Chapter 23
Resection of the Rectal Primary Tumor in the Setting of Metastatic Disease

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In 2014, The American Cancer Society estimated that 40,000 new cases of rectal cancer were diagnosed [1]. Approximately 15–25% of patients have metastatic disease at the time of diagnosis, with liver and lung metastases being the most common sites [2–5].

Historically, the treatment options were limited for these patients and the prognosis overall was fairly grim. Over the past several decades, however, there have been considerable advances in systemic chemotherapy, the more routine use of biologic agents and in surgical techniques which have translated into tangible improvements in the median survival and in the progression-free survival (PFS), even in those with advanced colorectal cancers. As a consequence, the overall survival of a patient with stage IV colorectal cancer was 20% in the 1980s and 1990s, but more recently, between 2003 and 2009, the 2-year overall survival (OS) was over 40% [6].

A multi-disciplinary approach to these patients is extremely important because of the variety of options available, as well as because of the variability in presentation and the coincident co-morbidities of these patients. Discussion of each individual case at a multidisciplinary conference is recommended [7]. For example, management of a 48 year-old healthy patient with rectal cancer and a solitary liver metastasis will likely be approached differently from an elderly frail patient with multi-site metastatic disease. The patient's symptoms, medical condition and distribution of disease need to be carefully considered.

The treatment planning for these patients has also changed in recent years with the development of effective chemotherapeutic agents. It is well established that systemic chemotherapy can improve the PFS and the OS for many patients with

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stage IV disease who have an acceptable performance status [8]. Currently, results from phase III trials addressing specifics regarding optimal sequencing of chemotherapy, radiation therapy and surgery are lacking.

Despite this uncertainty, clinical practice is changing. Analysis of the U.S. Surveillance, Epidemiology and End Results database has shown that 45% of stage IV rectal cancer patients underwent resection of the primary tumor from 1988 to 2000 [9]. In recent years, with more effective chemotherapy regimens, there is an increasing trend toward non-operative management of stage IV CRC with less than one-third of the cases undergoing a palliative resection in 2008 [10].

For the purposes of discussion, patients may be divided into individual categories; namely:

- Those patients with potentially curable metastatic disease
- Asymptomatic patients with questionably curable metastatic disease
- Symptomatic patients with metastatic disease
- Patients with incurable metastatic disease and reasonable health and
- Patients with significant medical co-morbidities or extensive burden of metastatic disease for whom palliation is the goal.

Patients with Potentially Curable Synchronous Metastases

The most recent NCCN guidelines recommend treatment based upon whether the circumferential resection margin (CRM) is clear as determined by MRI [11]. If the CRM is clear, systemic chemotherapy is the first treatment followed by either short course radiotherapy (preferred) or adjuvant long course chemoradiation. The patient is then restaged and if appropriate undergoes either staged or synchronous resection of the primary and metastatic lesions. If the CRM is involved, systemic chemotherapy combined with long course radiation, or short course radiotherapy may be recommended first. If systemic chemotherapy is given first, it is followed by chemotherapy with long course radiation. Either version of radiation therapy is followed by systemic chemotherapy. The patient is then restaged and if appropriate undergoes staged or synchronous resection of the primary and metastatic lesions. A European consensus document published in 2014 recommends either resection followed by six months of chemotherapy or 3 months of chemotherapy (especially if multi-site metastasis), resection and then 3 months post-operative chemotherapy. The first option is preferred for primary lesions that are T1-T3 or N0. If the final pathology reveals T3, positive lymph nodes, positive circumferential margins or perforation, then post-operative chemoradiation would be given before completing the chemotherapy. For lesions >T3 or N+ lesions, chemoradiation and 3 months of chemotherapy would be given before surgery. A more recent European expert panel recommended systemic chemotherapy with short course radiation as the preferred treatment but also acknowledged that other combinations are reasonable [12]. In 2014, the NCCN panel eliminated the surgery first option because "they believe that the majority of patients should receive preoperative therapy"

with the goal of eradicating micro metastases. There is acknowledgement that not all patients are candidates for chemotherapy and their care should be individualized. Supporting evidence for this position is not provided.

The necessity of pre-operative chemotherapy is still controversial for patients with early primary lesions and a solitary metastasis, however, it would typically be offered for the majority of patients with a primary lesion <T3 (and N0) with a metastasis. The next decision is then usually whether to perform staged or synchronous resections assuming that the metastasis is in the liver; options which are considered Chap. 24.

