short review

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Cure in metastatic disease: how to manage and who is the right patient in colorectal cancer?

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Summary Metastatic colorectal cancer was long considered for palliative therapy, until significant improvement in surgical techniques and more effective chemotherapeutic regimens changed the way metastatic colon cancer patients are being treated today. Prospective trials were designed to answer the question which patient with metastatic disease could potentially be cured by a multidisciplinary approach with medical oncologists, surgeons and radiation oncology using an induction chemotherapy in combination with a targeted agent and being monitored for resectability in multidisciplinary tumor boards. Patients with oligometastatic disease should be treated with the goal of curative resection. This review will highlight studies conducted over the past 15 years addressing this issue. An algorithm is proposed illustrating how every newly diagnosed mCRC (metastatic colorectal cancer) patient could be discussed in the tumor board to decide the best treatment sequence with the best chance of cure.

Keywords Liver metastases · Colorectal cancer · Chemotherapy · Liver resection · Multidisciplinarity

a. Resectable disease

Bernhard Nordlinger and colleagues designed the first sizeable prospective randomized trial, which was practice changing in the early 2000s [1]. Patients with up to 4 liver metastases were randomized into either 3 months of FOLFOX-4 followed by liver resection and additional 3 months of the same chemotherapy (periOP) versus surgery alone. A total of 364 patients were entered into the worldwide trial and the primary endpoint of prolonging the 3-year progression-free survival (PFS) was fulfilled in the resected patients with a HR of 0.73 (0.55–0.97, $p=0.025$) and an increase of PFS at 3 years by 9.2% from 33.2% to 42.4%. Although the trial was not powered to demonstrate an overall survival (OS) benefit, OS results demonstrated a nonsignificant increase in median OS by 7 months in the periOP chemotherapy group from 54.3 months to 61.3 months (HR 0.88, $p=0.34$) after a median follow-up of 8.5 years [2].

Unfortunately there is still no consensus in the interpretation of the findings in this large study which prevented successful completion of follow-up studies combining chemotherapy with targeted agents (EORTC-BOS, -BOS2). Therefore 10 years after the initial clinical trial by Nordlinger, this is still the only randomized sizable trial in resectable patients in 2018. Smaller trials adding, for example, bevacizumab to XELOX were performed demonstrating an increased response rate but failed so far to sufficiently increase the overall survival figures [3]. However two interesting and especially important findings for surgeons and pathologists were reported: first the protective effect of bevacizumab added to an oxaliplatin-containing regimen in its ability to significantly reduce the well-known destruction of liver sinusoids leading to the so-called sinusoidal obstruction syndrome (SOS). This mechanism was able to reduce the complication rate induced by the “blue liver” in patients undergoing liver resections for colorectal liver metastases after neoadjuvant chemotherapy [4]. Second important finding was the histopathological effects of the addition of bevacizumab to an oxaliplatin-

