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# Strategies for Management of Synchronous Colorectal Metastases

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**Abstract** The management of synchronous presentation of colorectal cancer and liver metastases has long been a topic of debate and discussion for surgeons due to the unique dilemma of balancing operative timing along with treatment strategy. Operative strategies for resection include staged resection with colon first approach, "reverse" staged resection with liver metastases resected first, and one-stage, or simultaneous, resection of both the primary tumor and liver metastases approach. These operative strategies can be further augmented with perioperative chemotherapy and other novel approaches that may improve resectability and patient survival. The decision on operative timing and approach, however, remains largely dependent on the surgeon's determination of disease resectability, patient fitness, and the need for neoadjuvant chemotherapy.

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## Introduction

Colorectal cancer (CRC) will account for over 136,000 new cases and 50,310 deaths in 2014 [1]. The liver is the most common site of metastasis, and up to 25 % of newly diagnosed patients may present with synchronous liver metastasis (sCRLM) [2]. The management of sCRLM has long been a topic of debate for surgeons due to the unique dilemma of balancing operative timing and strategy. This has been made manifestly more complicated with the emergence of efficacious systemic chemotherapy regimens, targeted biological agents, and adjunctive strategies (e.g., ablative therapies). Additionally, the surgical approaches to disease extirpation have become more aggressive as advances in critical care and anesthesia have decreased operative morbidity and mortality substantially. Confronted with this clinical scenario, the surgeon must answer three central questions:

(1) Should the primary and metastatic lesions be resected concurrently?
(2) If surgical resection is staged, should the primary or metastatic lesion be resected first?
(3) What is the role of perioperative chemotherapy with surgical resection?

In this review, we will present the current evidence for each of these three main strategies for resection ("conventional" staged resection with colon resected first approach, "reverse" staged resection with liver metastases

resected first, and one-stage, or simultaneous resection of both the primary tumor and liver metastases) in addition to discussion of the role of perioperative chemotherapy and other novel strategies that may be required to improve resectability and patient survival.

## Determination of Resectability

As is true of much in this field, the criteria defining resectable disease have significantly changed in recent years. Older criteria dictated that patients have fewer than four unilobar metastases, no extrahepatic disease and have resection margins greater than one centimeter. These criteria have given way to a paradigm where the primary consideration for resectability is the ability to gain a complete (R0) resection while maintaining adequate liver function. Modern criteria for determination of the resectability of liver metastatic disease were outlined by the Consensus Conference on Multidisciplinary Treatment of Colorectal Cancer Liver Metastases in 2012 [3••]. However, these guidelines continue to evolve and may differ between centers.

During the course of pre-operative staging, radiologic evaluation should provide the number and segmental distribution of sCRLMs in order to determine surgical resectability. With the improved accuracy of combined computed tomography (CT)-positron emission tomography, liver contrast-enhanced magnetic resonance imaging, and high resolution CT, the ability to detect small volume disease has been significantly enhanced [14]. The oncologic and technical criteria used to determine resectability are outlined in Table 1. Involvement of celiac and/or para-aortic lymph nodes is considered a poor prognostic marker, and patients with this finding will likely not benefit from hepatectomy [4•]. While patients with portal and/or retropancreatic lymphadenopathy also have a worse prognosis, their survival outcomes are significantly better than patients with celiac lymphadenopathy, indicating a potential role for resection in this population of patients particularly with the use of perioperative chemotherapy [5•]. These criteria highlight the need for a multidisciplinary team to help guide each patient through the range of therapeutic options and determine the timing of resection of the primary and sCRLM. Strong consideration should be given to referral of these patients to a specialized center given the complexity of treatment planning.

