Algorithms for Patients with Colorectal Liver Metastasis

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Introduction

We introduce a few concepts and their definitions that will be used in this chapter.

Moment of Diagnosis

Colorectal cancer is a potentially lethal disease in which the liver is the most common site of metastasis. By definition, synchronous metastasis (SM) is a condition

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when the patient presents with metastatic liver disease at the same time of presentation of the primary disease. SM represents unfavorable disease with poor long-term survival. For these patients, the standard approach comprises resection of the colorectal primary tumor, adjuvant chemotherapy, and then resection of the liver tumor. Other approaches are concomitant approach and reverse strategy (Fig. 12.1).

Metachronous liver metastases are classified as *early* metachronous metastases or *late* metachronous metastases depending on whether they have been detected within or more than 12 months after diagnosis or after undergoing a primary colorectal tumor surgery. Resectable metachronous liver metastases may be resected straightforward without the need for chemotherapy, specially when small in size and number. The traditional strategy of treatment is presented in Fig. 12.2.

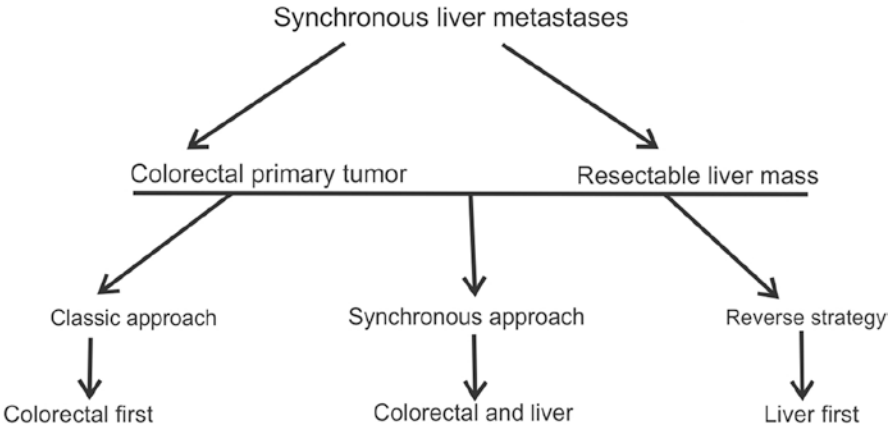

Fig. 12.1 Treatment for synchronous liver metastases

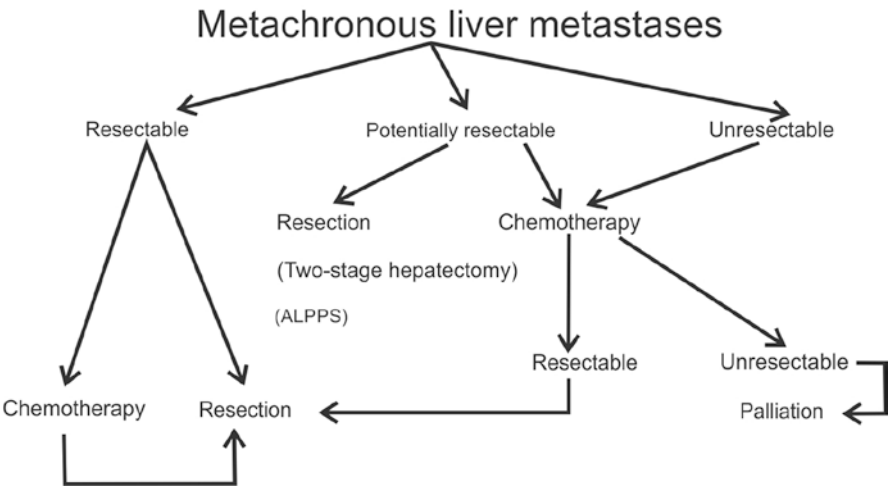

Fig. 12.2 Treatment for metachronous liver metastases

Resectability

Patients with colorectal liver metastasis are classified into three categories at the time of presentation: *resectable, potentially resectable,* and *unresectable*. Each condition is addressed in the following sections.