For patients with primary T3 or T4 or N+ lesions, chemoradiation may follow the initial 3 months of chemotherapy depending upon the response of the primary lesion. If not given before surgery, it may also be considered post-operatively if the risk factors for local recurrence are identified within the pathologic specimen [13, 14].

Further confounding this decision is the timing and the use of radiation. In this respect, Huh et al. published a retrospective review of 140 consecutive Korean patients from 1994 to 2010 with metastatic and locally advanced rectal cancer [15]. All patients underwent surgery but about 50% had either pre or post-operative chemoradiotherapy. Local recurrence was less for those receiving preoperative CRT when compared with postoperative CRT but neither group was significantly better off than the no radiation group. There was no difference in overall or disease-free survival with either pre- or post-operative CRT compared with surgery alone however, improvements in local recurrence-free survival with preoperative RT may suggest that a significant proportion of the patients die before a local recurrence occurs. Whereas a number of retrospective studies have shown that postoperative CRT does not improve OS in patients with metastatic rectal cancer [16–18], this is the first study to examine the effect of preoperative CRT in these stage IV rectal cancer patients.

Other studies have shown that preoperative radiation sandwiched with neoadjuvant chemotherapy (chemotherapy → radiation → chemotherapy) offers a survival benefit but only in those who can undergo a subsequent curative resection of the primary and a metastasectomy [18]. This study supports the concept that patients with locally advanced rectal cancer and limited metastatic disease are the best candidates for chemoradiation. If metastatic disease is more extensive, then survival may not be long enough for local recurrence to be an issue. Adjuvant chemotherapy will still be used in such cases even with curative intent resections (primary + metastasis) since further distant metastases are the most common manifestation of failure in stage IV rectal cancer cases. This would further explain why there is no beneficial effect of pelvic irradiation on either OS or DFS [19].

One concern about the use of chemoradiation is that the chemotherapy used for radiosensitization is not as effective systemically. If survival is the primary concern, then chemoradiation may delay effective systemic treatment. A recent phase II trial addressed that issue with a program of alternating systemic chemotherapy and chemoradiation [20]. The study was designed to determine feasibility. The majority (92%) of patients completed the 12-week treatment and response rates were encouraging. Further studies are needed to determine if this type of regimen would allow effective systemic and local therapy to be combined. The competing elements

of treatment create a dilemma concerning local treatment to avoid uncontrolled pelvic disease or the need for emergency surgery (for obstruction and/or perforation) or to commence first line systemic CT. Any local therapy will also significantly delay the commencement of palliative chemotherapy, even delaying the possibility in borderline performance status of ultimate metastasectomy. Future studies will need novel scheduling in order to address local and systemic problems induced by the advanced rectal cancer concurrently. The use of CT in the RT-free window will potentially reduce the degree of acceleration of the cell population which may have been induced after initial RT. Shorter, intensive CRT regimes may be associated with a lower toxicity whilst maintaining efficacy.

One advantage to chemoradiation therapy is the possibility of a complete clinical response locally which occurs in 15–20% of patients [8, 21]. Prolonged intervals between treatment and surgery and additional chemotherapy have resulted in even higher levels of response [22–25]. With the information currently available, the general recommendations for care of this group are shown in Fig. 23.1. Patient preferences and individual patient factors may alter this treatment plan.

For asymptomatic patients with questionably resectable metastatic disease, the NCCN guidelines recommend chemotherapy using regimens with "high response rates" [12]. Re-evaluation for potential resection should occur in 2 months time and then every 2 months as long as the chemotherapy is continued. The EURRECA document states that the current standard is 3–6 months of induction chemotherapy [13]. If re-evaluation finds that the metastatic lesions have become resectable, local treatment should be based upon local staging. Short-course radiation therapy is preferred but long-course chemoradiation should be considered if the circumferential margin is threatened. The concern here is that chemotherapy as administered with radiation has limited systemic impact. Following surgery, patients should receive postoperative chemotherapy for a total of 6 months of treatment. If re-evaluation finds that metastatic disease remains unresectable, then chemotherapy should be changed to second line with another re-evaluation planned after 3 more months. For larger liver metastases, selective portal vein ligation or embolization could be considered.