**Table 1** Guidelines for hepatic resection of colorectal liver metastases as outlined by the consensus conference on multidisciplinary treatment of colorectal cancer liver metastases on January 18, 2012

| |
|---|
| Oncologic criteria of resectability |
| Pretreatment radiologic staging evaluation |
| If there is extrahepatic disease, it is: |
| (1) Limited and amenable to surgical resection |
| (2) Or there is reasonable expectation of long-term control with adjuvant treatment |
| Defer resection if significant progression[a] of metastatic disease during treatment until disease is controlled with second |
| Technical criteria of resectability |
| Ability to remove all macroscopic tumor (i.e., R0 resection) |
| Ability to spare two contiguous liver segments |
| Ability to preserve adequate vascular inflow, outflow and biliary drainage |
| Ability to preserve an adequate FLR[b] |
| If projected FLR volume is marginal and/or patient has underlying liver disease, carefully assess FLR based on regenerative response after portal vein embolization (PVE) |

[a] Significant progression here refers to enlargement of more than three existing colorectal liver metastases and/or the development of multiple new lesions during optimal neo-adjuvant chemotherapy

[b] 20 % of a normal liver, 30 % of a liver in patients treated with chemotherapy

## Operative Timing and Approach

Without resection, median overall survival (OS) for patients with CRLM ranges from 20 to 24 months with modern chemotherapeutic regimens. With an R0 resection of all metastatic disease, 5-year OS has been reported to be as high as 58 % [6, 7••]. Liver resection, therefore, remains the most efficacious treatment strategy for achieving long-term OS and the only potentially curative option for CRLM [8•, 9•].

While there is an abundance of evidence demonstrating the benefit of hepatectomy for CRLM, there is only limited evidence available to empirically guide timing of resection for sCRLMs, and therefore this clinical scenario is primarily managed on a case-by-case basis. The conventional paradigm has been to first resect the primary tumor, and then perform a hepatectomy in a delayed fashion. This approach has the advantage of potentially avoiding complications associated with a larger, combined operation and also allows time for aggressive biology to manifest during the period in between operations to potentially save the patient from the extra morbidity of the hepatectomy [10, 11•]. This rationale was bolstered by observations that delaying resection did not appear to increase the risk of unresectability due to interval growth of CRLM, but rather due to the interval appearance of new liver and/or distant metastases [12•]. Additionally, the delay between operations allows for treatment with systemic chemotherapy that may decrease the risk of the appearance of new metastatic lesions and potentially improve OS [13•]. However, delayed hepatectomy may lead to increased hospitalization

and additional cost, as well as increased pain, anxiety and stress for patients as they endure two instead of one major surgical procedure [15, 16••].

Given the declining morbidity associated with hepatectomy, simultaneous resection of both disease sites remains a viable option in appropriately selected patients. There is a growing body of literature demonstrating similar short-term and long-term outcomes in patients undergoing simultaneous resection compared with patients undergoing delayed resection, even when a major hepatectomy (e.g., lobectomy) is performed [17•, 18, 19•, 20•] These studies contradict findings from other studies suggesting that operative mortality was significantly higher for those treated with simultaneous operations, particularly with major hepatectomies [11•, 21•, 22]. A recent multi-institutional retrospective analysis of 1,004 patients treated for sCRLM between 1982 and 2011 found no difference in postoperative complications or 90 day postoperative mortality between staged or simultaneous resection [23••]. In this study, a major hepatectomy was defined as resection of more than three segments, and the authors did observe that this was more commonly performed with a staged approach (39 %) versus a simultaneous approach (24 %).

These conflicting results highlight the gaps in knowledge currently present in this field. The lack of prospectively performed studies has necessitated the reliance on retrospective analyses of single or multi-institutional experiences and the potential interaction of selection bias with these results is strong. A recent meta-analyses by Slesser et al. [24••] compared the outcome of simultaneous and staged resections using 3,159 patients from studies published between 1991 and 2010. They found that while there were no significant differences in operative blood loss, duration of operation, post-operative complications, OS, or disease free survival (DFS), the 1,778 (56.3 %) of patients that underwent delayed resection had significantly larger liver metastases, with increased bilobar distribution and more of these patients underwent a major liver resection. Yin et al. [25••] performed a meta-analysis of studies including a total of 2,880 patients, and their findings were similar, although they did note a significantly lower incidence of post-operative complications in the simultaneously resected group. Of note, based on this analysis Yin et al. [25••] recommended the following criteria for selection of patients to undergo simultaneous resection: liver resection involving less than four segments, age less than 70 and exclusion of patients with severe comorbid conditions. Both of these meta-analyses confirm that in the absence of clear clinical criteria to guide surgical decision making toward delayed or simultaneous resection, the surgeon's judgment, tempered by the counsel of a multidisciplinary committee and the patient's overall fitness for major abdominal surgery, remains the primary determinant of treatment strategy. Table 2 provides an overview of study characteristics for many of the studies included in these analyses in addition to more recent studies.

