

Centralization of liver cancer surgery and impact on multidisciplinary teams working on stage IV colorectal cancer

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Abstract

Surgical resection is the most effective treatment approach for colorectal liver metastases but only a minority of patients is suitable for upfront surgery. The treatment strategies of stage IV colorectal cancer have shifted towards a continuum of care in which medical and surgical treatment combinations are tailored to the clinical setting of the individual patient. The optimization of treatment through appropriate decision-making and multimodal therapy for stage IV colorectal cancer require a joint multidisciplinary meeting in a centralized liver cancer unit.

Introduction

Colorectal cancer (CRC) is the commonest gastrointestinal malignancy and the second commonest cause of cancer death. 76% of all colorectal cancer patients are diagnosed between 65 and 85 years old but affecting a younger age in the developing world with the adoption of the western diet.^{1,2} At CRC diagnosis, 20-25% of patients have stage IV disease in which synchronous

CRC liver metastases (CRLM) are present in 15-25% of cases.²⁻⁶ Metastases are confined to the liver in 70-80% of these cases.³ CRLM is defined as liver metastases detected at or before diagnosis of the primary CRC.⁴ The reported percentage of synchronous CRLM (detected at time of diagnosis) is increasing compared with metachronous [detected in the following 5 years after surgery (35%)], probably due to improved imaging techniques leading to earlier diagnosis. Synchronous CRLM have less favorable cancer biology and expected survival than metachronous metastases as corroborated by their temporal presentation, but some studies showed no significant difference.^{7,8} In CRC staging, the tumor is first scored with respect to the TNM (tumor, node and metastasis) variables then assigned to stage I-IV (Tables 1 and 2). Current observations regarding the clinical course of the patients with CRLM support emerging arguments for a new staging system.⁹ The TNM staging system does not adapt to recent advances in metastatic treatment. For example, the survival of a patient with resectable solitary liver metastasis is better than that of a patient with stage II disease.¹⁰ Tumor deposits in adjacent vessels are associated with peritoneal disease, and tumor deposit with nodal disease has worse survival (N2).¹¹ The median survival of untreated CRLM following diagnosis is 6-12 months and 5-year survival is extremely rare.¹⁻³ Surgical resection is the most effective treatment approach for CRLM with an overall survival of about 40% in 5 years, but only a minority of patients are suitable for upfront surgery due to tumor size, tumor location or limited reserve capacity.⁹ With newer chemotherapy regimens, a significant proportion of unresectable patients are converted to resectable with similar survival benefit. With initially resectable metastases the use of neo-adjuvant¹² and adjuvant therapy¹³ to decrease recurrence risk and improve survival in patients are encouraging. The use of modern surgical techniques has resulted in a reduction of perioperative mortality and morbidity, whereas tumor ablation techniques, portal vein embolization (PVE), and staged procedures have positively influenced the expansion of patients for surgical resection.²⁻⁸

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The advanced multidisciplinary teams

The management of patients with stage IV colorectal cancer would be optimized by bringing together all the relevant specialists involved in colorectal metastatic disease to an advanced multidisciplinary teams (MDTs) meeting in a centralized high volume liver cancer surgery unit.¹⁴⁻¹⁶ A proficient advanced MDT for stage IV colorectal cancer includes surgeons specializing in colorectal surgery, hepatobiliary surgery and thoracic surgery, dedicated CRC medical and radiation oncologists, both imaging and interventional radiologists, dedicated CRC surgical pathologists, oncology nurse specialist, nurse counselor and the patient. The lead specialist is either the liver or colorectal surgeon.¹⁵ By avoiding referral to the appropriate anatomical-site specific MDT with

