



Is a surgical CURE in the future for colorectal cancer liver metastasis?

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Abstract

This review was constructed to evaluate the current advancements in the surgical management of colorectal cancer liver metastases. A shift from the classic conservative and palliative management of such cases has begun with transitions toward surgical management. This shift is due to multiple compounding factors of which many are being studied and presented individually. By combing these factors together, this review provides guidance on the most significant preoperative prognostic factors and suggests future treatment goals for these patients. A progressive conversion from conservative to surgical management also presents ethical implications to be considered. This review may direct future research on surgical resection of colorectal cancer liver metastases and provide advantageous information on the value of preoperative prognostic factors and the role of surgical intervention in this patient population.

Keywords: Surgical oncology, Colorectal cancer, Liver metastasis, Surgical resection, Carcinoembryonic antigen, Future liver remnant, Preoperative evaluation, Portal vein embolization, Percutaneous radiofrequency ablation, Conversion therapy, Chemotherapy, Mismatch repair protein

Introduction

Surgical resection of colorectal cancer (CRC) liver metastases is a controversial and evolving topic within the realm of surgical oncology. As medical management and surgical techniques continue to advance in safety and efficacy, metastatic diseases that were previously deemed terminal or nonsurgical are now being considered for surgical management. Specifically, CRC liver metastasis is only recently becoming a surgically managed diagnosis. In looking at this growing field of surgical oncology many questions are raised in the decisive factors that make a patient a good candidate for surgical resection.

The new era of surgical management for CRC liver metastasis is anchored in the identification of surgical resection as the only form of regional treatment that is known to produce a survival plateau. Previously CRC liver metastasis would only be removed if a case included no more than a maximum of 3 sites of metastases, resection margins of 1 cm were achievable, and portal lymph nodes were not involved. Throughout the last 15 years these ideas have been challenged by ever-improving medical and

surgical techniques that have led to increased patient survival in cases that break the status-quo for surgically resectable liver metastasis.

Preoperative assessments

Surgical resection of CRC liver metastases offers patients the best likelihood of cure with 1 case study reporting an average 5-year survival rate after resection of 58%. The involvement of lymph nodes, however, continues to be an obstacle for surgeons treating patients with liver metastases. Low-yield preoperative as well as intraoperative evaluations of lymph node involvement have made this area one of continued research. Although preoperative imaging may not yield useful information on lymph node involvement it is still seen as a necessary step in identifying the extent of disease to the best degree possible. Preoperative positron emission tomography (PET) scan has been sited to “significantly reduce the number of futile surgeries (28% vs. 45%) and prevented unnecessary surgery in 1 in every 6 patients”^[1]. Some treatment facilities may offer integrated PET/CT imaging, however, a recent study found no difference in survival among groups who were randomly selected to have integrated PET/CT imaging versus a control group who did not receive such imaging^[1]. A noted factor in preoperative imaging complications is that chemotherapy can reduce the sensitivity of PET scans. Chemotherapy regimens continue to vary although the National Comprehensive Cancer Network (NCCN) routinely updates guidelines. The choice of initial chemotherapy for patients with metastases whom are candidates for resection is still determined on a case by case basis with considerations for patient comorbidities and significance of possible lesion response. New research is suggesting immediate resection rather than chemotherapy in the majority of such cases. Similarly, when deciding between simultaneous versus delayed primary and metastatic resection, studies have shown higher rates of

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cure with lower rates of morbidity and mortality when both surgical interventions are performed simultaneously^[1]. In some cases, resection of liver metastases is delayed to improve selection of possibly curative hepatic mastectomies. During the interim, it is suggested that these patients undergo treatment with either percutaneous radiofrequency ablation or chemotherapy.