An alternative to these two approaches is the reverse, or liver first, staged resection in which the hepatectomy is performed prior to excision of the primary tumor. This approach is most often utilized for patients with rectal primary tumors as the timing dovetails conveniently with the waiting period after neoadjuvant chemoradiation therapy for the primary tumor has been completed. An added benefit is the avoidance of operative delay due to potential septic complications associated with resection of the primary rectal tumor. The liver first-staged approach can also be preceded by neoadjuvant chemotherapy specific for the metastatic lesions [15, 26•, 27]. This strategic therapeutic delay offers the theoretical advantage of allowing the tumor biology to manifest, which in turn may indicate the suitability of aggressive resection. In addition to the risk of interval progression during initial neoadjuvant chemotherapy, there is also the potential for chemotherapy-associated parenchymal damage that may complicate efforts to ensure an adequate future liver remnant (FLR) and necessitate the use of adjunctive techniques, such as portal vein embolization or ligation to enhance FLR.

If there is a robust response to treatment and metastases are no longer visualized on radiographic studies, these lesions still need to be excised as the rate of complete pathologic response is low and the risk of regrowth remains high [26•].

The outcomes of the liver first approach have been detailed in small case series as well as larger multi-institutional reviews that indicate that liver first staged resection is feasible with similar outcomes to either simultaneous or colon first staged resection [15, 23••, 28, 29].

## The Role of Perioperative Systemic Chemotherapy

Despite the improvements in surgical approaches of liver resection, recurrence of disease has been reported in up to two-thirds of patients, with half of these occurring in the remnant liver [30, 31]. This has lead to numerous studies highlighting the benefit of pre- and post-operative chemotherapy in improving outcomes after hepatectomy for metachronous CRLM. Non-randomized trials of adjuvant treatment with 5-fluorouracil (5-FU) based chemotherapy or the use of hepatic arterial infusion of floxuridine (FUDR) have demonstrated improvement in survival and decreased rates of recurrence [32–34] However, the recently concluded European Organisation for Research and Treatment of Cancer (EORTC) intergroup trial 40,983 failed to demonstrate any benefit for perioperative chemotherapy with liver

**Table 2** Characteristics of studies of simultaneous versus staged hepatectomy in sCRLM

| Author | Year | Simultaneous resection | | | | Staged resection | | | | Neoadjuvant chemotherapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Patients | Mean age | Liver mets | Major liver resection (%) | Patients | Mean age | Liver mets | Major liver resection (%) | One stage | Staged |
| Vogt [53] | 1991 | 19 | 56.5 | 1.79 | 32 | 17 | 56.5 | 1.24 | 53 | NA | NA |
| Jaeck [54] | 1999 | 28 | 56 | – | 32 | 31 | 60 | – | 52 | NA | NA |
| Weber [55] | 2003 | 35 | 58.0 | 1.9 | 31 | 62 | 60.0 | 3.7 | 52 | 44 % | 61.2 % |
| Chua [56] | 2004 | 64 | 63.0 | – | 16 | 32 | 61.0 | – | 40 | NA | NA |
| Tanaka [57] | 2004 | 39 | 64.0 | 2.2 | 13 | 37 | 65.0 | 5.3 | 59 | NA | NA |
| Minagawa [58] | 2006 | 142 | – | – | 11 | 18 | – | – | 38 | NA | NA |
| Capossotti [17•] | 2007 | 70 | 64.9 | – | 34 | 57 | 60.8 | – | 56 | NA | NA |
| Thelen [22] | 2007 | 57 | 60.0 | – | 38 | 179 | 59.7 | – | 79 | 7.5 % | NA |
| Reddy [59] | 2007 | 135 | 57.0 | 1 | 26 | 475 | 58.0 | 2 | 61 | 60.7 % | 79.2 % |
| Yan [60] | 2007 | 73 | 60.0 | 4 | 74 | 30 | 59.0 | 3 | 73 | NA | NA |
| Slupski [61] | 2008 | 28 | 59.4 | 2.9 | 29 | 61 | 60.2 | 3.8 | 48 | NA | NA |
| Martin [16] | 2009 | 70 | 58 | 3 | 47 | 160 | 61 | 3 | 40 | 52 % | 70 % |
| Brouquet [62] | 2010 | 43 | 58 | 2 | 35 | 72 | 56 | 3 | 67 | 11 % | 59 % |
| De Haas [63] | 2010 | 55 | 56.0 | 2 | – | 173 | 58.0 | 3 | – | 24 % | 95.4 % |
| Luo [64] | 2010 | 129 | 58.0 | – | 32 | 276 | 60.0 | – | 38 | 40 % | 61.2 % |
| Moug [65] | 2010 | 32 | 69 | – | 22 | 32 | 67 | – | 22 | 40.6 % | 53.1 % |
| Petri [66] | 2010 | 14 | – | – | 0 | 29 | – | – | 21 | NA | NA |
| van der Pool [67] | 2010 | 8 | – | 1 | – | 29 | – | 2 | – | NA | NA |
| Slesser [20•] | 2013 | 36 | 55.5 | – | 64 | 76 | 62.0 | – | 79 | 88 % | 99 % |
| Mayo [23••] | 2013 | 329 | 60.0 | – | 23.7 | 675 | 61.0 | – | 38.6 | 21.6 % | 20.1 % |