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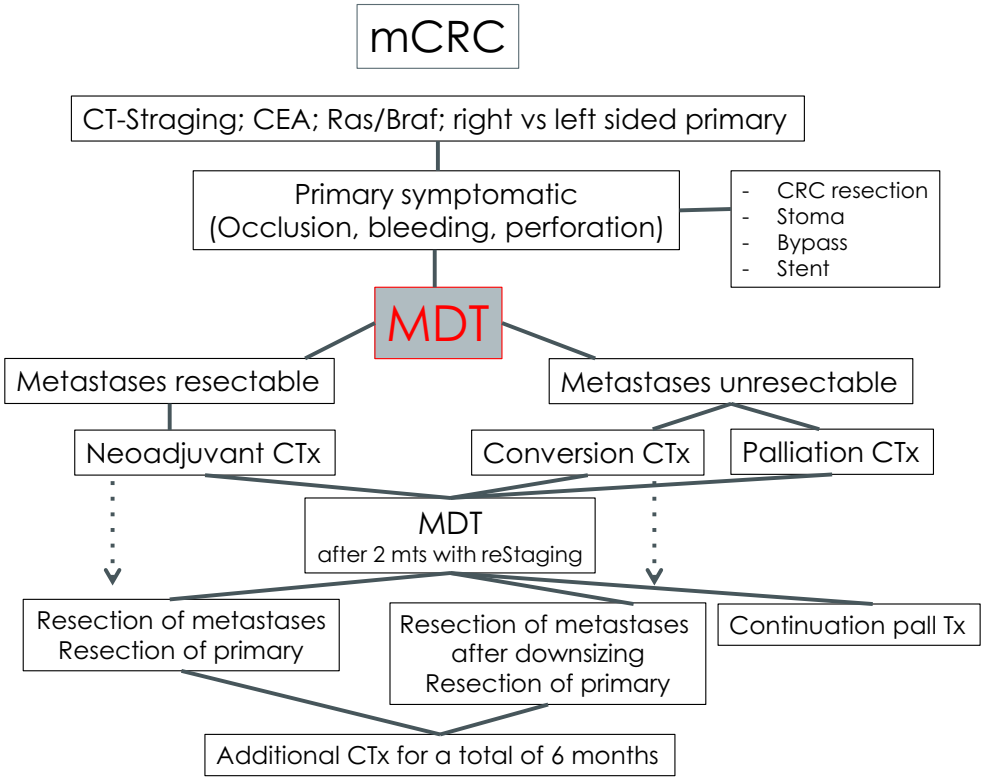

Fig. 1 Metastatic colorectal cancer

containing neoadjuvant regimen: the amount of remaining viable tumor cells in the resected metastases was significantly reduced leading to the first sign of improved patient outcome [5, 6].

b. Unresectable disease

The majority of mCRC patients however present with unresectable disease and a structured algorithm is required to offer them the potential of the most effective systemic therapy together with highly experienced surgeons to have a chance of cure after significant response [7]. The most important point in this initially unresectable situation is the discussion of the patient in a multidisciplinary tumor board (MDT), where all specialists treating mCRC patients should review and discuss the most effective therapeutic approach [8]. Patients are mostly diagnosed with synchronous disease; this raises the question whether the primary tumor is causing symptoms. We have learned in recent years that the primary responds to systemic therapy just as well as the metastases and that even mildly symptomatic patients improve after a single cycle of potent systemic therapy. Therefore our current algorithm starts with systemic therapy as soon as possible unless a patients presents clinically with obstructing symptoms such as an ileus. If a patient is unresectable the tumor board still has to discuss if sufficient tumor shrinkage may lead to potential curative surgery. Initial categorization and deciding on treatment goal is critical and selects the best chemotherapy combination which is also based on the patient's performance status [8]. Fit patients who are aimed for downsizing of their metastases may be offered triplet combinations with an antibody based on their Ras/Braf tumor characteristics. The triplet combination FOLFOXIRI has clearly demonstrated higher response rates than doublets and is therefore recommended at least for the first 2–4 months with regular review of the scans prior to a tumor board discussion regarding the achievement of potential resectability [9]. The triplet is combined with an EGFR-antibody or a VEGF-antibody dependent upon the initial tumor molecular characteristics and the experience of the treating physician since management of potential side effects is crucial. The most available published data are available from the combination of FOLFOXIRI with bevacizumab. These studies demonstrated improved response rates and secondary resection rates [10] which are highly clinically significant when discussing the potential of cure in initially unresectable patients [11]. Less consistent but still important results have been demonstrated with FOLFOXIRI and cetuximab or panitumumab [12–14]. When interpreting the results of downsizing and achieving secondary resectability, it is important to review the initial trial inclusion characteristics and the existence of a multidisciplinary team in the decision-making process. This has been nicely shown recently where it became obvious that far more could be achieved for mCRC patients if initial multidisciplinarity is compulsory [15]. It is not only important to involve liver surgeons into the attempt of

