

Management of Stage IV rectal disease – How to incorporate radiation therapy, chemotherapy and surgery

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ABSTRACT

Approximately 50–60% of patients diagnosed with rectal cancer either present with or will develop metastatic disease. Treatment for metastatic rectal cancer has evolved due to advances in both medical and surgery therapy and involves a combination of chemotherapy, radiation therapy and surgery. This multimodal therapy requires individualization due to a variety of patient and tumor characteristics and results in variability of regimens and the sequence of treatment for metastatic disease. In this article we will review various approaches to the treatment of metastatic rectal cancer combining multimodal chemotherapy, radiation and surgery.

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Introduction

Colorectal cancer is the third most common cancer in both the United States and worldwide with an estimated ~44,000 new diagnosis of rectal cancer expected in the United States in 2019.^{1,2} Of those diagnosed with rectal cancer approximately 30% of patients will present with synchronous metastatic disease, with the liver being the most common site of metastasis, and is associated with worse prognosis and survival than metachronous disease.^{3,4} Traditionally, treatment for synchronous metastatic rectal cancer was straightforward and addressed the primary tumor first, followed by adjuvant chemotherapy to treat the metastatic disease. However, this ‘classical pathway’ has been debated as metastatic disease may progress while addressing the primary lesion and data suggests that approximately 30% of patients experience post-operative complications and/or prolonged recovery preventing them from receiving adjuvant chemotherapy thus, their metastatic disease goes left unchecked.⁵ While this ‘classical pathway’ remains an option, treatment strategies have evolved over the last couple decades with the introduction of new chemotherapeutic agents and timing schedules, expanded criteria for resection of metastatic disease and improved morbidity and mortality after resection with the goal being complete resection of metastasis for stage IV colorectal cancer resulting in improved overall five-year survival rates from ~5–10% to approximately 30–50%.³ To achieve this, current treatment strategies involve a multimodal approach combining chemotherapy, radiation and surgery however there is no consensus on the optimal sequence. Determining the optimal sequence requires an individualized approach

taking into account both patient and tumor characteristics. In this article we review data regarding patient and tumor specific characteristics that factor into decision making and propose an algorithm in the multidisciplinary treatment of stage IV rectal cancer with synchronous metastases.

Determining the extent of disease

Once a pathologic diagnosis of rectal adenocarcinoma is made, staging workup includes a CT of the chest, abdomen and pelvis looking for metastatic disease, most commonly to the liver and/or lung, as well as a rectal magnetic resonance imaging (MRI) or endorectal ultrasound (ERUS) for local staging of the primary tumor. Blood work including a CEA (carcinoembryonic antigen) is obtained as well as determination of gene status of the primary tumor looking for mutations in BRAF and RAS as well as tumor microsatellite instability (MSI) and/or immunohistochemistry for mismatch repair genes (MMR) as these can help guide treatment options and response to therapy. Positron emission tomography (PET/CT) scan is not routinely obtained however can be helpful in patients with a contraindication to IV contrast or when there are equivocal findings or suspicion of metastatic disease without obvious proof, such as a discordance between a significantly elevated CEA in the setting of a negative staging CT scan. For those with suspected metastatic lesions, biopsy can be obtained as necessary and in the case of suspected hepatic lesions, dedicated liver MRI can be helpful in further elucidating the burden of hepatic disease and is useful for treatment planning. Once the diagnosis of metastatic rectal cancer is made, treatment warrants a multidisciplinary approach given the significant expansion in treatment options for rectal cancer and has been shown to result in improved patient outcomes.^{6,7} The potential for cure after resection of

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locregional and distant disease drives treatment strategy with the approach determined by the resectability of the metastatic disease as well as the severity of symptoms from the primary rectal lesion. (Fig. 1) However, there remains significant individual and institutional variability and to date there is no consensus on the appropriate sequence of treatment for stage IV rectal cancer with synchronous metastases.

