



The Role of the Advanced Multidisciplinary Team (MDT) in the Management of Stage IV Colorectal Cancer



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Abstract

A proficient advanced multidisciplinary team (MDT) in the management of stage IV colorectal cancer consists of a colorectal surgeon, liver surgeon, thoracic surgeon, medical and radiation oncologist, radiologist, nuclear medicine physician, pathologist and nurse counsellor. Its role in the management of stage IV colorectal cancer is reviewed.

Keywords: Advanced multidisciplinary team, Synchronous colorectal liver metastases, Surgery, Systemic therapy, Ablation

Abbreviations: CRCL: Colorectal Cancer; CRCLM: Colorectal Cancer Liver Metastases; MDT: Multidisciplinary Team; Bcrlm: Bilobar Colorectal Liver Metastases; CT: Computed Tomography; Mrimagnetic Resonance Imaging; PET: Positron Emission Tomography; FOLFOX: Folinic Acid Plus Fluorouracil Plus Oxaliplatin; FOLFIRI: Folinic Acid Plus Fluorouracil Plus Irinotecan; XELOX: Capecitabine Plus Oxaliplatin SIRT: Selective Internal Radiotherapy; TACE: Transarterial Chemoembolization

Introduction

Colorectal cancer CRC has become the third most common malignancy world- wide and fourth for cancer mortality [1]. At CRC diagnosis, 20-25% of patients have stage IV disease in which synchronous CRC liver metastases CRCLM are present in 15-25% of cases. Metastases are confined to the liver in 70-80% of these cases [2]. CRLM is defined as liver metastases detected at or before diagnosis of the primary CRC. Early and late metachronous metastases are defined as those detected <12 months and >12 months after surgery, respectively. The reported percentage of synchronous CRLM is increasing compared with metachronous metastases, probably due to improved imaging techniques leading to earlier diagnosis. The 5-year survival rates were shorter with synchronous than with metachronous metastases 3.3% vs 6.1% [3-6], but some studies showed no significant difference [7,8]. However, synchronous CRCLM have less favourable cancer biology and expected survival than metachronous corroborated by the latter being slow-growing and its later presentation [3,5,6]. 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 N0/N1 M1 is better than that of a patient with pericolic tumour deposit with nodal N2/3 M0 disease [4]. Presumably, tumour lymphatic spread may be more disseminating than portal venous spread. Surgical resection is the most effective treatment approach for CRCLM with an overall survival of about 40% in 5 years, but only a minority of patients are suitable for upfront surgery [4,7-9,10]. In addition, up to 90% of patients with hepatic metastases have irresectable disease at the time of presentation [4,5-9].

Discussion

The advanced MDT

By bringing together all the relevant specialties involved in colorectal metastatic disease management in an advanced MDT meeting in a centralized high volume liver cancer surgery unit, the management of patients with stage IV colorectal cancer would

be optimized [4]. The advanced MDT would avoid the delay in decision making and management and thus disease progression when these patients are otherwise referred to the appropriate subspecialty discipline involved with metastatic disease. It provides coordination, continuity of care, better patient care, cost effectiveness, decrease length of hospital stay, decrease postoperative mortality and a trend towards higher survival rates [4,11,12]. The utilization of protocols, appropriate preparation of patients, audit and trial recruitments are optimized [4]. The advanced MDT in stage IV colorectal cancer essentially consists of the liver surgeon, colorectal surgeon, thoracic surgeon, radiologist, medical oncologist, clinical oncologist, interventional radiologist, pathologist, nurse specialist, nurse counselor and the patient. To provide information on potential curability the use of high-quality contrast-enhanced computed tomography CT before chemotherapy is recommended. Magnetic resonance imaging is increasingly being used preoperatively to aid detection of sub-centimetric metastases, and alongside CT in difficult situations. To evaluate operability, radiology 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. Positron emission tomography PET and PET/CT may offer additive information in detecting extrahepatic disease which may either call the attention of other specialists particularly the thoracic surgeon for lung metastases which are usually amenable to ablative therapy after liver resection, being of more favourable biology than liver metastases, or suggest palliative treatment only [4,13,14]. Although the treatment strategy depends on the clinical scenario, the disease being systemic dictates for chemotherapy before surgery in most cases [15]. In patients with resectable colorectal liver metastases progression-free survival is increased with the addition of oxaliplatin and fluorouracil chemotherapy [16]. The addition of biologic agents, antibodies specific to the epidermal growth factor receptor important in cellular growth, proliferation and programmed cell death cetuximab and the key mediator of angiogenesis - vascular endothelial growth factor bevacizumab, enhance the response to conventional chemotherapy and have become the standard of care for the treatment of metastatic colorectal cancer. They, however, lack proven benefit as adjuvant treatment of primary colon cancer [4,10,17-19]. The addition of cetuximab results in an overall survival advantage in patients with advanced disease who have the KRAS exon 2 wild-type tumour genotype [20,21].

