



## What Are the Surgical Options in Patients with Synchronous Rectal Cancer?

Johannes H.W. de Wilt, Martinus J. van Amerongen,  
and Jorine 't Lam-Boer

### 53.1 Introduction

Approximately 20–25% of patients with colorectal cancer present with metastatic disease at the time of diagnosis [1, 2]. The incidence of metastases varies between different stages, where patients with locally advanced or node-positive tumors have a higher risk for metastatic disease compared to patients with early tumors. The risk and pattern of metastasis are also highly dependent on location of the colorectal tumor and histological subtype. As an example, histological subtypes such as mucinous adenocarcinoma have more often peritoneal metastases, and signet ring cell tumors have more often distant lymph node metastases [3]. Lung metastases are more often found in rectal cancer patients as compared to colon cancer patients, and the incidence is increasing over time, probably due to current improvements in imaging techniques [2].

Nowadays, nearly all colorectal cancer patients are staged with CT of the thorax, abdomen, and pelvis, whereas in the past only abdominal ultrasound and chest X-rays were performed. As a result, patients with rectal cancer and distant metastases are now accurately staged, and appropriate treatment regimens can be applied to each patient. Treatment of patients who present with rectal cancer and distant metastases depends primarily on the condition, age, and frailty of the patients, but obviously resectability of the primary tumor and the metastases is important. Involvement of modern multimodality treatment and thorough discussions in a multidisciplinary tumor board is important in optimizing patient outcome [4].

### 53.2 Rectal Cancer with Resectable Metastases

The majority of patients with metastases who undergo treatment of both the primary and the metastases have liver metastases. There are many papers in the literature describing results of patients undergoing resection for liver metastases with overall survival rates of 30–60% depending on the characteristics of the study population [5–8]. Various factors for the selection of patients who benefit most of resection have been described [9–11]. The most well-known clinical criteria are those established by Fong, which contains the

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J.H.W. de Wilt (✉) • J. 't Lam-Boer  
Department of Surgery, Radboud University  
Medical Center, PO Box 9101, 6500 HB,  
Nijmegen, The Netherlands  
e-mail: [hans.dewilt@radboudumc.nl](mailto:hans.dewilt@radboudumc.nl)

M.J. van Amerongen  
Department of Radiology and Nuclear Medicine,  
Radboud University Medical Center,  
PO Box 9101, 6500 HB, Nijmegen, The Netherlands

following risk factors: a CEA level >200 ng/ml, the node positivity of the primary tumor, number of liver metastases (>1) and size of the metastases (>5 cm), and a disease-free interval between primary tumor and metastases shorter than 12 months [10]. This last item is also included in this risk score, because survival of these patients is slightly lower compared to metachronous disease, although literature on this subject is contradictory [10, 12–14]. At present, metastasectomy should be considered for all patients with colorectal liver metastases when the patient is fit for surgery, when the expected remnant liver is at least 20% of the preoperative volume and if resection is possible with regard to vascular and biliary structures and when no unresectable extrahepatic metastases are present [15, 16].

As the criteria for resectability are evolving fast, determining resectability is challenging for non-liver surgeons. Even in high-volume centers (UK cancer network), almost two-thirds of patients with tumors deemed unresectable by non-liver surgeons were considered potentially resectable by a panel of specialist liver surgeons [17]. Therefore, patients with liver metastases should be discussed in hospitals with liver surgeons. On the other hand, it should be remarked that there is considerable interindividual variation in the decision-making process between liver surgeons [18], which highlights the importance of multidisciplinary liver tumor boards to optimize timing of surgical intervention and multidisciplinary treatment. A recent study in the Netherlands reported that between 2004 and 2012, the number of patients with colorectal cancer and synchronous metastases who underwent liver surgery increased from 4% to 24%, which can probably in part be contributed to improved referral patterns [8]. Several studies from different countries have demonstrated that there is still a considerable variation in the utilization of liver resection, which might indicate that further optimization of the evaluation of resectability will potentially lead to an important improvement in the identification of patients and might potentially lead to an improvement in overall survival [6].

Also surgical removal of extrahepatic metastases can often lead to long-term survival, such

as resection of lung metastases [19] or cytoreductive surgery of peritoneal metastases in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) [20].

### 53.2.1 Systemic Therapy

If metastases are considered resectable, systemic chemotherapy is not necessary in these patients. Results from the EORTC intergroup trial 40,983 demonstrated no survival benefit in patients with resectable liver metastases with or without pre- and postoperative chemotherapy [21]. Two retrospective studies demonstrated only a potential benefit for (neo)adjuvant chemotherapy for high-risk patients according to the Fong criteria [22, 23]. Systemic therapy should therefore preferably only be used in a randomized trial and not as standard therapy for patients with resectable liver metastases [24]. Although systemic therapy is not strictly indicated for treating liver metastases, several options are possible depending on the need for radiotherapy of the rectal cancer. If the rectal tumor has no obvious signs of lymph node involvement and the mesorectal fascia is not threatened, rectal surgery without additional treatment is possible. However, most patients with metastatic disease will have locally advanced tumors which need some form of radiotherapy for the rectal tumor in order to prevent local recurrence and improve overall survival.

### 53.2.2 “Liver-First Approach”

Although no data in the literature describe an improved outcome for patients treated with the “liver-first approach,” it seems a promising and straightforward way of treating patients without losing time to treat the primary rectal tumor. Patients who undergo 5-FU-based chemoradiation therapy for 5 weeks and have another 8–10 weeks waiting time before undergoing rectal surgery have to wait at least 3 months before liver metastases can be treated. The time to undergo liver surgery might even be further prolonged in case of complications which is not

uncommon in colorectal surgery. Using this liver-first approach, the liver metastases are preferably treated before or in the waiting time after (chemo) radiation therapy. With this approach, good results have been reported with a high number of patients undergoing both liver and rectal surgeries [25–27]. A possible concern for this approach is the progression of disease in initially resectable patients. However, if patients show progression of the primary tumor after resection of the liver metastases, it is a sign of less favorable disease, and further unnecessary colorectal surgery in such cases can be avoided.