It is noted that right and left-sided colon cancers appear similar microscopically and are known to have equivocal prognosis, however, in the presence of metastatic disease the prognosis of a right-sided carcinoma is worse compared with left-sided primaries. The data on this fact are limited, but it presents an intriguing topic for future research. Histologically the majority of CRCs are adenocarcinomas. Adenocarcinomas can be further broken down into the subtypes of aggressive signet ring cancers and medullary cancers that are associated with mismatch repair (MMR) protein deficiencies. Of the 2 subtypes, medullary subtype carcinomas reportedly have a better prognosis of survival. Primary CRCs located at distal areas of the colon also tend to contain regions of squamous cell differentiation which are associated with higher rates of mortality. It is similarly noted that an important factor in identifying tumor types is to isolate those that arise due to Lynch syndrome as they are highly unstable.

Tumors that present with MMR protein deficiencies have an improved prognosis and make it possible to use this factor in planning for future patient care such as the utilization of chemotherapy. The most important prognostic factor, however, in the survival of patients with CRC is pathologic stage of the carcinoma at presentation. In the event that patients receive neoadjuvant therapies, the pathologic stage after completion of therapy is the most accurate predictor. In these patients, identifying the degree of tumor regression is arguably the most important prognostic factor. The presence of lymph node involvement is also known to be a strong predictor following resection. There is a negative correlation with prognosis as more lymph nodes are involved. One study reviewed suggests a lymph node ratio as a means of stratification of prognosis according to the number of lymph nodes involved in relation to the number of nodes observed^[2]. Another factor of noted significance is carcinoembryonic antigen (CEA) levels. Having elevated CEA levels before surgical resection have been associated with poorer prognosis; even in the presence of negative lymph nodes compared with cases that were node-positive without elevated CEA levels^[2].

In addition to these factors, the volume of hepatic tissue necessary for a given resection was found to have a linear correlation to the extent of postoperative liver regeneration^[3]. Researchers have also identified a negative relationship between increasing obesity with decreasing regenerative abilities. More important to clinicians currently, is the implication of the preoperative determination of adequate future liver remnant (FLR). Retrospective reviews have correlated an increased risk of death with decreased volumes of FLRs. Per a recent article, 20% of a completely normal liver, 30% of a liver effected by steatohepatitis or moderate chemotherapy exposure, and 40% of a liver effected by cirrhosis or major chemotherapy exposure are suggestive of adequate liver remnants to allow for progression with hepatic resection surgery^[3].

Moreover, various contraindications for hepatic resection are also known. The Model for end-stage liver disease is 1 source of stratification that is not currently used directly in most clinical decisions but is identified as an aid in educating patients in their choice between resection and transplant. Aside from the

previously discussed FLR, patients who have identified preexisting liver disease such as cirrhosis or nonalcoholic steatohepatitis are at elevated disadvantages when considering hepatic resection due to CRC metastasis. Cirrhotic patients with Child-Pugh class C and class B with FLR < 40% are described as unquestionably unresectable cases^[3]. It is also reasonable that surgeons would consider patients with extrahepatic metastasis or metastatic disease involving major vessels, like the inferior vena cava, unresectable. Patients who simultaneously present with preoperative laboratory values that display significant liver dysfunction may not be adequate candidates to tolerate a resection.

The NCCN has taken note that previously unresectable carcinomas are now being considered for surgical management. The newest NCCN guidelines have set out to identify patients with initially unresectable metastatic CRC who have the potential to become resectable through preoperative treatment measures. Conversion therapy in patients with isolated CRC liver metastases that initially present as unresectable have been seen to have statistically significant responses, between 12% and 33%, to induction chemotherapy regimens^[1]. These treatments are subsequently allowing for complete metastatic resection.

Future treatment goals

One method now aiding patients who initially present as unresectable is portal vein embolization. This technique blocks flow to the affected lobe thereby acting as a catalyst for hyperplasia of the remaining liver lobe and it has been shown to be particularly effective for right-sided tumors^[3]. Similarly, smaller surgical margins are being increasingly pushed to the limits and controversy exists as to whether a margin as small as 1 mm, compared with the traditional 1 cm margin, is adequate in hepatic resections^[3]. Complications of any kind are understandably of significance in any surgery, and in hepatic resection major complications of bile leak, hemorrhage, hyperglycemia, coagulation dysfunction, and ultimately liver failure are to be avoided.