Decision- making

The diagnosis and decision making on the management of resectable, borderline resectable or non-resectable disease is expedited in the advanced MDT. When the primary CRC is asymptomatic, liver surgery may be performed first in resectable liver metastases reverse approach after neo-adjuvant chemotherapy [4]. The borderline resectable disease will

require induction chemotherapy and restaged whereas the non-resectable will usually undergo palliative or best supportive treatment. However, modern neoadjuvant oxaliplatin-based chemotherapy [16] and a combination with targeted biologic therapy [15-22] can downstage irresectable disease and enable surgery in up to 38% of patients [23]. There is, however, decreased overall survival in these patients [24]. Initial long-term results of 'rescue surgery' in the irresectable group compared favourably with those for patients with resectable metastases at the time of presentation [25-27]. However, the recurrence rate among patients who had neoadjuvant chemotherapy and surgery for initially irresectable liver metastases was extremely high, although re-resection is attempted whenever feasible [27]. When offering multiple chemotherapy the medical oncologist decides which combination and sequence to use after full discussion of the side effects with the patient [4,10]. 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 as second line treatment [28-30]. Radiological evaluation should assess response to preoperative chemotherapy for both the primary tumour and metastases, and provide information on the tumour, margin size and micrometastases. Hepatic resection is not denied to patients with stable disease after optimal chemotherapy, provided an adequate liver remnant with inflow and outflow preservation remains [27]. As a complete radiological response does not signify a complete pathological response liver resection should include all the sites of a tumour detected prior to systemic treatment [4,27].

Resection of the primary tumour in patients with stage IV cancer is often performed to deal with presenting primary tumour symptoms and to prevent further primary tumour complications such as obstruction, major bleeding, pain and side effects related to novel targeted therapy bleeding and perforation [4]. Conversely, the new-generation systemic therapy in combination with targeted therapy is associated with response rates of 40-60% [4-10]. By not only reducing the size of metastatic lesions, the shrinking of the primary tumour may reduce local complications, such as bowel obstruction. In addition, complications after resection of a primary tumour such as an anastomotic leak, may delay or prevent initiation of systemic therapy. Whether resection of the primary tumour improves disease control by reducing tumour bulk remains unknown [31-34]. Minor liver resections 2 segments or less may be safely performed at the same time as colorectal resection [35]

Liver resection in slow responders requiring 12 or more chemotherapy cycles and portal vein occlusion to achieve respectability, is associated with poor short and long-term outcome [5,35,36]. This is due to the impaired general status

of these patients, their damaged underlying parenchyma from prolonged chemotherapy chemotherapy-associated steatohepatitis and the technical challenge in obtaining adequate curative resection [37]. Thus the benefit of the more conservative parenchymal sparing approach especially with the background knowledge of the 20% recurrence rate even after anatomical resection in these patients [38]. The combined approach of resection and ablation techniques to bilobar colorectal liver metastases bCRLM results in less morbidity than two or more hepatic resections [39-41]. Recurrent liver metastases after resection are re-resected if technically feasible or ablated radiofrequency/microwave thermal, selective internal radiotherapy SIRT, transarterial chemoembolization TACE by the interventional radiologist, and have similar long-term survival as first liver resection [42]. Third time resection may also provide long-term benefit and so these patients can now live with their cancer if the tumour biology is favourable [27,43,44].

Conclusion

The management of stage IV colorectal cancer by the advanced MDT is considered from the diagnosis to the last treatment. 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: 1 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 tumour or by staged surgery for other patients. Ongoing trials may provide evidence for chemotherapy first as opposed to colon resection first. 2 For asymptomatic CRC and non-resectable synchronous CRLM, the consensus is for optimal chemotherapy first, with the aim of making the liver metastases resectable. This would then be followed by hepatic surgery and resection of the primary tumour; 3 For symptomatic CRC and resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours but not for tumours with bleeding causing anaemia, followed by chemotherapy and then surgery for liver metastases; 4 For symptomatic CRC and non-resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours, followed by chemotherapy and then surgery for liver metastases if tumour shrinkage is achieved. For tumours with bleeding causing anaemia, induction chemotherapy is recommended to downsize both the primary tumour and liver metastases, followed by surgery at the site with the most significant tumour load usually the liver; i.e. reverse approach. The advanced MDT thus optimizes the treatment of colorectal cancer liver metastases CRCLM.

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