Synchronous Hepatic Metastases

At the time of diagnosis of colorectal cancer, 20–25% of patients present with metastatic disease [1–4], with the liver being the dominant metastatic site. Synchronous hepatic metastases occur in 15–20% of patients [5], with 70–80% of these cases being liver-limited metastases [6]. The distinction between synchronous and metachronous metastases is not straightforward as most patients who develop metastases after the treatment of primary tumor might have already had them at the time of diagnosis. In fact, by definition, all metastases are synchronous, irrespective of whether they are occult or detectable at the time of diagnosis. Therefore, synchronous colorectal metastases should be defined as those "synchronously" detected with primary tumor.

It has been well known that synchronously detected colorectal metastatic disease carries a worse prognosis [7–9]. Overall survival is lower for patients who are diagnosed with metastases at or within 1 month versus more than 12 months after the primary tumor diagnosis [10, 11]. Indeed, presence of synchronous metastases has been incorporated in prognostic scoring systems for hepatic metastases resection, such as the Fong score [8]. In addition to conferring a more aggressive course than metachronous disease, synchronous liver metastases also add complexity in terms of surgical approach, when indicated. Patients may undergo simultaneous resection of both primary tumor and liver metastases or a staged resection, which includes either colorectal-first (classic) or liver-first (reverse) approach. When simultaneous resection is performed, the liver resection is typically performed first. If, during the liver procedure, a major complication (such as bleeding or clinical instability) occurs or hepatic resection would be greater than planned, the colorectal resection should be postponed and a staged approach adopted instead. When a major hepatectomy is performed (resection of >3 segments), simultaneous resection carries higher morbidity (36.1% versus 15.1%) and mortality (8.3% versus 1.4%) than staged resection. However, several studies have shown that the length of hospital stay and perioperative mortality are similar between simultaneous and staged colorectal metastatic liver resection [12–15]. In addition, simultaneous approach is associated with a significantly lower total cost [16]. Both strategies ensure similar oncological outcomes.

Unfortunately, there is no data from randomized studies to help guide treatment decisions in synchronous colorectal liver metastases that may be candidate for surgery. There is only one general agreement among specialists: multidisciplinary discussion is always necessary. Many factors come into play in synchronous disease,

such as disease burden, acuity of symptoms, liver metastases resectability, location of primary tumor, RAS and BRAF status, comorbidities, and age [17]. They may all influence the timing and sequence of surgical resection of the primary tumor and metastases as well as the choice of the chemotherapy regimen.

Most oncologists consider initial chemotherapy for a recently diagnosed resectable synchronous disease in order to assess the cancer biology prior to a surgical attempt. Patients who develop progressive disease during systemic treatment do not benefit from surgery and are consequently spared from it.

In the absence of randomized controlled trials, most recommendations come from experts' opinions, biological rationale, and personal experience [10].

Scenarios

There are six scenarios of synchronous colorectal liver metastases, depending on liver resectability, primary tumor location, and presence of primary tumor symptoms:

Clearly Unresectable—(Not Candidate to Conversion Therapy)—Asymptomatic Primary TUMOR

- Colon or upper rectal cancer: These patients are typically treated with systemic therapy, taking into consideration the choice of chemotherapeutic regimen, the RAS status, BRAF status, performance status, age, and adverse events profile [10]. Primary tumor resection is only indicated for those who develop symptoms, such as bleeding, obstruction, or perforation. Previous studies have demonstrated that 7–20% of patients with metastatic colorectal cancer will eventually require emergent surgical intervention of the primary tumor [18–20]. Nonetheless, there is still no available data from randomized trials regarding the benefits of primary resection in the context of unresectable metastatic disease.
- Middle or lower rectal cancer: The same concepts of systemic therapies apply to rectal primary tumors. In the majority of cases, initiation of chemotherapy should not be postponed in favor of local therapy, given the high response rates with systemic treatment and rarity of rapid progression through first-line regimens. The exception is for patients with a low burden of metastatic disease and a bulky (yet) asymptomatic rectal tumor, in which case there is a high likelihood of long-term overall survival and, therefore, patient may benefit from initial treatment of the primary tumor to prevent symptoms from progressive pelvic disease. In this scenario, traditional chemoradiotherapy with a fluoropyrimidine or short-course radiotherapy is reasonable before initiation of systemic treatment with consideration of surgery at some point. On the other hand, patients with high-volume systemic metastases and a small, asymptomatic rectal tumor are more likely to die of their systemic disease before the primary tumor causes significant symptoms. In such patients, systemic chemotherapy is usually most appropriate, with local pelvic therapy reserved only for palliation, if needed (Fig. 12.3).

