Oligometastatic Disease in Colorectal Cancer – How to Proceed?

Felix Aigner    Johann Pratschke    Moritz Schmelzle

Department of Surgery, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, Campus Virchow-Klinikum, Berlin, Germany

Keywords
Synchronous · Liver-first · Resectability · Oligometastatic · Multimodal

Summary
Background: Oligometastatic disease in colorectal cancer may affect the liver, lung, and peritoneum. This review mainly focuses on colorectal liver metastases (CRLM) and highlights recommendations and therapeutic strategies drawn from the current literature and consensus conferences. The following data address a paradigm shift in surgical approaches to CRLM, pushing the limits of multimodal treatment concepts. Methods: A systematic review of the relevant literature on multimodal treatment strategies for synchronous and metachronous CRLM is presented. Results: The choice of treatment strategy depends on the clinical scenario; however, perioperative chemotherapy and the liver-first concept in synchronous CRLM are favored with subsequent partial extended liver resection with or without various augmentation techniques for liver surgery. Conclusion: Surgical strategies should be strongly defined with regard to an adequate liver remnant. All patients with synchronous CRLM should be evaluated by a multidisciplinary team.

Prognosis
The prognosis of mCRC deteriorates with the synchronicity of the metastases and is worse when metastases are detected at or 1 month before the diagnosis of the primary tumor versus up to 6 months or 6–12 months after diagnosis [2]. The 5-year survival after R0 resection of colorectal liver metastases (CRLM) has been reported to be 25–40% [3].

Methods
Recommendations within this review are derived from data from the current literature. A PubMed search was carried out with the following search terms: ‘colorectal cancer’, ‘metastases’, ‘treatment’, ‘oligometastatic’, ‘consensus’.

Results
Definition/Subgroups
Patients with mCRC can be principally divided into four clinical groups according to treatment intention [1]:

Introduction
Colorectal cancer (CRC) is the second most frequent cancer and represents 13% of all cancer cases in Europe. Approximately one fourth of all patients show metastases at the initial diagnosis, and almost 50% of CRC patients will develop metastases. The CRC-related 5-year survival rate approaches 60% [1]. The primary sites of colorectal metastasis are the liver and lungs; however, peritoneal carcinomatosis may result from T4 CRC, especially in connection with tumor perforation.

Discrepancies exist in the definition of synchronous metastases in the literature, such as metastases detected at or before diagnosis or surgery of the primary tumor, or metastases detected up to 3–6 months. Also, in the absence of data from randomized controlled trials, no treatment algorithm can be provided to date [2]. A multidisciplinary approach for selecting the best treatment strategy is mandatory in metastatic CRC (mCRC).

The aim of this review is to offer recommendations as to how to proceed with oligometastatic disease in CRC.
(1) Patients suitable for resection of liver and/or lung metastases.
(2) Patients with metastatic disease potentially resectable with curative intent, but requiring downsizing with the most active ‘induction’ chemotherapy to enable secondary surgery.
(3) Patients with disseminated disease, technically never/unlikely resectable metastatic disease suitable for intermediate intensive treatment.
(4) Patients with clearly unresectable mCRC.

However, the outcome of patients with mCRC has remarkably improved over the last years with convincing survival rates [1].

Diagnosis
Routine CRC staging includes clinical examination, complete colonoscopy, histology of the primary tumor, computed tomography (CT) scans of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) and endorectal ultrasound in rectal cancer, and tumor marker status (carcinoembryonic antigen (CEA)). Clinical examination with regard to intensive chemotherapy should include blood counts, liver and renal function tests, and CEA.

Imaging Studies
The best methods for staging CRLM are CT and MRI. The sensitivity of MRI can be enhanced using liver-specific contrast agents such as gadoxetic acid (Primovist®/Eovist®; Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA) and gadobutrol (Gadovist®; Bayer Shering Pharma, Berlin, Germany). A diagnostic bias, however, appears with the incidence of vanishing liver metastases after neoadjuvant treatment. Many studies that have described the phenomenon of vanishing liver metastases only used CT and intraoperative ultrasound (with only scarce evidence for perioperative detection of vanishing liver metastases even with contrast enhancement [4]) to assess the response to neoadjuvant systemic therapy.