consequent delay in decision-making and management, disease progression is minimized. The advanced/ multi-specialist MDT meeting provides coordination, continuity of care, better patient care with cost effectiveness, decrease length of hospital stay and post-operative mortality.¹⁷⁻²² The utilization of protocols, appropriate preparation of patients, audit and trial recruitments are optimized. Non-adherence to MDT decisions has been shown to result in a trend towards lower survival rates.^{20,21} Written information about the treatment decision including rationale is sent to patient's clinic consultation of the specialist hepatobiliary unit, the patient's colorectal surgeon and general practitioner and if desired a copy to the patient.¹⁶⁻¹⁹ The main determinants of the decision-making process are the tumor statuses of both the primary tumor and metastases, the need for emergency surgery of a complicated primary tumor and the resectability of both tumor sites.^{22,23} The four clinical scenarios are: i) the asymptomatic CRC and resectable synchronous CRLM; ii) the asymptomatic CRC and non-resectable synchronous CRLM; iii) the symptomatic CRC and resectable synchronous CRLM; and iv) the symptomatic CRC and non-resectable synchronous CRLM.^{15,22} The diagnosis and decision making on the management of resectable, borderline resectable or unresectable metastatic disease is expedited in the advanced MDT. The easily resectable will be completely resected with good margins and disease-free survival. The borderline resectable disease may require induction chemotherapy and then restaged. It may be marginally resectable with no margins, leaving a small liver remnant, and may have concomitant resectable extrahepatic disease. Resectability may be achieved by portal vein embolization (PVE) or 2-stage hepatectomy to increase hepatic functional reserve or by combination of surgery and ablation. The definitely unresectable may have widespread hepatic disease, non-resectable extrahepatic lesions, or multiple metastatic sites.^{15,22,23} The principal goal of treatment in most patients with unresectable metastases is to prolong survival, and only about 10%-15% patients are alive at 5 years.²⁻⁴ Administration of systemic chemotherapy may convert unresectable into resectable disease. Local ablative therapies [transarterial chemoembolization (TACE), radiofrequency/ microwave ablation and selective internal radiation therapy (SIRT)] may be employed in isolation to patients unfit for surgery, or as an adjunct to resection in patients with bilobar disease.^{24,25} However, because of the potential morbidity of treatment and the impact on quality of life for these patients, best supportive treatment must also be considered.

The role of Imaging and pathology

The complex decision to determine resectability requires detailed anatomic imaging to determine tumor location, exclude unresectable extrahepatic metastases, and assess the adequacy of the liver parenchyma after surgery. Advances in body and hepatic imaging has allowed for more accurate selection of patients and obviating the need for staging laparoscopy. To provide information on potential curability of stage IV colorectal cancer the use of high-quality contrast-enhanced thoraco-abdominal computed tomography (CT) before chemotherapy is recommended.¹⁵ Alongside CT, magnetic resonance imaging (MRI) is used preoperatively to aid detection of sub-centimetric metastases.²⁶ To evaluate operability, MRI would provide information on nodule size and number, segmental localization and relationship with major vessels, response after neoadjuvant chemotherapy, non-tumoral liver condition and anticipated remnant liver volume. It is the best imaging technique for assessing residual disease and delineating those patients with a *true* radiological complete response to

chemotherapy.^{27,28} Contrast-enhanced intra-operative ultrasonography would detect an additional 10%-15% of the *disappearing* liver metastases (DLM).²⁹ If a contrast-enhanced CT of the chest, abdomen and pelvis shows the patient has extra-hepatic metastases that could be amenable to further radical surgery a positron emission tomography-CT (PET-CT) of the whole body is appropriate. It is more advantageous in identifying extrahepatic and possible unresectable metastases, which could be a contraindication to liver resection.^{15,30} It is considered in patients with recurrent disease or high tumor load (multinodular and/or large metastases) or for whom difficult hepatic resections are planned.^{15,30} The imaging would be discussed with the appropriate anatomical-site specialist such as the thoracic surgeon for lung metastases (5%), which ironically have a better median survival (24 months) than liver metastases (18 months). Thus, in the presence of synchronous, resectable lung metastases, clearance of the liver lesions should be undertaken.

Table 1. The 7th edition of the AJCC-TNM classification system.

TNM	Disease extension
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	
a	Tumour invades through the muscularis propria
b	T1 or T2 tumour with satellite deposits in pericorectal tissues
T4	
a	Tumour penetrates the visceral peritoneum
b	Tumour directly invades or is adherent to other organs or structures
N0	No regional lymph node metastasis
N1	
a	Metastasis in 1 regional lymph node
b	Metastases in 2 to 3 regional lymph node
N2	
a	Metastasis in 4 to 6 regional lymph nodes
b	Metastases in 7 or more regional lymph nodes
M0	No distant metastases
M1	
a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node)
b	Metastases in more than one organ/site or the peritoneum

T, tumour stage; N, lymph node involvement; M, distant metastasis.

Table 2. The 7th edition of the AJCC-TNM classification system.