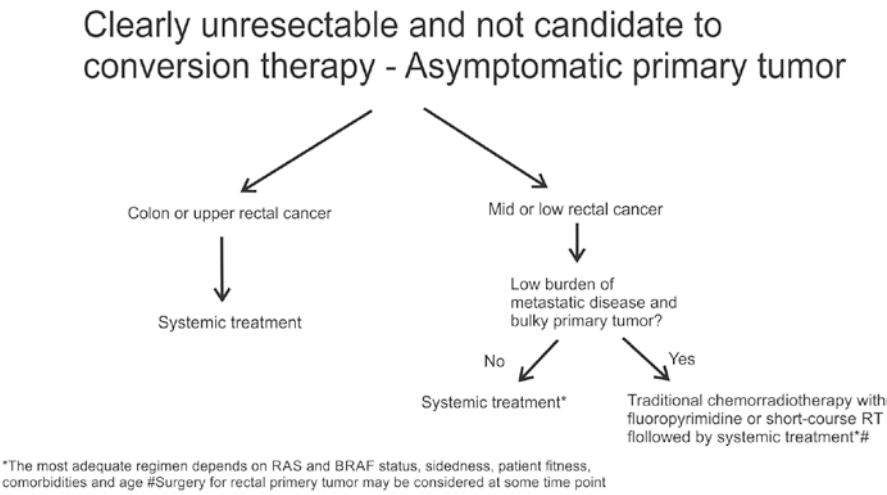

Fig. 12.3 Treatment for clearly unresectable asymptomatic primary tumor

Clearly Unresectable (Not Candidate to Conversion Therapy)—Symptomatic Primary TUMOR

- Colon or upper rectal cancer: These patients should undergo resection of the primary tumor before considering initiation of systemic treatment in order to avoid complications related to the primary tumor. After surgery, systemic chemotherapy is indicated according to RAS status, BRAF status, performance status, age, and adverse events profile [10]. When bevacizumab is considered, there should be at least 6 weeks from surgery to its use due to healing problems.
- Middle or lower rectal cancer: In patients with perforated tumors, immediate surgery is necessary followed by systemic treatment. For those with excessive bleeding, initial chemoradiotherapy or short-course radiotherapy (RT) followed or not by surgery might be preferred before initiation of systemic treatment. However, for patients with obstructive symptoms, the type of surgical intervention depends on the volume of systemic disease. For those with high volume of metastases, confection of a diversion colostomy followed by aggressive systemic treatment is indicated. On the other hand, those with low volume of systemic disease, short-course RT followed by radical surgery and then systemic treatment may be preferred due to better future pelvic control. After primary tumor treatment, systemic therapy should be initiated (Fig. 12.4).

Unresectable (But Potentially Convertible to Resectable)—Asymptomatic Primary Tumor

- Colon or upper rectal cancer: These patients should undergo optimal chemotherapy first (doublets or triplets in combination with biological agents). The best systemic combination therapy depends on RAS and BRAF status, as well as presence of bilaterality. For fit patients and for those with RAS- or