In up to 80% of resected regions in which vanishing liver metastases had been observed, viable tumor residuals were detected, and conservative management of radiologically disappeared liver metastases resulted in 19–74% local recurrence, mostly within 2 years [5]. Hence, even liver metastases that disappear after neoadjuvant chemotherapy require an aggressive surgical approach, and restaging modalities should include at least a combination of CT and contrast-enhanced MRI.

Positron emission tomography (PET)-CT scans can be employed for the detection of extrhepatic metastatic or recurrent disease; however, studies have not demonstrated any beneficial effect on disease-free or overall survival through decision-changing regarding treatment management following PET-CT performance [3].

Regarding liver resection response based on size, morphological criteria of CRLM following RECIST and assessment of steatosis and signs of portal hypertension as well as evaluation of the predicted future liver remnant are key indicators of response that should be provided by the radiologist.

Molecular Biology
Synchronous and metachronous CRLM are still not distinguishable by biomarker studies; however, specific biomarkers such as epidermal growth factor receptor (EGFR, KRAS wild-type expression) mutations have been associated with worse disease-free and overall survival following CRLM resection [2, 6].

Liver Resection – Strategy and Technical Aspects

Liver Surgery – General Aspects
During the last decade, surgery has become an established part of multimodal therapy concepts in CRLM. Based on recent prospective data and multiple retrospective analyses, 5-year survival rates of 30–50% could be repeatedly demonstrated at experienced centers [7, 8]. Importantly, survival rates after liver resection do not differ between patients undergoing surgery for synchronous or metachronous CRLM [8].

Consequently, surgery is recommended as first-line therapy for technically resectable CRLM in patients suitable for operation according to various national guidelines [3]. Patients with R0 resectable liver and lung metastases should be considered for primary surgery depending on their clinical status. This decision must be discussed and made within a multidisciplinary board. Symptomatic primary tumors (bleeding, obstruction, or perforation) must be considered for emergency surgery in most cases (except for bleeding) as the primary treatment concept. It should be kept in mind that resectability of liver metastases is not only defined by technical but also functional and oncological criteria. Technical resectability is dependent on the center and the surgeon [9], and is not limited by the number or size of the metastases or bilobar involvement.

Surgery in Multimodal Therapy Concepts
Although survival data after liver resection for CRLM are promising, intra- and extrahepatic recurrence is evident in 50–70% of patients within 5 years of surgery [10]. Prognosis with regard to recurrent liver metastases can be preoperatively evaluated using scoring systems according to Fong et al. [11], Nordlinger et al. [12], and Rees et al. [7]. Even in patients with recurrent disease, surgery has risen to the forefront of promising treatment strategies as a vital part of multimodal therapy concepts in patients suffering from CRLM.

To date, the timing of liver resection and the management of the primary tumor in synchronous CRLM are still being debated. Some expert panel recommendations focus on neoadjuvant chemotherapy before surgery of the CRLM in patients with more than one poor prognostic factor (i.e. multiple CRLM, >5 cm in diameter, lymph node-positive primary, and high tumor markers [11, 13]), even if the metastases are technically resectable [14]. Neoadjuvant chemotherapy before liver surgery addresses micrometastases and circulating tumor cells in order to reduce recurrent metastatic disease in resectable CRLM, and downsizes liver lesions with the aim of achieving resectability in initially unresectable CRLM. However, neoadjuvant treatment strategies with cytotoxic doublets (e.g. oxaliplatin- or irinotecan-based therapy) and targeted agents (e.g. bevacicumab or cetuximab) cause time-dependent liver dam-
age due to vascular lesions (sinusoidal obstruction syndrome) following oxaliplatin-based chemotherapy and steatohepatitis with higher rates of infectious complications following irinotecan-based chemotherapy, resulting in increased 90-day mortality due to liver failure after surgery [15]. Therefore, the duration of preoperative chemotherapy should be limited to 3 months. Neoadjuvant chemotherapy, especially when adding targeted agents like anti-vascular endothelial growth factor antibodies with augmented chemotherapy-induced hepatic lesions and diminished regeneration after resection, should be stopped at least 6 weeks prior to surgery for bevacizumab and 3–4 weeks for 5-fluorouracil/leucovorin (5-FU/LV) [14].