Stage*	T	N	M	
I	T1	N0	M0	
	T2	N0	M0	
II	T3	N0	M0	
	T4a	N0	M0	
	T4b	N0	M0	
III	a	T1-T2	N1	M0
		T1	N2a	M0
	b	T3-T4a	N1	M0
		T2-T3	N2a	M0
	c	T1-T2	N2b	M0
		T4a	N2a	M0
		T3-T4a	N2b	M0
		T4b	N1-N2	M0
		Any T	Any N	M1

en first. Patients with minimal liver disease and extrahepatic disease (EHD) in the lung undergoing metastectomy had comparable survival.³¹ Thus, the evolving landscape of multimodality therapy. If contrast-enhanced CT suggests disease in the pelvis, an MRI of the pelvis is offered and plan of management discussed with the colorectal and urological surgeon if the genito-urinary tract is involved. An initial CT of the chest, abdomen and pelvis may also confirm the diagnosis of mechanical obstruction and determine whether the patient has metastatic disease or colonic perforation. The colorectal surgeon together with an endoscopist or a radiologist may have inserted a colonic stent in patients presenting with acute large bowel obstruction.²⁵ Pathological evaluation would assess response to preoperative chemotherapy for both the primary tumor and metastases, and provide information on the tumor, margin size and micrometastases. RAS (NRAS and KRAS) mutations have been associated with worse disease-free and overall survival following CRLM resection, independent of anti-epidermal growth factor receptor (EGFR) therapy.^{32,33}

Chemotherapy

Although the treatment strategy depends on the clinical scenario, the disease being systemic dictates for chemotherapy before surgery in most cases.^{34,35} As colorectal tumor biology supports the arguments for aggressive surgical and adjuvant treatment, preoperative chemotherapy is useful for assessing tumor sensitivity in patients with advanced disease.⁴⁻⁸ Although preoperative chemotherapy can delay surgery of an asymptomatic primary tumor, survival is not compromised.^{1,8,15} In patients with resectable colorectal liver metastases progression-free survival is increased with the addition of oxaliplatin and fluorouracil in neoadjuvant chemotherapy.^{12,36,37} The addition of biologic agents, specifically epidermal growth factor (EGFR) receptor blocker (cetuximab) and vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) have become the standard of care for the treatment of metastatic colorectal cancer but lack proven benefit as adjuvant treatment.^{4,5,38-40} The addition of cetuximab results in an overall survival advantage in patients with advanced disease who have the *KRAS* exon 2 wild-type tumor genotype (the new EPOC study).^{41,42} When CRLM are unresectable, the goal of chemotherapy is to downsize tumors to allow resection [9,35]. When offering multiple chemotherapy the medical oncologist decides which combination and sequence to use after full discussion of the side effects and the patient's preferences. One of the following sequences is considered: FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first line treatment then single agent irinotecan as second-line treatment or FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan 3) as second line treatment.^{15,25,43,44} Second line therapy is for the 70-90% that remain unresectable or are progressive.¹⁵ Chemotherapy delivered by hepatic arterial infusion represents a valid option in patients with liver-only disease, although it is best delivered in experienced centers.^{24,25}

Surgery of the liver

The aim of any liver-directed treatment (*e.g.*, surgical resection) is to safely remove all viable tumor with a clear margin (>1 cm).^{2,6,15,22} Hepatic resection has evolved from a rare procedure

associated with considerable mortality to a routine surgery with an operative mortality risk of about 2%.^{9,10} Preoperative blood transfusion, positive lymph nodes, abnormal liver function tests, a C-reactive protein (CRP) or neutrophil/lymphocyte ratio of more than 5:1 are found to be significant negative prognostic factors in predicting disease-specific survival after these resections.^{45,46} When the primary CRC is asymptomatic, liver surgery may be performed first (reverse approach).²² However, the rationale in using preoperative chemotherapy for resectable patients has been supported by the better prognosis obtained with neoadjuvant chemotherapy, compared to upfront surgery in patients with synchronous CRLM. It will be associated with a lower rate of positive surgical margins and would identify the subgroup of patients who will develop progressive disease while on chemotherapy.¹⁵ Hepatic resection should, however, not be denied to patients with stable disease after optimal chemotherapy, provided an adequate liver remnant with inflow and outflow preservation remains.^{22,47,48} This may be achieved through specific techniques to increase resectability including intra-operative ultrasound at the time of resection.¹⁵ Unresectable unilobar disease may be treated by neoadjuvant chemotherapy followed by extended liver resection (with or without portal vein embolization depending on the size of future liver remnant). In the presence of bilobar diseases, clearance may be achieved by staged resections or a combination of resection and ablation.^{13,22} Preoperative chemotherapy with an interval of about 6-8 weeks before surgery will allow tumor response and shrinkage and patient recovery.⁴⁻⁶ The optimal timing for assessment of response to chemotherapy is 2 months^{13,25,49} and following preoperative chemotherapy and resection, adjuvant chemotherapy should be considered. An overall total duration of 6 months of perioperative (preoperative and adjuvant) chemotherapy is recommended. The extent of liver resection should be determined by pre-chemotherapy imaging (CT or MRI) and not post-chemotherapy imaging. A complete radiological response depends on the quality and completeness of preoperative imaging.^{22,50} As a complete radiological response does not signify a complete pathological response liver resection of curative-intent should include all initial and currently known sites of disease.²² Patients operated on for initially unresectable colorectal metastases with *missing* metastases (a sign of good response to treatment and indicative of good prognosis) experience a favorable long-term outcome.⁵¹ Liver resection in slow responders requiring 12 or more chemotherapy cycles and portal vein embolization to achieve resectability, is associated with poor short and long-term outcome.⁵² This is due to the impaired general status of these patients, their damaged underlying parenchyma due to prolonged chemotherapy (chemotherapy-associated steatohepatitis) and the technical challenge in obtaining adequate curative resection. Thus the benefit from more conservative parenchymal sparing approaches especially with the knowledge of the 20% recurrence rate, which may require further resection.^{22,53} With longer overall and median survival rates, indications for surgery are increasing with R1 surgery (complete tumor resection without safe margins) being justified for patients with a response to preoperative chemotherapy.^{54,55} The combined approach of resection and ablation techniques to bilobar colorectal liver metastases (bCRLM) results in less morbidity than two (or more) hepatic resections.⁵⁶⁻⁵⁸