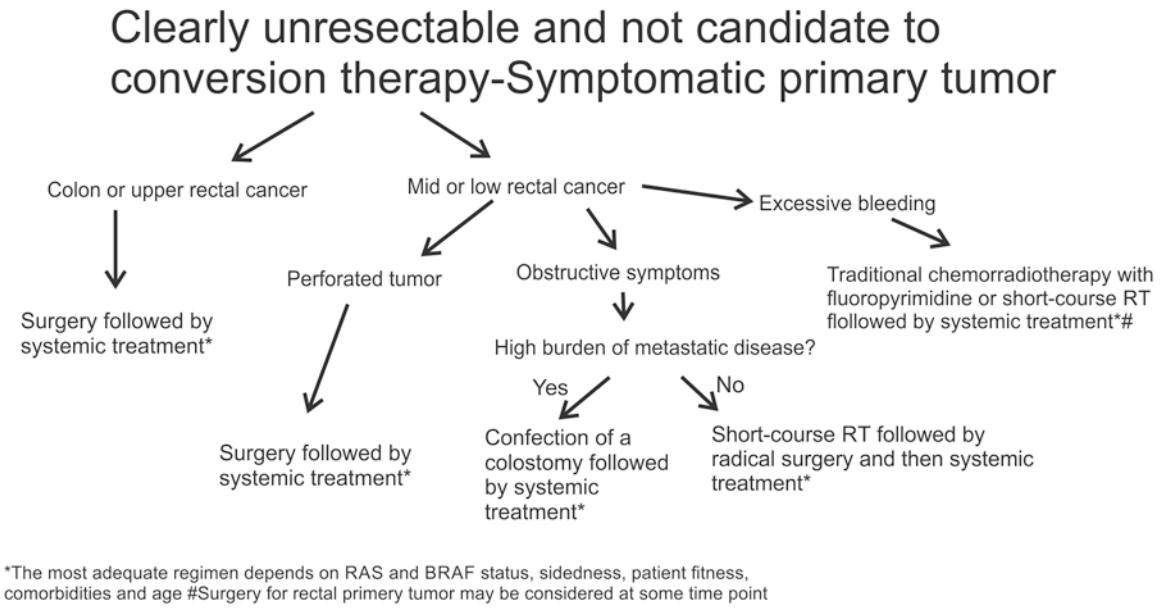

Fig. 12.4 Treatment for clearly unresectable symptomatic primary tumor

BRAF-mutated tumors, a triplet (FOLFOXIRI) with or without bevacizumab is associated with higher response rates. For those with RAS and BRAF wild-type cancers, either a doublet along with anti-EGFR therapy or FOLFOXIRI with or without bevacizumab is indicated [17]. Although data with FOLFOXIRI plus anti-EGFR therapy is very promising for RAS and BRAF wild-type tumors, more studies with this combination are necessary, and so far, it cannot be routinely indicated. Optimal timing for assessment of response to chemotherapy is probably every 8 weeks [17]. As soon as (and if) the liver metastases become resectable, surgery should be performed in order to avoid chemotherapy-induced liver toxicity, which include nonalcoholic steatohepatitis (NASH), steatosis, centrilobular necrosis, and sinusoidal changes [21, 22]. Liver resection should be delayed at least 4 weeks after completion of chemotherapy and panitumumab or cetuximab, and 6–8 weeks if bevacizumab was a component of therapy. The recommendation is for a *reverse* surgical strategy, with resection of the liver metastases before the primary tumor, mainly due to extensive hepatic involvement in this scenario. One-stage surgery should not be performed unless there is limited hepatic disease and an "easy-to-resect" primary tumor. In most retrospective studies, simultaneous procedures included fewer, smaller, and more often unilobar synchronous colorectal liver metastases, which have led to the recommendation that simultaneous procedures should only be pursued when they involve minor hepatic resections, which is usually not the case in patients with initially unresectable disease [23]. Simultaneous procedures with major hepatectomies should be performed only in very carefully selected patients and by an experienced hepatobiliary team.

If complete resection is achieved, most oncologists prefer to complete a total of 6 months of systemic therapy. The only drugs associated with overall survival benefit for micrometastases are fluoropyrimidines and oxaliplatin. Therefore, even though irinotecan and/or targeted therapies were used preoperatively, following surgery we complete 6 months with FOLFOX or XELOX. However, although there are no evidence-based data to support the use of targeted therapies after resection, if a regimen is highly effective in the preoperative setting, the same regimen is used postoperatively.