Given that the goal of treatment is longevity and quality of life, systemic chemotherapy is the first line treatment for these patients. Benefits of upfront chemotherapy include the ability to down stage metastases from unresectable to potentially

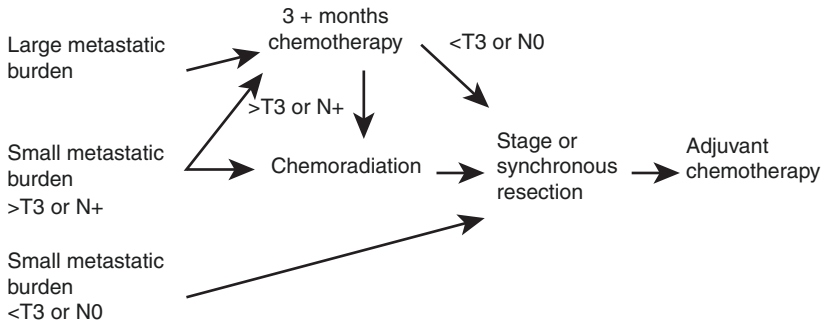

Fig. 23.1 Suggested management flow chart for patients presenting with potentially curable metastases from rectal cancer

resectable. With prompt initiation of systemic therapy, approximately 12–30% of patients may convert to resectable disease that is suitable for complete surgical removal of the primary and metastasis [26–29]. There have also been reports of up to 7% complete pathological response after preoperative chemotherapy alone for stage IV rectal cancer [28].

Patients who are able to undergo complete surgical resection of their colorectal liver metastasis and the primary lesion have a 30–50% survival at 5 years [30]. In this subset of patients, the next decisions are whether they should have a combined procedure with resection of both the primary and metastatic disease as well as the use of pre-operative radiation.

While care must be carefully individualized, a general plan is outlined in Fig. 23.2 for this subset of patients.

Patients with Unresectable Metastases

For those with metastatic disease, over 75% are considered unresectable [31]. The goal of treatment for these patients is to balance length of survival, palliation of symptoms and optimization of quality of life. Treatment decisions should be based upon whether the patient is experiencing symptoms from the primary lesion.

For asymptomatic patients, the NCCN guidelines recommend systemic chemotherapy with periodic assessment for resectability of the metastatic disease when appropriate. The NCCN panel believes that risk of resection of the primary outweighs any potential benefit [12]. The EURRECA group recommends an "escalation strategy" for chemotherapy for completely asymptomatic patients [13]. Intensive (maximal response) chemotherapy is recommended for patients with symptoms related to the metastases. For patients who are symptomatic from the primary lesion, avoidance of surgery is recommended. Radiation therapy, stent placement and diverting stoma should be considered to alleviate symptoms as appropriate rather than surgery. Unless there are specific indications for acute management of the primary in this setting, provided that patients are under surveillance the majority will not require emergent surgery for intestinal obstruction and/or perforation [32]. Although some studies have demonstrated a survival benefit for primary resection [33], the

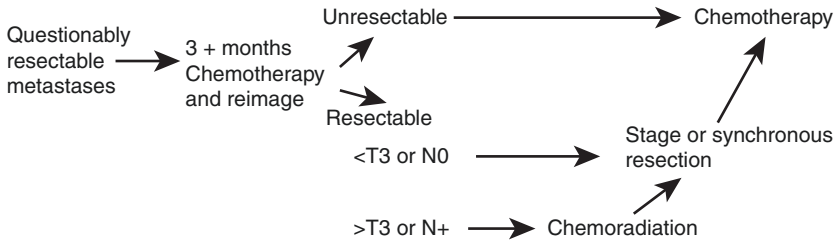

Fig. 23.2 Suggested management flow chart for patients presenting with questionably resectable metastases from rectal cancer

data are biased towards patients with a better performance status and better prognosis (less metastatic sites involved).

In practice there is still discussion about the best option. Resection of the primary tumor in those with unresectable metastatic disease is often considered in cases where the primary tumor is symptomatic. Ten to thirty percent of patients undergo surgery for the primary at the time of diagnosis [34, 35]. The standard indications for resection of the primary include perforation, obstruction not amenable to stenting and refractory bleeding. If the sole indication for surgery is bleeding, radiation is an alternative treatment [36].

Although expert panels recommend avoiding upfront surgery in favor of systemic chemotherapy, there remains controversy in those patients with incurable stage IV disease and minimal to no symptoms from the primary tumor where the patient is healthy enough to undergo surgery. The literature in this circumstance is very mixed (Table 23.1) [34, 35–49].