*NA* not available

resection of CRLM [35••]. This trial was a randomized, controlled, parallel-group, phase 3 study involving 78 hospitals in which patients with CRLMs (up to 4) were randomly assigned to surgery alone or perioperative FOLFOX4, (5-FU, folinic acid and oxaliplatin) chemotherapy. The perioperative chemotherapy regimen consisted of six 14-day cycles before and after hepatectomy. Despite initial reports that perioperative chemotherapy had improved progression-free survival, the long-term results indicate that there is no difference in 5-year OS. Another recent study by Faron et al. [36] examined the impact of pre- and post-operative chemotherapy separately in patients with resectable CRLM. This study found that while pre-operative chemotherapy did not improve OS, postoperative chemotherapy was an independent predictor of increased OS and DFS. The current data do not indicate that pre-operative chemotherapy has a proven role prior to hepatectomy for CRLM, although this question merits further study, especially with regards to the specific benefit of adjuvant therapy.

The effect of chemotherapy-related hepatic toxicity must also be considered when pre-operative chemotherapy is used. Regimens containing irinotecan have been associated with steatohepatitis in up to 66 % of patients, and hepatic sinusoidal abnormalities have been seen with oxaliplatin based regimens [37, 38]. The addition of bevacizumab has been demonstrated to increase the frequency of tumor regression when utilized in conjunction with oxaliplatin or irinotecan, but is associated with increased toxicity and the need to delay hepatectomy for up to 4 weeks after the last dose due to its prolonged half life [39, 40].

In patients with sCRLM that are deemed resectable, the National Comprehensive Cancer Network guidelines recommend either simultaneous resection followed by adjuvant therapy—with FOLFOX or CapeOx (capecitabine, oxaliplatin)—or neoadjuvant therapy for 2–3 months prior to operation [41]. Recommended neoadjuvant regimens include FOLFIRI (folinic acid, 5-FU and irinotecan), FOLFOX, or CapeOx with or without bevacizumab. If the tumor is KRAS wild-type, the use of FOLFOX or FOLFIRI with or without panitumumab or cetuximab (monoclonal antibodies against EGFR) may be considered [41, 42].

## Adjunctive Strategies for Initially Unresectable Disease

Seventy-five to 85 % of patients with sCRLM have unresectable disease due to either the size, location, multifocality of metastases or have an inadequate projected FLR [43]. Several established and emerging therapeutic strategies

have been used to attempt to convert patients to resectability. In patients deemed to have unresectable disease, the use of systemic chemotherapy has demonstrated conversion of 15–20 % of patients to undergo surgical resection with a 5-year OS of 33–42 % [44, 45]. In this clinical scenario, the regimens outlined in the previous section are recommended by the NCCN. In addition, there are many novel therapeutic combinations that have been described, but are beyond the scope of this review.