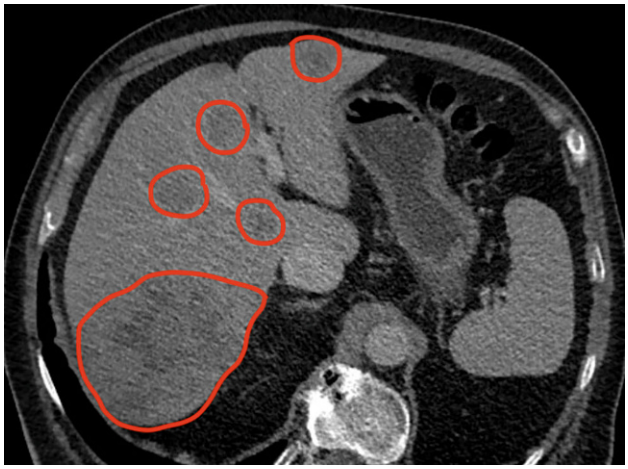

Fig. 2 Multiple liver metastasis. *Red circles* demonstrate liver metastasis

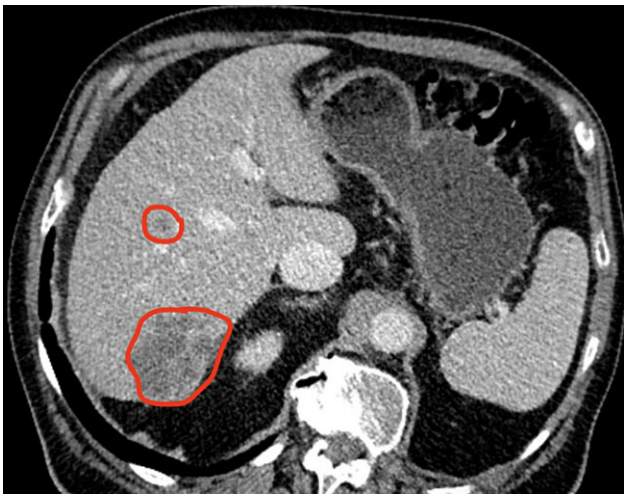

Fig. 4 Significant downsizing. *Red circles* remaining liver metastasis

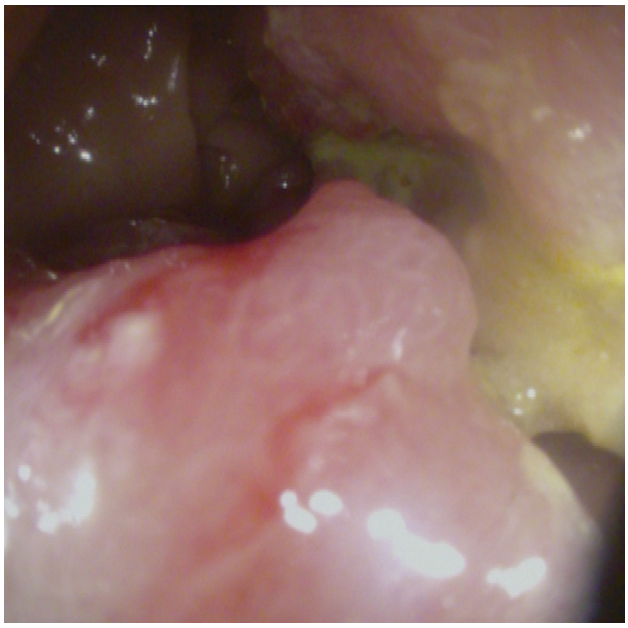

Fig. 3 Coloscopic view of the primary

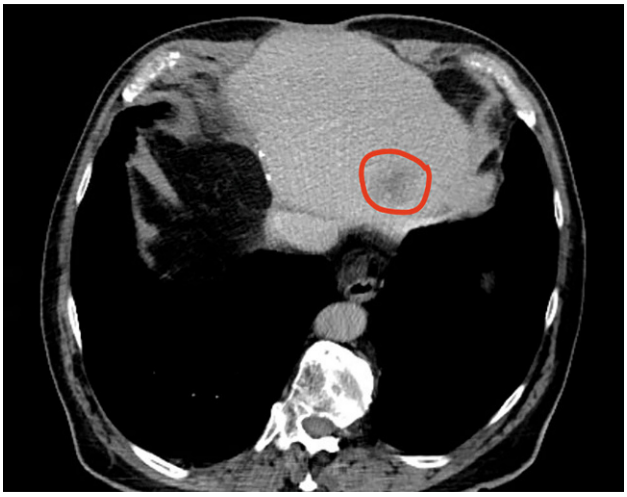

Fig. 5 Recurrent liver metastasis in left lobe. *Red circle* liver metastasis

cure, but similarly lung surgeons for responding lung metastases [16, 17]. For the discussions in the tumor board it is essential to keep in mind that we should consider curative resection in responding metastases as soon as possible because in most cases only patients with the resected metastases have the chance of cure [18]. If the removal of all metastases is technically demanding or impossible a combination of surgery with a tumor-destructing device (radiofrequency ablation [RFA] or microwave ablation [MVA]) is possible and has demonstrated an impressive improvement in long-term outcome compared with systemic therapy alone [19].

If a complete macroscopic tumor removal has been achieved after sufficient downsizing of the metastatic disease, it is important for the patients to remain in the treatment algorithm of an experienced team to decide upon composition of the adjuvant therapy, the length of it and the follow-up restaging intervals. Last but not least the same team has to decide how to treat a potential recurrence detected in a follow-up scan which with short intervals of, for example, 3 months can again be potentially curative. Patients with initial wide spread disease often require multiple attempts of surgery to resect all remaining metastases; therefore it is not unusual to perform a second or third liver resection prior to long lasting recurrence-free survival times [20].

Summary

Metastatic colorectal cancer is a heterogeneous disease and can be a complex diagnosis. For example mCRC can include patients with a single metastasis developed years after lymph node negative primary colorectal cancer removal or a patient diagnosed synchronously with a T4 primary CRC and numerous metastases in several organs. Therefore the most important step in the decision tree towards the best treatment for mCRC patients is a proper initial staging including a CT scan of thorax and abdomen together with tumor markers (CEA, CA 19-9), enough biopsy material of any tumor site to perform Ras/Braf analyses, knowledge of the location