### 53.2.3 “One-Staged or Two-Staged Resection”

Treatment of the primary tumor and the liver metastases can be performed in one surgical procedure. Obviously this depends on the availability of both an experienced colorectal and liver surgeon but also on the extent of the surgical procedure. The combination of a major liver resection and rectal surgery has a higher risk of complications; however, by omitting a secondary resection, the total amount of complications and total hospital stay and costs are lower in a one-staged approach. Arguments for a two-staged resection of the primary and liver metastases are the opportunity for recovery between surgeries and the possibility for selection of patients with less favorable disease, meaning patients with progression of disease after initial resection [28, 29]. Although there are different advantages to each of the two techniques concerning the short-term results, reports have been described which show excellent results for the one-staged surgery. Furthermore, no differences are found concerning the overall survival between a one-staged and two-staged approach [29–31]. Since the outcomes between the two treatment strategies are comparable, the choice for either one- or two-staged surgery should depend on individual patient characteristics such as tumor burden and expected technical difficulties during surgery. For example, patient who would undergo a straightforward procedure for both primary and

liver metastases could be eligible for a one-staged approach. However, if patients present with borderline resectable or initially unresectable disease which require downstaging, preference should be given to a more staged approach [32].

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## 53.3 Rectal Cancer with Unresectable Metastases

Liver metastases can be unresectable at the time of diagnoses due to the number of metastases, lack of reserve liver parenchyma, ill location, or the presence of extrahepatic disease. Especially in patients with liver-only metastases, various treatment modalities have been introduced in recent years such as induction systemic therapy, two-staged liver resection, portal embolization, and different ablation techniques [18, 33–35].

### 53.3.1 Potentially Resectable Metastases

Neo-adjuvant systemic therapy is widely used for potentially resectable liver metastases and makes tumors resectable in 15–60% of cases with excellent results [18, 33]. Again, criteria for being not resectable before or after neo-adjuvant chemotherapy are not well defined as well as the optimal systemic therapy. Not only the presence of dedicated liver surgeons but also a dedicated medical oncologist is demonstrated to be important in considering patients suitable for neo-adjuvant chemotherapy in patients with liver metastases [36]. A nationwide trial with a liver expert panel and various induction therapy options is now running in the Netherlands to study and determine the optimal treatment [37].

Other treatment options to provide curative treatment to patients with unresectable liver metastases have been developed including but not limited to cryosurgery, microwave ablation (MWA), and radiofrequency ablation (RFA). Of these different modalities, RFA is currently the most used, which uses alternating current to induce coagulation at the site of the tumor [35].

RFA can be performed either during the surgery (open/laparoscopic) or percutaneously. The open/laparoscopic approach is most invasive but has the benefit that it can be combined with additional resections [38]. RFA shows low complications rates, typically ranging between 6% and 9%; however, patients develop more often local recurrent disease. Ablative techniques achieve the highest local success in solitary tumors or few metastases ( $\leq 5$ ) no larger than 3 cm in diameter. Despite the higher rate of local recurrence, the 5-year overall survival of patients with limited hepatic metastases treated with RFA is reported around 40%. In case resection is not possible, even after downstaging, RFA provides an increased survival as compared to palliative chemotherapy and should be used in clinical practice on a case-by-case basis [38–40].

### 53.3.2 Unresectable Metastases

In the majority of patients, metastases have spread in such way that no curative options are available. Treatment in patients with unresectable metastatic CRC should be based on two objectives: first, to improve or maintain the quality of life, and, secondly, to prolong the survival. The increasing use of palliative systemic therapy during the past two decades has led to a remarkable increase in overall survival [41].

Traditionally, primary tumor resection was preferred in patients with incurable stage IV rectal cancer to prevent, or treat, complications such as bleeding, obstruction, and perforation [42]. When such complications do already exist, the indication for surgery seems obvious. However, in some cases, the tumor might be unresectable, or surgery is not feasible for other reasons (e.g., because of the patient's condition). In such cases, stenting could provide feasible palliation for patients with bowel obstruction [43].

In recent years, prophylactic resection of the primary tumor in asymptomatic patients has become more controversial. The 30-day mortality rates after elective surgery of the primary tumor in patients with stage IV disease range

between 1.3% and 11.7%, which is higher than reported after surgery in stage I–III patients [44]. Additionally, initial resection delays starting chemotherapy, and local control might be reached with systemic treatment and/or radiation as well [45–47]. Indeed, when no resection is performed, only a small portion of patients would require surgical treatment for complications of the primary tumor [48–50]. On the other hand, retrospective studies show that survival of patients with synchronous unresectable metastatic disease is significantly higher in patients who underwent resection of the primary tumor, compared to patients with the primary tumor in situ [51–54]. Currently, several randomized controlled trials are ongoing to investigate the benefit of palliative primary tumor resection in asymptomatic patients [55, 56].

### Conclusion

Management of rectal cancer patients with synchronous metastases is a common clinical challenge, and treatment is based on various clinical items. Many treatment options are available for rectal cancer patients with metastatic disease depending on the general condition of the patient and extent of both the primary tumor and the metastases. A patient-tailored multidisciplinary approach is essential to give each patient the best available treatment. Various international studies are currently including patients in randomized trials to further define the best curative and palliative options for rectal cancer patients with synchronous metastases.

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