Figures 1 and 2 show possible clinical scenarios and treatment options for synchronous CRLM.

Whether CRLM should be treated by surgery combined with perioperative chemotherapy or surgery alone followed by palliative chemotherapy in unresectable recurrent disease is still controversial. In the recent EPOC trial, no difference was found in overall survival after addition of perioperative chemotherapy with FOLFOX4 (oxaliplatin, 5-FU, LV) compared with surgery alone for CRLM [16]. However, the previously observed benefit in progression-free survival with the addition of perioperative chemotherapy might indeed favor perioperative chemotherapy, although no change in survival was seen (EORTC new study [16]). As demonstrated in figures 1 and 2, doublet or triplet chemotherapy including oxaliplatin and irinotecan and targeted agents depending on RAS status are promising strategies which can increase the proportion of potentially resectable patients by approximately 30% [17].

Moreover, significant differences in overall survival exist favoring patients with left-sided tumors, who had a markedly better prognosis than those with right-sided tumors within the RAS wildtype population [18].

Proposed benefits of neoadjuvant chemotherapy include a preoperative selection of biologically aggressive metastases. According to a LiverMetSurvey Registry analysis of 12,465 patients, the overall survival of patients with disease progression after neoadjuvant chemotherapy followed by surgery is approximately 15% compared to 40–45% in patients with complete or partial response or stable disease after neoadjuvant chemotherapy followed by surgery [19]. Of note, patients with disease progression should not generally be excluded from liver resection; however, radiological response to chemotherapy in combination with the evaluation of other biological prognostic factors, e.g. size and number of metastases or CEA levels [7], might help to individualize therapy concepts.

**Unresectable Liver Metastases**

Irrespective of the question of whether perioperative chemotherapy should be favored or not, patients with technically unresectable CRLM should be scheduled for conversion chemotherapy. Bischof et al. [20] reported successful down-sizing leading to secondary resectability in up to 20% of initially unresectable CRLM. Remarkably, all patients included in the phase III FIRE-3 study considered initially unresectable and scheduled for intensive systemic treatment of CRLM were recently re-evaluated by an expert panel of experienced hepatobiliary surgeons. This review
Combination Therapy with Surgery and Ablation

According to a recent meta-analysis, liver resection of singular CRLM appears to be associated with superior survival rates when compared to radiofrequency ablation (RFA), with no differences in postoperative morbidity and mortality. However, patients with unresectable CRLM following chemotherapy might indeed be evaluated for individual therapy concepts, e.g. combined resection/ablation approaches using additional intra- or postoperative RFA or brachytherapy. Given the low evidence of retrospective single center analyses per se, strong recommendations for combined resection/ablation approaches cannot be given so far [23]. However, according to convincing experience in early hepatocellular carcinoma [24], small but unresectable metastases are being increasingly addressed by ablation in experienced hepatobiliary centers if the predominant number of metastases can be technically addressed by resection. Low evidence even suggests that individual therapy concepts favoring surgery might be indicated in selected patients with resectable CRLM and local peritoneal spread [25].

Strategies in Synchronous Liver Metastases

Based on historical data, combined resection of the primary colorectal tumor together with major liver resection of synchronous CRLM should be avoided due to increased morbidity and perioperative mortality rates. This dogma has led to novel strategical approaches, e.g. the liver-first concept. Resection of CRLM 4–6 weeks before colorectal surgery for the primary tumor can be performed with morbidity and mortality rates comparable to established primary-first paradigms [26]. The liver-first concept has immense advantages and should be favored in cases where progression of CRLM is suspected after colorectal surgery, resulting in presumed unresectability, e.g. evident in large metastases or metast-
safe performance of liver surgery, especially after chemotherapy.

using liver function tests such as LiMAX [28] is essential for the
tive morbidity. However, evaluation of the functional liver capacity
therapy of ALPPS) after sufficient hypertrophy. Of note, neoadjuvant chemo-
liver resection 4–6 weeks or even earlier after 1–2 weeks (following
branches with or without transection of the liver parenchyma (as -
embolization (PVE) or ligation (PVL) of the right-sided portal vein
nomenon is called hypertrophy and can be induced before ex-
pacity of the liver to regenerate after loss of liver volume. This phe-
 metastases close to large vessels or in patients at high risk of a delayed
treatment course following colorectal surgery due to complica-
tions. Local control of the primary tumor (e.g. rectal cancer in the
mid or lower third) without delaying neoadjuvant treatment of CRLM can be achieved by short-course radiation with subsequent induction chemotherapy using cytotoxic doublets/triplets and/or targeted agents.