Symptomatic primary lesion

In addition to the extent and resectability of metastatic disease, one of the key factors determining the sequence of treatment for stage IV rectal cancer involves whether the patient has symptoms from their primary rectal tumor such as bleeding, obstruction or perforation. (Fig. 1) For tumors with slow bleeding, with or without anemia, treatment should be supportive utilizing transfusions and iron supplementation followed by initiation of chemotherapy as often the bleeding will slow or stop with commencement of treatment. In fact, data from Poultides, et al. demonstrate that in the absence of a surgical emergency, a majority (93%) of patients undergoing upfront chemotherapy for their metastatic disease do not require palliative surgical intervention for their primary tumor during treatment.⁸ However, in cases of more severe or massive bleeding, surgical resection according to oncologic principles and total mesorectal excision (TME) is indicated as simple diversion may not alleviate significant bleeding. In the setting of a tumor emergency such as massive bleeding or perforation, post-operative morbidity approaches 20% or more and consideration of an ostomy in lieu of an anastomosis should be contemplated to reduce the post-operative morbidity and allow the patient to proceed onto systemic therapy expeditiously.⁹ In those patients presenting with near or complete obstruction, options include surgical diversion with or without resection versus a self-expanding metal stent (SEMS). However, SEMS is not routinely an option for low-lying rectal lesions as this is associated with significant pain and tenesmus. The appeal of SEMS in acute malignant obstruction lies in alleviating the obstruction and converting an emergency surgery into an elective surgery thus reducing post-operative

morbidity and allowing for a reduction in the rates of stoma creation. SEMS has been shown to provide clinical success, as defined by alleviation of an acute obstruction, in almost 80% of patients when followed by urgent surgical resection and when compared to surgery alone in those with curable disease, SEMS results in lower post-operative morbidity and stoma formation.¹⁰ However, when used in more a long-term setting as a bridge to surgery, SEMS does not appear to provide an advantage in with regard to overall complication rate or post-operative morbidity when compared to surgery alone in those with curable disease. In fact, data reveals that in the long term SEMS is associated with a significant rate of stent-related perforation, up to 13%, with some studies suggesting an association between stent perforation and a higher tumor recurrence rate.¹¹ Thus, the role of SEMS as a ‘bridge to surgery’ is not currently recommended. Instead, surgical diversion with an ostomy and mucous fistula of the distal limb is preferred as this can be done expeditiously, either open or laparoscopic, and alleviate the obstruction while allowing the patient to proceed onto systemic therapy with minimal delay.

Asymptomatic primary lesion with resectable hepatic metastasis

Asymptomatic primary rectal lesions with resectable synchronous lesions are the most controversial patient group with regard to options and sequence of treatment strategies. The liver is the most common site of metastasis and in general, criteria for liver resectability includes the ability to obtain a R0 resection, at least two functional contiguous segments with intact portal and arterial inflow as well as venous and biliary outflow/drainage, limited extrahepatic disease that is resectable and adequate post-operative liver volume and function. Data show that after resection of the primary tumor and distant metastases, patients with metastatic rectal cancer may experience long-term survival of over 30%, and a small subset may be cured, likely owing to the introduction of newer chemotherapeutic drugs such as oxaliplatin and irinotecan, biologic agents such as bevacizumab, as well as radiotherapy and improved surgical techniques.¹² More recent data from Conrad et al., reveal that incorporation of these novel therapies as well as a more individualized approach to the