New standards for what is surgically acceptable includes patients who have > 3 metastatic lesions involving multiple hepatic lobes. One study showed that patients with ≥ 4 sites of metastasis had a 5-year survival rate of 47% and those with ≥ 8 sites of metastasis had a significant 5-year survival rate of 24%^[1]. Surgery remains the only option for cure in patients with liver-isolated metastatic CRC, therefore, in medically fit patients with ≤ 4 metastatic lesions; hepatic mastectomy should be preferred to initial chemotherapy. In patients who present with unresectable liver metastasis, chemotherapy should be considered for possible conversion of lesions to surgically resectable standards with note that longer neoadjuvant chemotherapy regimens increase risk for liver toxicity and postoperative complications. Whenever possible, 1-stage operations should also be performed.

Through review of the vital functions of the liver it is easily concluded that the mechanisms responsible for liver regeneration are a topic of ever increasing research. Furthermore, it is noted that larger studies with analysis of multiple prognostic factors and their subsequent interactions with each other is still needed to develop a more consistent outline that would aid in determining treatment routines.

Conclusions

Several preoperative prognostic indicators have been identified although few have been studied in conjunction with each other relative to significance. In the patient initially presenting with metastatic disease several factors should be considered. A low number of metastatic lesions is a positive indication for possibly curative hepatic resection. Medullary subtype carcinomas reportedly have better a prognosis compared with signet ring cell tumors, those with squamous cell differentiation, and those associated with Lynch syndrome. FLR volume plays a big role in deeming patients as surgical candidates for resection versus transplant. In preoperative planning, having a FLR of adequate size is a prominent positive preoperative factor. As is echoed in many of the reviews on this topic, the more functioning viable liver tissue a patient has to begin with, the better the overall prognosis for cure. The same can be said for cases that allow for immediate resection instead of utilization of radiofrequency ablation or chemotherapy preoperatively, which also signifies better preoperative imaging capabilities. The fact that chemotherapy may reduce the sensitivity of PET scans preoperatively may lead to additional studies needed in the future as more initially unresectable cases are converted to resectable cases using neoadjuvant chemotherapy and portal vein embolization. Adequate margin volumes will likely continue to be an area of research for years to come as surgical instruments continue to advance and surgeons continue to push the traditional limits. Smaller margins are becoming gradually more acceptable in such resections due to advances both in surgical equipment and intraoperative surgical technique. This will likely continue to be questioned on an ethical basis for what the standard of care should be since the ramifications of unequivocal surgical standards could lead to increased morbidity and mortality in this patient population. That increase could in turn cause a rise in legal cases of malpractice.

Low CEA levels before surgery is becoming more important as previously discussed, and presents a positive prognostic indication for surgical cure that should continue to be researched as this is a common test measured in this patient population that is relatively inexpensive. Conversion of nonsurgical cases into cases of cure via surgical resection with the initiation of chemotherapy treatments is an exciting transition in the overall care for metastatic CRC patients. The need for this conversion, however, means that such patients initially had higher risks for noncurative surgical results. Although this area has more to be discovered, if the degree of tumor regression following conversion therapy is a better prognostic indicator for cure; then perhaps more patients should be treated with chemotherapy even if they initially present with an unresectable metastasis. This transition to urging patients to undergo tough chemotherapy regimens may have ethical resistance as some patient's value quality of life versus longevity of life. In addition, more patients undergoing chemotherapy would likely lead to higher medical bills for patients and insurance companies that could eventually become a theme in oncological care and lead to an overall increase in the price of health insurance for these patients. Such concerns should be

considered in the progression of surgical treatment for CRC liver metastasis as it is the only present option to produce a survival plateau in these cases.

Ethical approval

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