- Middle or lower rectal cancer: The same concepts of systemic therapies apply to rectal primary tumors. For cT1–2 cN0 rectal primaries, RT is not necessary and the same concepts of colon cancer apply here. However, for bulky, yet asymptomatic rectal primary tumors, as soon as liver metastases become resectable, short-course RT followed by reverse strategy (liver-first surgery followed by primary rectal resection) should be used in order to decrease local recurrence risks. Because rectal procedures are technically more challenging than colon procedures, with a higher risk of morbidity and mortality, most groups prefer a liver-first strategy followed by rectal tumor resection. However, some studies have demonstrated that combined rectal and hepatic resection is safe in high-volume centers [24–26] (Fig. 12.5).

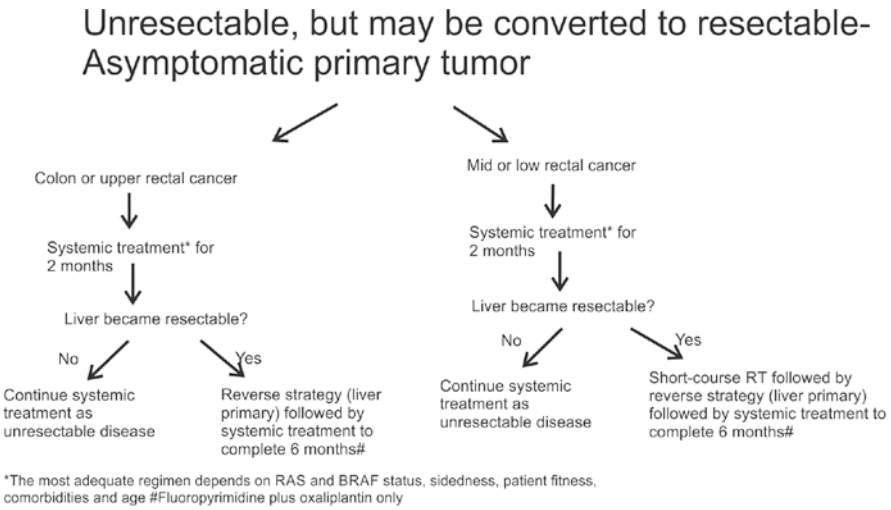

Fig. 12.5 Treatment for unresectable (may be converted to resectable) asymptomatic primary tumor

Unresectable (But Potentially Convertible to Resectable)—Symptomatic Primary Tumor

- Colon or upper rectal cancer: These patients should undergo resection of the primary tumor before considering initiation of conversion systemic treatment in order to avoid complications related to the primary tumor. As soon as liver metastases become resectable, surgery is indicated followed by chemotherapy with fluoropyrimidine and oxaliplatin for a total of 6 months. Simultaneous hepatic resections should not be performed during an emergent colorectal resection for bleeding, perforation, or obstruction, because apart from increased morbidity, they may also lead to a higher chance of distant metastases [26–28].
- Middle or lower rectal cancer: In patients with perforated tumors, immediate surgery is necessary followed by systemic treatment. For those with excessive bleeding, initial chemoradiotherapy or short-course radiotherapy (RT) followed or not by surgery might be preferred before initiation of systemic treatment. However, for patients with obstructive symptoms, the type of surgical intervention depends on the volume of systemic disease. For those with high volume of metastases, confection of a colostomy followed by aggressive systemic treatment is indicated. On the other hand, for those with low volume of systemic disease, short-course RT followed by radical surgery and then systemic treatment may be preferred due to better future pelvic control. After primary tumor treatment, systemic therapy should be initiated (Fig. 12.6).