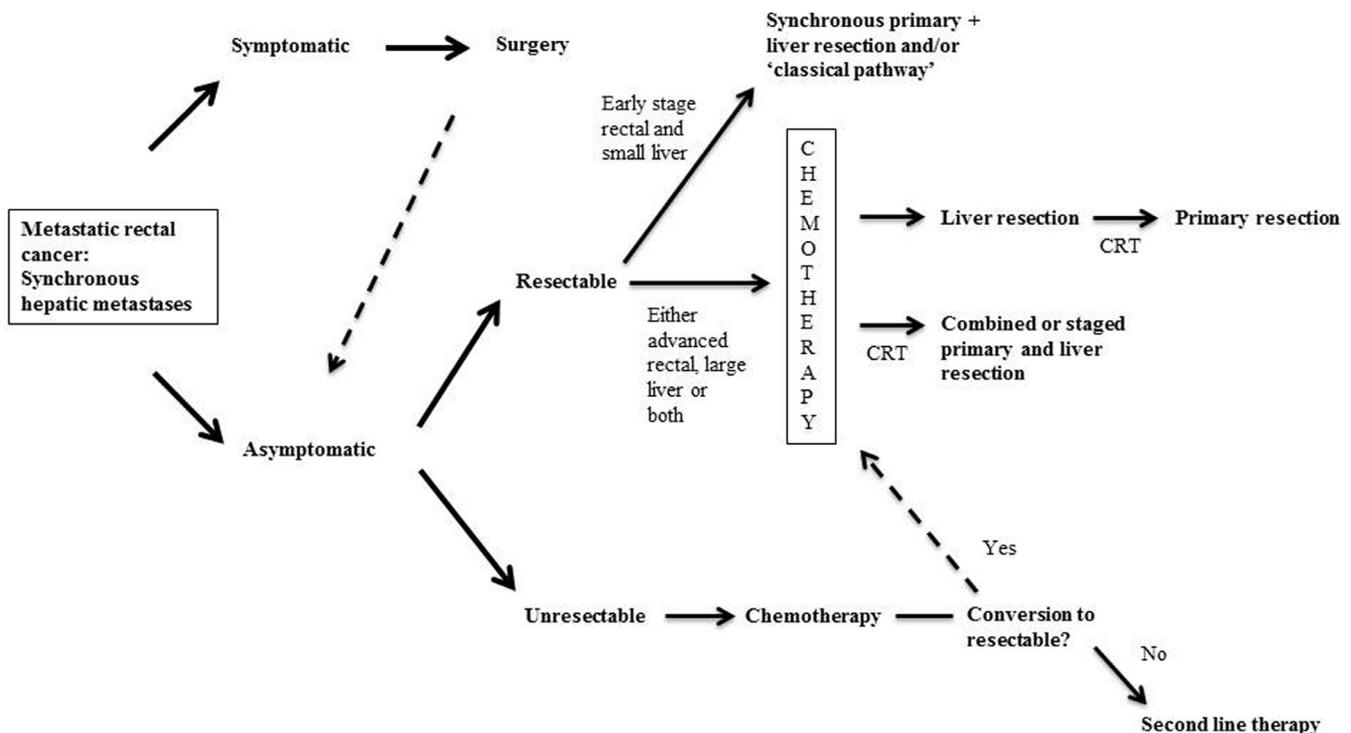


Fig. 1. Proposed treatment algorithm for Stage IV rectal cancer with synchronous liver metastases. CRT = chemoradiation therapy

sequence and treatment of rectal cancer with isolated liver metastases results in increased 5-year overall survival rates of 45% from 1999–2003 to 76% from 2009–2014.¹³ Therefore, aggressive yet individualized medical and surgical treatment is warranted in patient with metastatic rectal cancer with an asymptomatic primary and resectable hepatic metastasis.

As mentioned previously, prior treatment strategies for metastatic rectal cancer followed the 'classical pathway' with resection of the primary rectal lesion first, followed by adjuvant chemotherapy and re-evaluation as to the resectability of the liver disease. A similar approach is the 'combined pathway' which offers upfront synchronous resection of both the primary and metastatic lesion. Both of these approaches are useful in cases of a symptomatic primary rectal tumor with an accompanying low burden of liver disease or, for those patients with low volume early stage disease at both primary and hepatic sites as patients may benefit from upfront resection of the primary tumor and/or metastases. However, one of the major drawbacks includes delay in time to chemotherapy which may allow for metastatic disease progression, especially in the case of post-operative complications after surgery for the primary tumor. Additionally, data comparing surgery alone versus surgery plus adjuvant chemotherapy found that adjuvant chemotherapy improved disease free survival but not overall survival.¹⁴ In 2006, Mentha and colleagues published data describing yet another pathway, what is now known as the 'reverse pathway', which starts with neoadjuvant chemotherapy first (FOLFOX or FOLFIRI), followed by liver resection and then colorectal surgery last with the concept that upfront chemotherapy does not result in complications from the primary tumor but instead allows for early treatment and down-staging of the metastatic disease.^{8,15} This allows for a window of opportunity for hepatic resection as well as avoidance of complications such as anastomotic leak that may otherwise compromise the entire classical pathway with a primary first approach. Additionally, this strategy may also avoid unnecessary rectal surgery in patients with incurable or progressive metastatic disease while on neoadjuvant chemotherapy. Initial data suggested that with the 'liver first approach' starting with neoadjuvant chemotherapy and resection of liver metastases followed by chemoradiation therapy and primary resection, a majority of patients (74%) were able to undergo curative treatment of both the primary and metastatic disease.¹⁶ Subsequent data showed that when compared to the classical and combined pathways this sequence has similar outcomes and seems to be especially beneficial in those with a large burden of hepatic lesions and has allowed for the expansion of resectability in patients with synchronous hepatic metastases.¹⁷ However, this early data was limited by its retrospective nature of small population, single institution studies and this 'liver first' or 'reverse pathway' approach remains controversial. Results of a randomized controlled trial across 78 hospitals in Europe demonstrated that neoadjuvant chemotherapy followed by liver resection improved progression-free survival without a difference in overall survival compared to surgery alone.¹⁸ In fact, their data revealed a higher rate of post-operative complications in those receiving neoadjuvant chemotherapy versus surgery alone (25% vs 16%; $p=0.04$) thus highlighting one of the pitfalls of neoadjuvant chemotherapy. Specifically, one of the factors to consider using neoadjuvant chemotherapy prior to liver resection is chemotherapy associated liver injury, as the use of irinotecan and/or oxaliplatin based regimens are associated with the development of steatohepatitis and oxaliplatin specifically is also associated with sinusoidal injury and vascular obstruction known as the blue liver syndrome.¹⁹ The addition of bevacizumab has been shown to decrease the rate of sinusoidal injury. However, this does not translate to a decreased risk of post-operative hepatic insufficiency.²⁰ Thus, to ensure sufficient remnant liver after neoadjuvant chemotherapy, treatment is typically limited to only 2–3 months prior to restaging and in general, liver metastases are considered resectable if able to maintain at least a 30% future liver remnant (FLR)

