Triplet chemotherapy in patients with unresectable mCRC

Study	Eligibility criteria	Biomarker defined subgroup	Regimen	ITT population		Unresectable liver-only mCRC		
				n	ORR (%)	n (% of trial population)	ORR (%)	R0 resection rate (%)
Triplet chemotherapy alone								
Falcone et al [23] (Phase III)	Unresectable mCRC	No	FOLFIRI FOLFOXIRI	122 122	34* 60*	42 (34) 39 (32)	NA NA	12 36
Ychou et al [24] (Phase II)	Unresectable CRC liver metastases	No	FOLFIRINOX	34	70.6	34 (100)	70.6	26.5
Anti-EGFR agents								
Masi et al [26] (Phase II)	Unresectable mCRC	No	FOLFOXIRI + bevacizumab	57	77	30 (53)	80	40
Anti-VEGF agents								
POCHER [25] (Phase II)	Unresectable CRC liver metastases	No	Chrono-IFLO + cetuximab	43	79.1	43 (100)	79.1	60

*Independently reviewed. CRC: Colorectal cancer; FOLFIRINOX/FOLFOXIRI/Chrono-IFLO: Oxaliplatin, irinotecan, leucovorin, fluorouracil; FOLFIRI: Irinotecan, leucovorin, fluorouracil; ITT: Intention to treat; mCRC: Metastatic colorectal cancer; NA: Not available; ORR: Overall response rate. Please refer to the publications for details of dose and schedule.

advice from an HPB surgeon, is required from the outset to ensure accurate assessment of the initial resectability of liver metastases.

It is estimated that approximately 15% of patients with liver-limited disease are resectable with curative intent at the time of detection [7]. Use of first-line conversion therapy for patients with initially unresectable liver-limited disease may allow subsequent resection in a further 24–54% of patients [8]. Studies of neoadjuvant regimens suggest that the addition of the EGF receptor antagonist cetuximab to doublet chemotherapy (FOLFOX or FOLFIRI) in patients with KRAS wild-type disease improves response rates and resection rates versus doublet chemotherapy alone [16]. Based on these findings, NICE recommends the combination of cetuximab and FOLFOX or FOLFIRI for use in the neoadjuvant treatment of unresectable colorectal liver metastases [17].

Through the implementation of guidelines on MDT management and conversion therapy, outcomes for patients with mCRC may be improved, and inequalities reduced.

References

1. National Institute for Health and Clinical Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer. Clinical Guideline 131.NICE, 2011.
2. Adam R, Hoti E, Folprecht G, Benson AB. Accomplishments in 2008 in the management of curable metastatic colorectal cancer. Gastrointest Cancer Res 2009;3:S15–S22.
3. Van den Eynde M, Hendlisz A. Treatment of colorectal liver metastases: a review. Rev Recent Clin Trials 2009;4:56–62.
4. The Association of Coloproctology of Great Britain and Ireland. Guidelines for the management of colorectal cancer. 3rd edition. 2007.
5. Morris EJA, Forman D, Thomas JD et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg 2010;97:1110–1118.
6. Andreou A, Aloia TA, Brouquet A, Vauthey J-N. Recent advances in the curative treatment of colorectal liver metastases. Gastrointest Cancer Res 2011;4:S2–S8.
7. Nordlinger B, Van Cutsem E, Rougier P et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer 2007;43:2037–2045.
8. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005;16:1311–1319.
9. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 1997;84:1136–1140.
10. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125–135.
11. Taylor A, Langeberg WJ, Primrose JN et al. Survival after surgical resection of hepatic metastases from colorectal cancer: a systematic review and meta-analysis. European Society of Medical Oncology 2010:Abstract 632P.
12. de Haas RJ, Wicherts DA, Adam R. Oncosurgical strategies for unresectable liver metastases. In: Liver metastases. London: Springer-Verlag London Limited, 2009.
13. Ho WM, Ma B, Mok T et al. Liver resection after irinotecan, 5-fluorouracil, and folinic acid for patients with unresectable colorectal liver metastases: a multicenter phase II study by the Cancer Therapeutic Research Group. Med Oncol 2005;22:303–312.
14. Alberts SR, Horvath WL, Sternfeld WC et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol 2005;23:9243–9249.
15. Barone C, Nuzzo G, Cassano A et al. Final analysis of colorectal cancer patients treated with irinotecan and 5-fluorouracil plus folinic acid neoadjuvant chemotherapy for unresectable liver metastases. British Journal of Cancer 2007:97:1035 – 1039
16. Kohne CH, Bokemeyer C, Heeger S et al. Efficacy of chemotherapy plus cetuximab according to metastatic site in KRAS wild-type metastatic colorectal cancer (mCRC): Analysis of CRYSTAL and OPUS studies. ASCO 2011 Abstract & Poster 3576.