Resectable Liver Disease and Asymptomatic Primary Tumor

- Colon or upper rectal cancer: There is no "right" approach to integrating systemic chemotherapy with surgical resection of hepatic colorectal metastases that

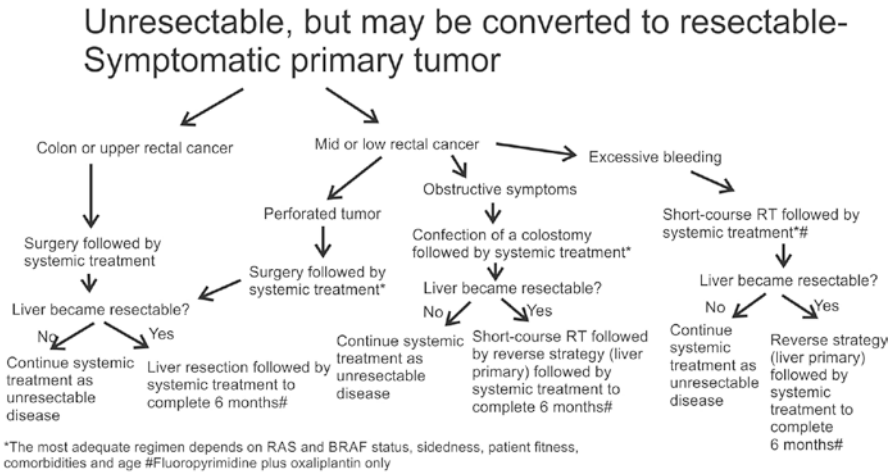

Fig. 12.6 Treatment for unresectable (may be converted to resectable) symptomatic primary tumor

are resectable upfront. At some centers, if the hepatic metastases are resectable and the patient has an asymptomatic primary colon cancer, upfront surgical resection rather than initial chemotherapy may be offered for medically fit patients with fewer metastases. On the other hand, most centers prefer to deliver systemic treatment before surgery, especially in patients who have more than four metastases (unless all are localized to a single lobe), radiographic suspicion for portal node involvement, or bilobar disease [27]. The strategy of starting with systemic treatment (fluoropyrimidine and oxaliplatin) instead of surgery allows the evaluation of the biological behavior of the tumor and futile surgeries are avoided. Patients whose disease progresses while on chemotherapy or who develop extrahepatic disease have biologically aggressive tumors that would not benefit from resection. For resectable liver metastases, most oncologists prescribe a fluoropyrimidine (either 5-FU or capecitabine) with oxaliplatin based on the EORTC trial for a total of 6 months [28–31]. Although the authors study used six cycles of chemotherapy before and after surgery, most oncologists and liver surgeons prefer to deliver four cycles preoperatively followed by restaging in order to avoid chemotherapy-induced liver toxicity. If the disease proves to stabilize or if it responds, surgery is recommended.

- Middle or lower rectal cancer: Initially, patients with cT3/cT4 and/or lymph node positive tumors are preferentially treated with systemic therapy. If patients show partial response or stable disease after three to four cycles of chemotherapy and if liver disease remains resectable, then these patients may be considered candidates for short-course radiotherapy followed by reverse surgical strategy (liver-first approach) and systemic treatment until completing 6 months of treatment. On the other hand, patients with cT1/cT2 and negative lymph node tumors should be initially treated with systemic treatment (fluoropyrimidine and