Liver Resection for Bilobar Metastases
Patients with bilobar liver metastases have been considered not
good candidates for liver resection in the past. Nowadays, it is well
accepted that even patients with bilobar metastases might benefit
from liver resection and should be evaluated for technical resecta-
ability. Different techniques and strategies have been established for
bilobar liver metastases within the last years including two-stage
approaches and techniques for liver augmentation.

Two-stage hepatectomy strategies are based on the natural ca-
pacity of the liver to regenerate after loss of liver volume. This phe-
nomenon is called hypertrophy and can be induced before ex-
tended right hepatectomies by several techniques, e.g. portal vein
emobilization (PVE) or ligation (PVL) of the right-sided portal vein
branches with or without transection of the liver parenchyma (as-
ociating liver partition with portal vein ligation for staged hepa-
tectomies (ALPPS)) between the left lateral (segments 2 und 3) and
left medial (segment 4) sector [27]. In the case of bilobar liver me-
tastases, left lateral metastases are cleared in a first operation com-
bined with PVE, PVL, or ALPPS, followed by an extended right
liver resection 4–6 weeks or even earlier after 1–2 weeks (following
ALPPS) after sufficient hypertrophy. Of note, neoadjuvant chemo-
therapy of ≤5 cycles does not significantly increase the periopera-
tive morbidity. However, evaluation of the functional liver capacity
using liver function tests such as LiMAX [28] is essential for the
safe performance of liver surgery, especially after chemotherapy.

Table 1 demonstrates the variety of resection or local ablative treat-
ment options for CRLM.

Minimally Invasive Liver Surgery
Minimally invasive surgery has several benefits over conven-
tional open surgery and has been established during the last years
in the field of colorectal surgery and others. Several studies con-
firm that laparoscopic surgery is a safe and radical approach
with non-inferior oncological results compared to open colorectal
surgery [29]. Possible approaches for laparoscopic liver resection
were limited to non-anatomical resections or anatomical minor re-
sections, e.g. bisegmentectomy, for many years. During the last
years, techniques in laparoscopic liver resection have dramatically
improved, allowing laparoscopic liver resections to be performed
safely nowadays [30]. Even major liver surgery, e.g. (extended)
hemihepatectomy, can be performed safely in experienced hepatob-
iliary centers on a routine basis. Even though randomized con-
trolled trials comparing open with laparoscopic surgery for CRLM
are still missing, recent meta-analyses have confirmed the well-
known clinical advantages of laparoscopic surgery in the treatment
of CRLM (e.g. lower blood loss, shorter hospital stay, and lower
local recurrence rates) with no significant differences in postopera-
tive mortality, 5-year disease-free-survival, and overall survival
[31]. One of the most common indications for laparoscopic liver
resections is CRLM. From our point of view, conventional open
hemihepatectomy should be limited to selected cases and is gener-
ally no longer indicated for resectable CRLM. Even suspected hilar
lymph node metastases requiring radical hilar lymphadenectomy
no longer represent a contraindication for laparoscopic ap-
proaches. Conventional minimally invasive laparoscopy might be
switched to hand-assisted laparoscopy in complex cases to allow
safe and radical lymphadenectomy in experienced hands. Further-
more, the laparoscopic approach is beneficial for staged or multi-
modal surgical strategies for addressing stage IV CRC (e.g. simulta-
nous primary resection and atypical liver resection or intraopera-
tive local ablative techniques).

Conclusion
A multimodal approach to oligometastatic disease in CRC is
mandatory for optimal patient treatment, especially with regard to
staged liver approaches. Patients with stable disease after induction
chemotherapy should not be denied hepatic resection. Surgical
strategies should be strongly defined with regard to an adequate
liver remnant. All patients with synchronous CRLM should be
evaluated by a multidisciplinary team.

Disclosure Statement
The authors declare no conflict of interest.