In this patient population with an overall but variable mean survival of 16–75% [9] a frank discussion with the patient is necessary so as to lay out the potential risks of leaving the primary in place and proceeding with upfront chemotherapy versus the risk of upfront surgery and the potential complications that may delay or even preclude the initiation of systemic therapy.

Proponents of upfront resection also cite the risks of an intact primary lesion including future obstruction, bleeding, pelvic pain and the need for emergency surgery or other intervention whilst on systemic therapy. Limited, mostly retrospective data are available but it may help guide discussions with the patient.

Table 23.1 Summary of studies favoring or not favoring resection of primary tumor first

Reference	Study type/design	Tumor site
Favors resection		
Ruo (2003)	Retrospective	Colon & rectum
Konyalian (2007)	Retrospective	Colon & rectum
Galizia (2008)	Retrospective (case matched)	Colon& rectum
Bajwa (2009)	Retrospective	Colon & rectum
Venderbosch (2011)	Retrospective of 2 RCTs	Colon & rectum
Karoui (2011)	Retrospective	Colon
Verberne (2012)	Retrospective	Colon & rectum
Ferrand (2013)	Retrospective	Colon & rectum
Does not favor resection		
Scoggins (1999)	Retrospective	Colon & rectum
Tebbutt (2003)	Retrospective	Colon & rectum
Michel (2004)	Retrospective	Colon & rectum
Benoist (2005)	Retrospective	Colon & rectum
Seo (2010)	Retrospective	Colon & rectum
McCahill (2012)	Retrospective	Colon & rectum
Yun (2014)	Retrospective/propensity score matching	Colon & rectum

RCT randomized controlled trial

In this respect, the rates of bowel obstruction whilst on chemotherapy for stage IV colorectal cancer where there is still an intact primary, range from 6% to 29% with a mean of 22% [10, 29, 48–51]. In 2003 Tebbutt and colleagues sought to define the rates of intestinal complications with chemotherapy in patients with metastatic colorectal cancer where there was still an intact primary. The incidence of peritonitis, fistula formation and intestinal hemorrhage were all low at 2.4%, 3.7% and 3.7% respectively [45]. Obstruction occurred in 13% of patients with an intact primary. Of interest, similar raw numbers of intestinal obstructions were reported in the cohort who underwent initial palliative resection of the primary, underscoring the difficulty in discerning if the obstruction is at the level of the tumor or elsewhere within the peritoneal cavity. Tebbutt concluded that the incidence of major intestinal complications is low amongst patients with synchronous CR metastasis and an intact primary. As expected, obstruction is more common in those with peritoneal and omental disease.

Another risk of leaving the rectal cancer primary intact is that symptoms of local disease may be more pronounced and the need for a stoma more likely. Between 14% and 60% of patients without resection of the primary may require proximal diversion or other intervention whilst on palliative chemotherapy [35, 52–54]. Sarela et al. reported a 14% incidence of late symptoms from the unresected primary rectal cancer [55].

With modern combination chemotherapy regimens for unresectable stage IV colorectal cancer, Poultsides et al. reported that the overall incidence of primary tumor-related complications was only 15% [29]. Only 6% required surgical intervention, with an additional 9% requiring non-operative interventions such as stenting or radiation. Another similar study found that 22% of patients undergoing palliative chemotherapy required intervention and that about 50% required operative intervention [10, 49]. In this Korean study, the location of the primary tumor in the rectum and a tumor size >5 cm both independently predicted the need for intervention on multivariate analysis. Michel and colleagues reported that 21% of patients in a non-resection group required intervention for obstruction [46] and that a location of the primary in the rectum increased the risk.

While the incidence is low, the mortality rate for urgent surgery is significant at 12.5%. Temple and colleagues found that the post-operative mortality increased from 9% to 26% when surgery was performed after chemotherapy [56]. In addition, perforation and fistula formation each occur at a rate of 11% and may require urgent diversion or other intervention where emergency surgery in this group has a significantly higher mortality and morbidity, suggesting that a balance needs to be made between the low risk of complications in an observed group and that of emergent or semi-emergent surgery [54]. Monitoring of the primary either with endoscopy or radiologic imaging may reduce the need for urgent surgery [57].

Pelvic pain can also have a significant impact on quality of life in patients with locally advanced rectal cancer. Studies show significantly less pelvic pain in those who had undergone a resection of the primary, 4% vs. 15% [52]. There is also less pelvic sepsis in this resection group, 9% vs. 14%. Others have also reported fewer pelvic symptoms following resection [58, 59] although these reports, however, predate modern chemotherapy and radiation therapy advances.

