



Refining the surgical playbook for treating colorectal cancer liver metastases

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Adenocarcinoma of the colon and rectum (CRC) is the second leading cause of cancer-related mortality. Surgical resection of disease offers the best long-term survival. Unfortunately, >50% of patients have liver metastases at the time of diagnosis, or develop colorectal cancer liver metastases (CRLM) subsequent to treatment of primary disease. Metastasectomy of CRLM has proven to extend survival, with up to 50% 5-year overall survival in contemporary series. However, only the minority of patients present with resectable disease; technical resectability is the ability to remove all carcinoma with negative microscopic margins while leaving adequate future liver remnant (FLR). FLR volume serves as a surrogate for functional reserve, and a FLR of $\geq 30\%$ in chemotherapy-treated patients is considered the minimum necessary volume to prevent complications of liver failure. In cases where predicted FLR is inadequate, vascular modulatory techniques such as portal vein embolization (PE) alone or in combination with two-stage hepatectomy (TSH-PE) or associating liver partition-and portal vein ligation for staged hepatectomy (ALPPS) have been shown to augment small FLR and provide an opportunity for curative resection. However the more radical the resection the higher the chance of a major complication after surgery (1). Thus, it is imperative to consider both the technical resectability of liver lesions along with the underlying tumor biology in order to weigh the benefit of radical resection for CRLM. Here we discuss recent findings from Mor *et al.* in perioperative outcomes

after TSH-PE and discuss the current landscape of surgical approaches available for combating liver metastases from colorectal cancer.

Mor *et al.* present their experience from a single institutions retrospective review of ten years of patients who underwent TSH-PE for CRLM, and compared the observed perioperative complications with a cohort of patients who underwent right hepatectomy for CRLM (2). In these cohorts of patients, the observed major complication rate and overall-survival was similar between TSH-PE and RH cohorts (17.2% and 20% major complication rate, 3.7% and 0% perioperative mortality respectively). Notably the authors reported a high utilization rate of ablative strategies to spare liver volume (79.2% of patients completing the second stage). This is noteworthy given the available data which suggests that ablative approaches have a four-fold risk of recurrence compared to resection (3). Nonetheless, this report adds further evidence to the feasibility of major hepatic resection and vascular modulatory techniques for aggressive treatment of colorectal liver metastases.

Approaching bilobar CRLM with TSH-PE is now routinely utilized, with reported perioperative morbidity and mortalities which eclipse major hepatic resections. Beyond TSH-PE, ALPPS has more recently become adopted for insufficient FLR, and a body of evidence has accumulated demonstrating it offers superior resectability and improved overall survival when compared head to head with TSH-PE in a multi-centered randomized-

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controlled trial (4). Respectively, both approaches should be viewed as tools which can extend the option for patients with disseminated liver metastases. However, technical resectability does not belie favorable biology.

Surgical treatment of metastatic disease at its core is a calculated gamble, one where the approach should have a reasonable chance of long-term disease control based on the natural history of the underlying malignancy. As we know, not all colorectal cancers behave the same. Disease aggressiveness can be predicted in part based on site of origin, response to chemotherapy, nodal involvement, and the time from the development of the primary tumor to the discovery of liver metastases (5). Furthermore, molecular analyses of driver oncogenes have shown the intracellular machinery which drives recurrence, metastases, and treatment failure. The more we learn about anatomic, temporal, and molecular markers of aggressiveness, the more we are able to gauge disease biology. Thus, as patients present to our clinics with CRLM of various lobar distributions but also tumor phenotypes, we must incorporate both assessments of technical and oncological resectability.

Perhaps the prime example of this concept is now being employed around the world in centers performing liver transplantation (LT) for CRLM. Work from prospective trials have shown five year overall-survival which approach 80% in highly selected patients who are offered LT as a means of local tumor control (6). To date, eight trials have been registered to study the efficacy of LT for CRLM, and many other centers have begun to offer LT for CRLM within institutional treatment protocols. Central to the rationale of this approach is the implementation of selection criteria which identify patients who have favorable tumor biology. Thus, centers require a minimum period of tumor

response to chemotherapy, and some exclude patients based on driver oncogene status. In addition, patients must have no evidence of extrahepatic disease, and must have had their primary tumor addressed prior to consideration.