Recurrent liver metastases after resection are re-resected if technically feasible or ablated [radiofrequency/microwave thermal, selective internal radiation therapy (SIRT), TACE] by the interventional radiologist, and has similar long-term survival as first liver resection.^{25,59,60} Third time resection may also provide long-term benefit and so these patients can now live with their cancer if the tumor biology is favorable.^{61,62} The recurrences present

with the same time interval after the primary tumor and subsequent metastases, indicating that recurrent disease may not be a sign of explosive fast progressing metastatic disease.³ If the diagnosis of a hepatic or extra-hepatic recurrence remains uncertain the patient is kept under clinical review and offered repeat imaging at intervals agreed by the advanced MDT.^{15,22}

Surgery of the primary tumor

Resection of the primary tumor in patients with stage IV cancer is often performed to deal with the presenting primary tumor symptoms and to prevent further primary tumor complications such as obstruction, major bleeding, pain and side effects (bleeding and perforation) related to the novel targeted therapy.^{63,64} Although this may improve the survival rate,⁶⁵ the tumor burden and performance status are the significant prognostic factors.⁶⁴ Conversely, new-generation systemic therapy in combination with targeted therapy is associated with response rates of 40-60%.^{42,61} By not only reducing the size of metastatic lesions, the shrinking of the primary tumor may reduce complications, such as bowel obstruction. In addition, the response to chemotherapy will select the right patients for surgery.^{4,5,8,9} The decision to resect the primary asymptomatic tumor may be associated with selection bias as these patients usually have a better performance status. Thus, the delay of chemotherapy may not negatively affect the survival rate of these patients.⁶⁴ However, complications after resection of an asymptomatic primary tumor may delay or prevent initiation of systemic chemotherapy.⁶⁶ Preoperative chemotherapy is required for high volume disease (>3 metastases or bilobar). For unresectable liver metastases, chemotherapy is given first and surgery on the primary is only indicated for the complications (perforation, bleeding) of chemotherapy. Even so, for unresectable CRLM, it remains unknown whether resection of the primary tumor improves disease control by reducing tumor bulk and enhancing chemo-efficacy.⁶⁴⁻⁶⁷ Despite the uncertain survival benefit, a high rate of surgical resection of the primary tumor has been reported in patients with unresectable metastatic disease.⁶⁶ A systematic review and meta-analysis supported non-curative (palliative) resection of the primary tumor^{66,68} but randomized trials are warranted to exclude selection biases.⁶⁴

One stage (simultaneous) or staged procedure?