after preoperative chemotherapy. While CT and MRI imaging can help determine liver volumes and FLR with use of volumetric software, determining function of the liver remnant is much more challenging and requires the surgeon to take into account other patient characteristics such as non-alcoholic steatohepatitis (NASH) when determining resection candidacy and extent of hepatectomy.

In addition to determining the sequence of therapy, one of the other major factors in metastatic rectal cancer with resectable liver lesions is deciding on a synchronous or staged surgical approach to the resection of the primary tumor and hepatic metastases. Proposed advantages of a synchronous resection of both the primary lesion and liver metastasis is that it only requires one surgery and one anesthetic which can decrease length of stay and hospital costs as compared to two separate surgeries. Additionally, combined resection allows for earlier completion of surgical intervention and can prevent delays in the initiation of chemotherapy or other treatments due to post-operative complications. However, one of the main disadvantages of a synchronous approach to surgical resection includes the possibility of increased morbidity and mortality when combining two large surgical procedures. Data from Reddy, et al. show that a synchronous colorectal and liver resection is safe however, the extent of hepatic resection is a key determinant in outcome such that patients who underwent colorectal resection along with a major hepatic resection had higher rates of severe morbidity when compared to staged patients, 36.1% vs 15.1%, $p=0.004$.²¹ Alternatively, synchronous resections of the primary lesion with minor hepatic resections did not result in an increase in severe complications and morbidity when compared to staged resections, 14.1% vs 12.5%, $p=0.84$. In a subsequent meta-analysis, Chen, et al. concur that simultaneous resections are safe in appropriately selected patients with an important determinant being the extent of liver resection however, the specifics of selection are not obvious as the study is limited by the heterogeneity of the studies included.²² Overall, resection of the primary lesion and the hepatic lesion can be done in either a staged or simultaneous approach at the discretion of the surgeon based on tumor characteristics and oncologic principles, the patient's overall health status and consideration of a combination of risk factors that contribute to overall prognosis: extrahepatic sites of metastasis, elevated CEA >100, disease free survival of less than 12 months, as well as a higher number (>3) of metastatic lesions.²³

There is no data supporting the routine use of one pathway versus another however, combining the data above with what we know about the benefit of preoperative versus post-operative chemoradiation therapy in locally advanced rectal cancer, we propose an algorithm for metastatic rectal cancer with liver metastases by first stratifying patients based on symptoms and resectability and then tailoring the treatment approach based on the individual's risk of either distant disease failure or primary disease failure.²⁴ (Fig. 1) For example, patients with a high burden of hepatic metastases and a small, asymptomatic rectal tumor are more likely to succumb to their systemic disease before the primary tumor causes significant symptoms and as such, we recommend starting with systemic chemotherapy. However, in those with a low burden of metastatic disease yet a large, bulky rectal primary lesion, patients may benefit from upfront total neoadjuvant therapy (TNT) with both chemotherapy and treatment directed at the primary tumor, either long or short course chemoradiation therapy, in order to prevent symptoms of progressive pelvic disease.