The Mortality of Urgent Surgery: Stents and Stomas in Stage IV Rectal Cancer Cases

As already stated, one argument for elective resection of the primary is to avoid urgent surgery. About 15% of patients on aggressive chemotherapy even with radiation will go on to need palliative intervention for obstructive symptoms [59]. In this regard, there is a significant increase in 30 day post-operative mortality when the results of elective surgery are compared with emergent surgery, 2.5% vs. 10% [60].

Given the approximate 15% mortality rate associated with emergency surgery for left-sided colorectal cancers, decompression with minimally invasive techniques such as stenting has been studied as an alternative [61]. The success overall of stenting is highly variable, but some series have reported as high as a 40% perforation rate in those with left-sided colorectal cancers treated with palliative stenting [62]. A recent meta-analysis of studies comparing stenting with emergency surgery found no difference in hospital mortality or overall morbidity and recommended that stenting be considered cautiously as an alternative to surgery [63]. However the European and American Societies of Gastrointestinal Endoscopy recommend self-expanding stent placements as the preferable treatment in a palliative situation except in patients being treated with antiangiogenic drugs [64]. In a recent randomized controlled trial comparing stent placement with emergency surgery for incurable large bowel obstruction, about 20% of patients had rectal cancer [65]. Stent insertion in this Australian study was successful in 73% of patients and overall, the stent group had fewer stomas, a lower 30 day mortality and better measurable quality of life parameters. The median survival was equivalent in the two groups (5.2 months surgery *vs.* 5.5 months stenting).

Concerns with resection of the primary in the setting of unresectable metastasis include the possible 40% risk of postoperative morbidity [42, 66] and the attendant 0–8% peri-operative mortality rate [42, 52, 66, 67]. Nash and colleagues from Memorial Sloan-Kettering reported a 1% perioperative mortality in this group with a 15% major peri-operative morbidity rate with resection of the rectal primary without neoadjuvant radiotherapy in their series [66]. A recent study suggests that laparoscopic versus open resections result in fewer overall complications [68]. Of consideration is the fact that postoperative complications can delay and prevent the administration of systemic chemotherapy in 12–40% of cases [42, 66]. Delays in adjuvant chemotherapy for rectal cancer are strongly influenced by postoperative complications. Median overall survival is significantly worse in those that had a greater than 2 month delay in starting adjuvant chemotherapy [69].

Anastomotic leaks specifically also have a complex impact on survival. In a study of 123 patients with metastatic rectal cancer undergoing resections, anastomotic leaks occurred in 6.5% [70]. The 3-year overall survival was significantly worse (32% *vs.* 72%) in patients with a leak. This finding may relate to a delay of systemic chemotherapy use for over 2 months in 50% of the patients. Kleepsies and colleagues reported anastomotic leaks in 24% of rectal cancer patients, although only 6.5% required re-operation [71]. Post-operative treatment was administered

in 72.6% vs. 91.9% of patients without complications. In many cases, the surgical resection of a rectal cancer in the setting of unresectable metastatic disease results in a colostomy (between 20% and 66% of series) [66, 71].

Survival

When assessing the impact on survival for patients with CRC and unresectable metastases, there are limited data comparing initial primary tumor resection *vs.* upfront chemotherapy. The studies are not randomized and most represent retrospective single institution reports. A Cochrane review in 2012 found that "resection of the primary tumour in asymptomatic patients with unresectable stage IV colorectal cancer who are managed with chemo/radiotherapy is not associated with a consistent improvement in overall survival. In addition, resection does not significantly reduce the risk of complications from the primary tumour (i.e. obstruction, perforation or bleeding). Yet there is enough doubt with regard to the published literature to justify further clinical trials in this area" [72].