The ability to safely perform a major hepatectomy has expanded the extent of liver resection that surgeons may consider in order to extirpate all metastatic lesions. A fundamental factor governing this decision, however, is the FLR. In general, a goal of retaining 20–25 % of a normal liver, or 30–35 % of liver in patients treated with chemotherapy is necessary for the FLR to be deemed adequate. This can be assessed with volumetric CT imaging. The most common maneuvers employed to enhance the FLR are either radiologic portal vein embolization or operative portal vein ligation of the side of the liver that is planned for resection. This approach allows for hypertrophy of the residual liver in four to 6 weeks for adequate FLR when an extended hepatectomy may be necessary to achieve an R0 resection.

Another approach to managing bi-lobar disease is a two-stage hepatectomy, as this allows for residual liver regeneration in the 6–8 weeks between hepatectomies. Extreme surgical approaches involving ex vivo hepatic resection, vascular exclusion, and hypothermic perfusion have also been reported, but these are performed only in highly specialized circumstances in close collaboration with liver transplantation teams.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a technique that has gained much attention in recent years and combines aspects of the techniques outlined above. This technique is a modification of both two-stage hepatectomy and extended right hepatectomy in which the right portal vein is ligated and the hepatic parenchyma is split in situ during the initial operation [47•]. The extended right lobe is covered with a plastic bag to prevent formation of adhesions in the interval between operations. Regeneration of hepatic parenchyma is measured at post-operatively via volumetric CT (at a median of 9 days in the original study), and if the FLR is adequate then the second operation is scheduled for the following day. During the second operation the extended right hepatic lobe is removed by ligating the right hepatic artery, right and middle hepatic veins and bile ducts The initial results of this approach were reported by Schnitzbauer et al. [47•] and indicated that the left lateral section volume increased 74 % at a median of 9 days after the initial operation. A subsequent study by de Santibanes et al. [48] demonstrated 40–80 % hypertrophy of the FLR 6 days after the initial operation [48]. Several groups have adopted and refined this technique, and it remains an area of expanded use and surgical innovation.

Ablative therapies offer another strategy to downsize or eliminate metastatic lesions. Ablative approaches may be used in circumstances when the patient may not tolerate a liver resection, or in conjunction with surgical resection in the presence of bi-lobar disease when attempting to achieve a curative resection, particularly when extended hepatectomy may not allow for an adequate FLR.

Cryotherapy induces tumor necrosis through the circulation of liquid nitrogen through a metal probe that is inserted either percutaneously or intra-operatively (laparoscopic or open) and the resultant rapid freezing of tissue leads to tumor destruction. Its use has diminished in recent years, however, due to higher complication rates and technical limitations compared with radiofrequency ablation (RFA) [49].

The most widely used thermoablative modality is RFA. In this technique, an electrode is inserted into the tumor, and then a high frequency alternating electrical current generates frictional heat resulting in coagulation necrosis of tumor tissue. A single electrode can ablate a two to three cm lesion with a 1-cm margin, but larger tumors require either multiple electrode placements or the deployment of an electrode array in order to encompass the entire area [50]. The utility of RFA in patients with unresectable disease has not been well established; however, an American Society of Clinical Oncology (ASCO) clinical evidence review of the existing data on RFA concluded that there is currently a compelling need for more study in this area [51].

Microwave ablation is another modality that can be employed intraoperatively or through image guidance. Tissue heating results from the agitation of water molecules, resulting in hyperthermia and coagulation necrosis. In a trial of microwave ablation versus hepatic resection for CRLMs performed by Shibata et al. [52] demonstrated a similar OS between the groups.

Select patients that present with pulmonary metastases in addition to CRLM may be considered for combined or staged pulmonary and liver metastasectomy. These patients are evaluated in conjunction with a thoracic surgeon, usually after receiving a period of systemic chemotherapy verifying the lack of progression of disease, if all the pulmonary disease can be removed without compromising pulmonary function [46].

## Conclusion

Management of patients who present with sCRLM is complex and evolving at a rapid pace. There is no clear

evidence to indicate that there is an optimal approach to timing of resection of the primary tumor or metastatic disease, and the evidence that is available indicates that there is no significant difference in outcomes between approaches. The availability of effective chemotherapy regimens and innovative surgical and ablative approaches allows for an array of therapeutic modalities to optimize patients outcomes. The decision on operative timing and approach, then, remains largely dependent on the patient's response to systemic therapy, the surgeon's determination of disease resectability and patient symptomatology and fitness.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Jason A. Castellanos and Nipun B. Merchant declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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