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17. National Institute for Health and Clinical Excellence. Cetuximab for the first-line treatment of metastatic colorectal cancer (Technology Appraisal 176). London: NICE, 2009.
18. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38–47.
19. Folprecht G, Gruenberger T, Bechstein W et al. Progression free and overall survival after neoadjuvant treatment of colorectal liver metastases with cetuximab plus FOLFOX or FOLFIRI – results of the CELIM study. ASCO GI 2012 Abstract & Poster 540
20. Saltz LB, Clarke S, Diaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–2019.
21. Cassidy J, Cunningham D, Berry S et al. Surgery with curative intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer: First BEAT and NO16966. ASCO 2008, Poster 4022
22. Wong R, Cunningham D, Barbachano Y et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol 2011;22:2042–2048.
23. Falcone A, Ricci S, Brunetti I et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25:1670–1676.
24. Ychou M, Viret F, Kramar A et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases Cancer Chemother. Pharmacol. 2008:62:195–201
25. Garufi C, Torsello A, Tumolo S et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. Br J Cancer 2010;103:1542–1547.
26. Masi G, Loupakis F, Salvatore L et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial Lancet Oncol 2010:11:845–52
27. Jones RP, Vauthey JN, Adam R et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. Br J Surg. 2012:99(9):1263-9.
28. Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757–1765.
29. Normanno N, Tejpar S, Morgillo F et al. Implications for KRAS status and EGFR-targeted therapies in metastatic CRC. Nat Rev Clin Oncol 2009;6:519–527.
30. De Roock W, Jonker DJ, Di Nicolantonio F et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA 2010;304:1812–1820.
31. Siena S, Sartore-Bianchi A, Di Nicolantonio F, Balfour J, Bardelli A. Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer. J Natl Cancer Inst 2009;101:1308–1324.

Panel: Biomarkers and targeted agents

The use of biomarkers has opened up an era of personalised medicine, in which the likelihood of a patient's response to a targeted agent is evaluated before the therapy is given. Tumour biomarkers may reflect oncogenic mediators that are turned on during cancer development, or tumour-suppressor factors that are turned off in cancer.

There are a number of hurdles to the development of clinically useful biomarkers, notably:

- A good understanding of the disease pathology and the targeted agent
- Establishment of the prognostic and predictive effects of potential biomarkers, using disease models and clinical trials, and requiring interaction between pharmaceutical companies and regulatory bodies, adequate funding and effective research networks

These hurdles have been overcome for the biomarker, KRAS, now validated to predict the response of mCRC to cetuximab-based therapy. Analysis of patients with tumours characterised by KRAS wild-type mutational status showed a significant benefit in efficacy to cetuximab monotherapy compared with best supportive care, versus no significant treatment effect in patients with mutated KRAS [28].

KRAS encodes a protein essential to the EGF-receptor signalling mechanism [28]. Approximately 40% of CRC tumours have one or more activating mutation in exon 2 of this gene, which may make the cells unresponsive to EGF receptor inhibitors, such as cetuximab.

Clinical message:
Test CRC tumours to identify patients with KRAS wild-type status; if they have (or develop) metastatic disease, these patients may benefit from cetuximab therapy

Further work is underway to refine the biomarkers for prediction of response to cetuximab therapy. Not all KRAS mutations are alike. Although nearly 80% of mutations in KRAS occur in codon 12 (e.g. G12D, 32.5% of mutations; G12V, 22.5%; G12C, 8.8%; others, 14.9%), mutations in codon 13 (G13D) account for 19.5% [29]. Interestingly, in contrast to mutations in codon 12, data suggest that mutations in this codon may not be predictive for resistance to cetuximab-based therapy [30].

Not all patients with KRAS wild-type respond to cetuximab. This may be due to the impact of genes for other elements of the EGF-receptor signalling pathway, receptor ligands and other related receptors in the same family of receptors (e.g. human epidermal growth factor receptor 2 [HER2] and human epidermal growth factor receptor 3 [HER3]) [31]. However, currently these biomarkers have no practical use in clinical practice as they have yet to be validated.

Clinical message:
Other potential biomarkers to target the use of cetuximab are not yet validated for clinical use

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