Asymptomatic primary lesion with unresectable metastasis

Of those who present with metastases, only 10–20% are deemed resectable at diagnosis.²⁵ For those with an asymptomatic primary lesion and unresectable or borderline resectable liver metastases at the time of diagnosis, treatment begins with systemic chemotherapy. It is general accepted that patients receiving chemotherapy undergo

imaging and surgical re-evaluation every 2–3 months while on therapy to evaluate for progression of disease versus down-staging and candidacy for surgical resectability, termed conversion. In a recent meta-analysis, data demonstrated that in patients with unresectable metastatic disease at the time of diagnosis initially treated with chemotherapy, an estimated 30–50% of patients have a significant response to chemotherapy and 23% had down-staging allowing for an R0 resection.²⁵ Frequent restaging with surgery as soon as the patient becomes resectable is also recommended to reduce the risk of hepatotoxicity from prolonged chemotherapy as data shows that prolonged chemotherapy (>9 cycles) is associated with an increased risk of post-operative hepatic insufficiency.²⁰ The addition of cetuximab to standard chemotherapy seems to improve response rates with overall response rates of 62% and an R0 hepatic resection rate of 34% in those initially thought to be unresectable at the time of diagnosis.²⁶ Additionally, those who underwent an R0 resection had an improved overall and disease free survival compared to those who did not undergo resection with a 46.2% 5-year survival rate for R0 resected patients who underwent conversion chemotherapy.²⁷ Thus aggressive and tailored treatment of initially unresectable metastatic disease can improve patient outcomes.

For patients with an intact asymptomatic primary lesion and unresectable metastases, the need for resection of the primary lesion is controversial. Traditionally, prophylactic surgery for the primary tumor has been offered to avoid complications during systemic therapy with some earlier studies demonstrating a survival benefit.²⁸ However, what is interesting is that in these same studies, simple diversion does not result in the same survival benefit. Subsequent analysis of the National Cancer Database (NCDB) demonstrated similar results with improved survival after formal resection of the primary tumor despite unresectable metastasis however, a majority of these patients had primary colon tumors as patients with a tumor location in the rectum were less likely to undergo surgical resection, 8.2 vs 46.7%, $p < 0.001$.²⁹ A subsequent Cochrane analysis of over 1000 patients with metastatic colorectal cancer, did not identify an overall survival benefit in asymptomatic Stage IV unresectable colorectal cancer patients compared to those managed with chemotherapy alone with or without radiation.³⁰ Unfortunately, these studies are limited by their population heterogeneity, patient selection bias, and lack of well-designed randomized control trials thus, there is no consensus on the role for primary tumor resection in the setting of unresectable metastatic disease.

For tumors that remain unresectable after initial chemotherapy, non-operative liver-directed therapies may be considered such as radiofrequency ablation (RFA), radioembolization using yttrium-90 spheres and stereotactic body radiation therapy. Portal vein embolization or hepatic arterial infusion in combination with systemic chemotherapy may increase the rates of conversion to resectability and thus improve long-term survival.^{31,32}

Lung metastasis

The lung is the second most frequented site of metastatic disease and compared to hepatic metastases, the data regarding the treatment of isolated pulmonary and/or combined hepatic and pulmonary metastasis is sparse. In general however, the treatment recommendations discussed for colorectal hepatic metastases apply to pulmonary metastases such that surgical resection is widely accepted as the treatment of choice in order to improve survival and potential cure, as untreated pulmonary metastases have a low 5-year overall survival rate of ~5–10%.³³ Regimens combining chemotherapy and surgery have increased survival after metastasectomy and allowed for tumor downsizing allowing for conversion to resectability in patients previously unsuitable for surgery with 5-year overall survival rates of ~40%.³⁴ The use of either traditional thoracotomy vs VATS (video assisted thoracoscopic surgery) as the resection technique for

pulmonary metastasis from colorectal cancer does not seem to influence recurrence or survival rates however, VATS is associated with a decreased hospital stay.³⁵

Summary

Colorectal cancer is one of the most common cancers in the United States and worldwide however, mortality from this disease is decreasing likely related to advances in systemic chemotherapeutic agents as well surgical techniques and perioperative care across all stages of the disease. Therefore, aggressive yet individualized medical and surgical treatment is warranted in patients with metastatic rectal cancer often requiring multimodal therapy to achieve the goal of complete resection of metastasis for stage IV colorectal cancer.

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