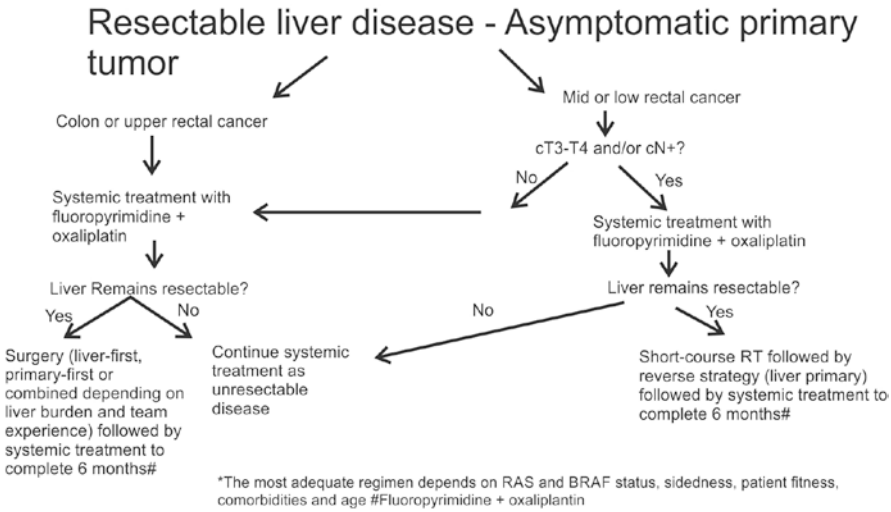

Fig. 12.7 Treatment for resectable liver disease—asymptomatic primary tumor

oxaliplatin). If patients show partial response or stable disease after three to four cycles of chemotherapy and if liver disease remains resectable, then these patients may be considered candidates for reverse surgical strategy (liver-first approach) followed by systemic chemotherapy until completing 6 months of treatment (Fig. 12.7).

Resectable Liver Disease and Symptomatic Primary Tumor

- Colon or upper rectal cancer: These patients should undergo resection of the primary tumor before considering initiation of systemic treatment with fluoropyrimidine and oxaliplatin in order to avoid complications related to the primary tumor. Liver resection can be performed concomitantly in "easy cases"—low burden, colonic primary, or easily resectable upper rectum cases. In other cases, CT should be started after resection of the primary tumor. If there is no progression of the disease after three or four cycles of chemotherapy, then liver metastasectomy should be performed followed by completion of systemic treatment for up to 6 months. Utilizing the liver-first approach may delay resection of the primary tumor and increase the risk of developing complications related to the colorectal tumor [18, 19, 31–33].
- Middle or lower rectal cancer: If the patient presents with a perforated tumor, immediate surgery of the primary lesion should be performed followed by systemic treatment with fluoropyrimidine and oxaliplatin. If there is no evidence of failure to control the disease after three to four cycles of chemotherapy, hepatic metastasectomy should be performed followed by completion of 6 months of chemotherapy. However, if the initial presentation is an obstructive tumor, a diversion colostomy should be performed immediately followed by systemic treatment. If there is no disease progression after three to four cycles of

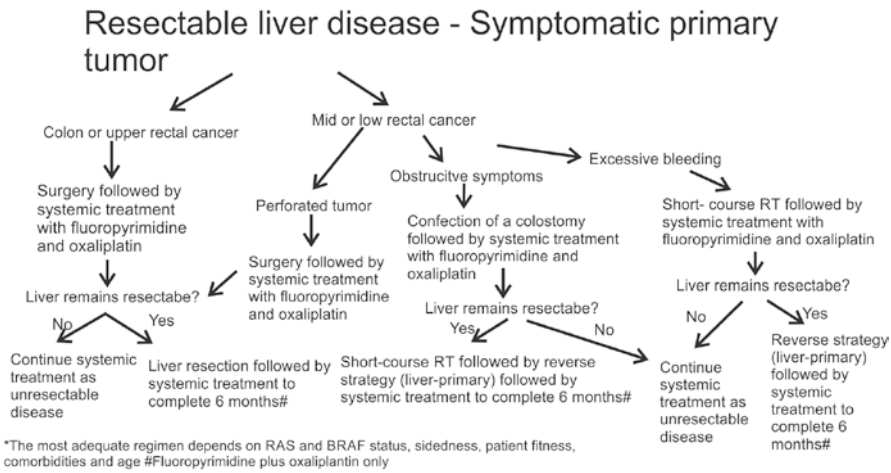

Fig. 12.8 Treatment for resectable liver disease—symptomatic primary tumor

chemotherapy, short-course radiotherapy should be indicated. After that, a reverse strategy (liver-first approach and then the primary tumor) should be performed and, at last, systemic treatment with fluoropyrimidine and oxaliplatin should be carried out until the completion of 6 months. On the other hand, if the main symptom is excessive bleeding, then short-course radiotherapy followed by systemic treatment with fluoropyrimidine and oxaliplatin is preferable. However, if the metastatic disease in the liver remains resectable, the patient should undergo surgery with a reverse strategy (liver-first approach and then the rectal primary tumor) followed by systemic treatment until the completion of 6 months (Fig. 12.8).

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