Theoretically, the removal of the primary lesion would reduce the total tumor burden, potentially making chemotherapy more effective on the residual tumor. The literature is in this respect, however, mixed in terms of the survival benefit of resection of the primary. A recent meta-analysis included retrospective and cohort studies within the past 15 years involving 44,226 patients with either colon or rectal cancer where two-thirds of the patients underwent resection [73]. The study demonstrated a survival advantage with resection of the primary in CRC when compared with chemotherapy alone. Patients who had a resection lived a mean of 6 months longer, 95% CI 5.0–7.8; $P < 0.001$ [31, 60]. Those undergoing resection were more likely in this cohort to have metastatic disease confined to the liver, (usually as single metastases) as well as tumors in the colon and not the rectum. Those with advanced rectal cancer were more likely to receive palliative surgical procedures such as a stoma rather than resection of their primary in this retrospective analysis. In this approach, there is an inherent selection bias because of the retrospective nature of the study, as surgery may be offered more commonly to patients with a better performance status and lower disease burden. Consequently this data should be viewed and interpreted with caution. Two other reviews have also found that resection provided better or equivalent survival but these did not find that the tumor location in the colon or rectum had any significant impact [31, 60].

One of the studies included was a retrospective analysis of the data in two phase III trials of various chemotherapy regimens for metastatic colon cancer patients [40]. The patients undergoing resection were compared with those who were unoperated. In both analyses, the median overall survival (16.7 *vs.* 11.4 months, respectively; $P < 0.001$) and progression-free survivals (6.7 *vs.* 5.9 months, respectively; $P = 0.04$) were better in the resection groups.

There are a few studies specifically examining rectal cancer with variable findings regarding the impact on survival of resection the primary. Verberne reported a

consecutive series of 88 patients between 2002 and 2006 with stage IV rectal cancer [42]. Thirty percent of the cohort underwent resection. Those who had resection of the primary were compared with patients with an intact primary who received chemotherapy or supportive care only. Those who underwent palliative resection had a significantly better survival than those unoperated (OR 0.38 95% CI *vs.* 0.173–0.831, respectively). In this study there was a 38% peri-operative morbidity but no attendant 30-day mortality. Other studies have not demonstrated a survival advantage with resection of the rectal primary [45]. Statistical techniques have been used to manage potential biases in these reports where after propensity score matching, Yun et al. has shown that resection of the primary was not associated with an improvement in overall survival [10, 27].

Both the extent of metastatic disease and the response to initial chemotherapy are strong and independent determinants of prolonged survival in patients with metastatic rectal cancer [66]. In a study by Nash et al. from the Memorial Sloan-Kettering Cancer Center, greater than 50% hepatic replacement and more than 1 comorbidity were independent determinants of postoperative morbidity. In a similar study by Kleespies and colleagues from Munich, survival was impacted by T4 or node positive disease, >50% extent of hepatic replacement, local tumor clearance (R0/R1-2) and failure of administration of postoperative therapy, suggesting that in these higher risk cases that surgery may actually be contraindicated [71].

Conclusions

The management of the primary rectal tumor in patients with unresectable metastases is challenging. Finding the appropriate strategy to balance the future risk of symptoms from an intact primary with the morbidity of surgical resection can be difficult. Based upon the limited data available, the approach to each patient must be individualized and should be discussed with a multidisciplinary team. Resection or diversion should be considered for symptomatic patients. For those asymptomatic patients with widely disseminated disease who are likely to remain unresectable, aggressive chemotherapy is recommended. That recommendation is made understanding that approximately 15% of patients may go on to become symptomatic and need intervention including focused radiation, diversion or stenting. Patients with Stage IV rectal cancer who remain unoperated require close monitoring so as to avoid the need for emergency surgery for complications such as obstruction and/or perforation, both of which may in advanced metastatic disease have a prohibitive morbidity and mortality. For those patients with more limited metastatic disease and a good performance status, upfront chemotherapy is used to assess tumor responsiveness. If there is a favorable response to chemotherapy and the patient transitions to a potentially resectable situation, the primary lesion should then be treated as in a patient without metastatic disease, including the use of neoadjuvant chemoradiotherapy when appropriate. Whether resections should be synchronous or staged for hepatic metastatic disease in

particular is discussed elsewhere in this book section. Peritoneal disease, the extent of liver involvement and the performance status are all factors that may limit a patient's benefit from surgery and which increase the morbidity and make the recommendation for resection less likely. There are ongoing randomized controlled trials such as the multicenter Spanish NCT02015923 trial comparing surgical resection and postoperative CT (without specific protocol) with CT alone [74] which will hopefully provide clearer guidance for decision making on these complex patients. Recently a clinical trial conducted at University College Hospital London has completed, examining overall survival in asymptomatic stage IV CRC cases treated with CT alone or with resection of the primary + CT. The results at the time of writing remain unpublished (NCT01086618; http://clinicaltrials.gov).

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