One interesting finding from the early experience of implementing LT for CRLM is a surprisingly skewed distribution of recurrent disease. For example, patients who undergo major hepatectomy for CRLM experience hepatic recurrence about 40% of the time in the remnant liver. However, patients who undergo LT experience far lower rates of liver recurrence (3%) (7). This may be due to the preselection of patients prior to LT, but an alternative explanation may be the effects of total hepatectomy and removal of micrometastases. As more experience accumulates with this approach, there may come a day when we consider LT for patients with borderline resectable tumors and favorable oncologic characteristics, if indeed total hepatectomy can improve long term-disease control in highly selected patients. However for now data must accumulate to understand the derived benefit of LT for CRLM, and further refine a consensus criteria for offering this option to patients.

In summary, recent advances in vascular modulatory techniques including TSH-PE and ALPPS have expanded the armamentarium for treating CRLM with acceptable perioperative morbidity and good overall survival. Total hepatectomy and LT appears to be both feasible and beneficial in the right patient population. However, we must continue to build knowledge and stratification criteria for selecting the right surgical approach when treating patients with metastatic colon cancer through multi-institutional trials. To this effect, we present our institution's approach when assessing the biology and anatomy of patients' CRLM (*Figure 1*).

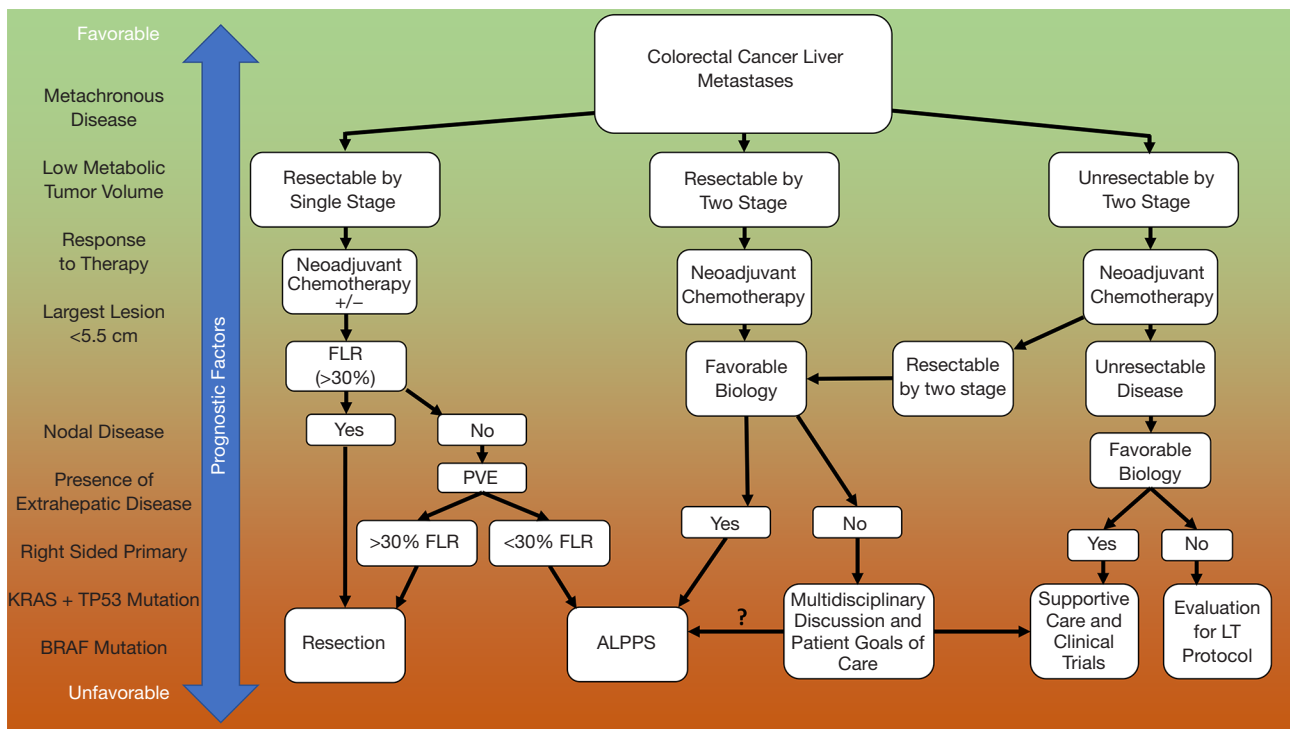


Figure 1 Decision diagram for evaluating patients with colorectal liver metastasis who present without evidence of extrahepatic disease. Tumor characteristics are critical to evaluating favorable and unfavorable biology, and are demonstrated on a spectrum to the left.

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