The decision as to whether the operations for the primary tumor and liver metastases are done at the same time (simultaneous) or separately (staged) is being made at the advanced MDT meeting and in discussion with the patient.^{15,25,66,67} The advantages of a one stage (simultaneous) operation are: i) the decreased risk of disease dissemination (transperitoneally); ii) no repeated postoperative immunosuppression causing increased tumor growth; and iii) lower costs. A staged procedure: i) allows assessment of biological behavior of metastases; ii) avoids operating on patients who are progressing while on chemotherapy; and iii) allows more precise selection for curative surgery.⁶⁹ Delayed hepatic resection may not impair survival but help select those patients most likely to benefit from hepatic resection *i.e.* stable disease.^{70,71} For mid and low rectal primary tumors, radiotherapy is often needed and in addition to a difficult resection a one-stage surgery is not recommended. One-stage surgery is not advocated for complex colonic and upper rectal primary tumors, for high-risk patients or when hepatectomy is major (>3 segments).¹⁵ A simultaneous major hepatectomy and

complex rectal surgery is not performed, due to significantly higher postoperative mortality and morbidity particularly in the presence of comorbidity.⁶⁸ Minor liver resections (2 segments or less) may be safely performed at the same time as colorectal resection (open or laparoscopic) when both the primary tumor and the metastases are easily resectable.⁶⁸⁻⁷⁰ The outcomes are similar to sequential surgery in this scenario.⁷²⁻⁷⁵

Outcome of the advanced multidisciplinary teams

The surgical treatment of colorectal hepatic metastases represent the only potentially curative therapeutic option to achieve long-term survival. However, the optimization of multimodal therapy through appropriate decision-making is the goal of the advanced MDT's stage IV colorectal cancer management. The management of these patients without the involvement of a multi-specialist MDT team (*i.e.*, non-specialist decision-making) may lead to inappropriate management and patients being denied potentially curative treatments.⁷⁶⁻⁷⁸ The overall perioperative mortality of liver resection ranges between 0% and 5% in most published series,¹⁵ and is strongly influenced by perioperative blood loss, liver function and extent of liver resection.^{17,22} The principal causes of death are liver failure and sepsis.¹⁵ The surviving patients following treatment of stage IV colorectal cancer with curative intent (40% at 5 years) have reached 10 years. A number of series with sufficient long-term follow-up indicate that the 10-year survival after resection can be expected in 20%-30% of patients.⁷⁹ The recommended surveillance for colorectal cancer patients are a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years and regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).²⁵ Follow-up screening after treatment for colorectal liver metastases will be discussed by the MDT. If long distances are involved it may be carried out by the local colorectal unit using agreed protocols.⁷⁸

Conclusions

From all the levels of evidence, the impact of the advanced MDT consensus on the management of the four clinical scenarios of stage IV colorectal cancer are as follows: i) for the asymptomatic CRC and resectable synchronous CRLM, chemotherapy is first with or without radiotherapy, followed either by surgery in a one-stage procedure (for patients with limited hepatic disease and easy to resect primary tumor) or by staged surgery (for other patients). Ongoing trials may provide evidence for chemotherapy first as opposed to colon resection first; ii) for asymptomatic CRC and non-resectable synchronous CRLM, the consensus is for optimal chemotherapy first, with the aim of making the liver metastases (LM) resectable. This would then be followed by hepatic surgery and resection of the primary tumor; iii) for symptomatic CRC and resectable synchronous CRLM, recommendations are for resection of the primary tumor for perforated or occlusive tumors (but not for tumors with bleeding causing anemia), followed by chemotherapy and then surgery for LM; iv) For symptomatic CRC and non-resectable synchronous CRLM, recommendations are for resection of the primary tumor for perforated or occlusive tumors, followed by chemotherapy and then surgery for LM if tumor shrinkage is achieved. For tumors with bleeding causing anemia, induction chemotherapy is recommended to downsize both the primary tumor and LM, followed by surgery at the site with the most significant tumor load (usually the liver; *i.e.*, reverse approach).

Patients with untreated CRLM have a poor prognosis. Resection of CRLM has shown to prolong survival but the proper selection of patients who would benefit is important. The improved survival in stage IV colorectal cancer is associated with a better diagnosis and evaluation, proper decision-making, improved chemotherapy and the adoption of parenchymal-sparing hepatic resections. It is therefore important to regularly evaluate the outcome of the advanced MDT meetings so as to maintain the improvements in treatment goals as compared to a general colorectal MDT meeting. It is also useful to compare with other centers on effect of survival. Better patient selection through improved imaging techniques and identification of genomic markers as well as further advances in chemotherapy will further improve the outcome of the advanced MDT's management of stage IV colorectal cancer.

Key points

- An advanced/joint MDT meeting optimizes the treatment of stage IV colorectal cancer.
- The treatment is considered as a whole, from the diagnosis to the last treatment at the same center.
- A proficient multispecialist MDT consists of a colorectal surgeon, liver surgeon, medical and radiation oncologist, radiologist, nuclear medicine physician and pathologist.
- It is important to audit MDT outcomes to assess improvements in treatment goals.

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