of the primary CRC (sidedness) and not of minor importance the knowledge of the performance status and the wishes of the patient. As soon as all the above information is available the patients has to be discussed in a multidisciplinary tumor board with specialists of radiology, surgical-, medical- and radiation oncology, pathology, interventional radiology, gastroenterology AND most importantly the case manager who knows the patient and is his guide throughout the upcoming treatment. The tumor board decides which therapy should be given and the effectiveness of this decision will be rediscussed after 2 months with repeated staging investigations. If treatment decisions follow this algorithm, the potential of cure for mCRC patients becomes apparent.

Algorithm

The decision tree for patients newly diagnosed with mCRC from the initial diagnose to a potential curative approach is shown in Fig. 1.

Typical patient scenario

A 78-year-old patient, ECOG 0, presents with asymptomatic sigmoid colon cancer with bilobar liver metastases. The diagnosis was made coincidentally during an ultrasound of the liver as restaging for his superficial bladder cancer, which had been treated in the past. CT staging revealed numerous liver metastases (Fig. 2) and an asymptomatic sigmoid cancer (Fig. 3); molecular pathology revealed a Ras/Braf wild type tumor, the initial CEA was markedly elevated with 1670 µg/L, the CA19-9 was normal.

In the MDT meeting 2 months of FOLFOXIRI + bevacizumab was recommended and after in total 4 months of CTx the patient presented with sufficient radiological partial response (Fig. 4; the CEA dropped to 79!); a two stage liver resection (ALPPS) was performed after his liver was trained with a specific fasting therapy. The primary sigmoid cancer was removed 4 weeks after the second liver resection. The patient received adjuvant FOLFOX plus bevacizumab for additional 2 months which resulted in a total of 6 months of chemotherapy. In a follow-up CT scan a recurrent liver metastasis (Fig. 5) was detected 7 months later and the MDT board decided for a repeat liver resection, which was done uneventfully. Patient remained in 3 monthly follow-up for 2 years and is currently in half yearly controls 3 years after his initial diagnosis of unresectable mCRC without recurrent disease.

Conflict of interest T. Gruenberger, P. Jonas, R. Lutz, and B. Gruenberger declare that they have no competing interests.

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