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Resection of Colorectal Liver Metastases

Eddie K. Abdalla

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Abstract
Introduction The gold-standard treatment for colorectal liver metastases (CLM) is liver resection. Advances in staging, surgical technique, perioperative care and systemic chemotherapy have contributed to steady improvement in oncologic outcomes for patients following surgery in this subset of patients with stage IV colorectal cancer. The limits of resection continue to expand to include patients with more, larger and bilateral CLM, yet outcomes continue to improve with 5-year overall survival exceeding 50% following resection. Chemotherapy is an important element of treatment for patients with CLM, and chemotherapy can be combined safely with surgery to improve outcomes further.
Methods Tailored approaches to patients include major (anatomic) resection, minor (wedge) resection, liver volumetry, and preoperative enhancement of the volume and function of the planned future remnant liver using portal vein embolization.
Results Assessment of response to chemotherapy, analysis of liver remnant volume changes following portal vein embolization, and consideration of the surgical recovery following multistage surgical resection of bilateral CLM enable remarkable survival even among properly selected patients with extensive disease.
Conclusions Until laboratory, pathologic, biologic, or genetic studies can define which patients will benefit most from surgical and other treatments, careful application of proven diagnostic and therapeutic approaches to patients with advanced disease will continue to allow surgeons to direct tailored, patient-centered treatment as part of a multidisciplinary team.

Keywords Colorectal liver metastases · Liver resection · Hepatectomy · Portal vein embolization · Liver volumetry

Introduction

The gold-standard treatment for colorectal liver metastases (CLM) is resection, which leads to 58% 5-year overall survival in this minority of patients with stage IV colorectal cancer who are candidates for complete removal of all of their disease. This increase in overall survival (compared to the historical rate of about 36% 5-year overall survival) has occurred despite significant expansion of criteria for resectability, including patients with more, larger, and bilateral CLM. Framing the discussion of resection for CLM is the consensus definition of resectable disease, which focuses on complete resection of tumor-bearing liver sparing an adequate liver remnant volume,[1] with focus on the liver that will remain rather than the characteristics of the resected tumors to define which patients are considered for surgery. Actually tailoring treatment to the patient includes consideration of the patient's overall health, the condition of the underlying liver, and to the disease extent and "biology" of the patient's oncologic disease. This brief overview touches briefly on the practical approach to tailored resection of CLM.

E. K. Abdalla (✉)
Department of Surgical Oncology—Unit 444,
The University of Texas M. D. Anderson Cancer Center,
1400 Holcombe Boulevard, Suite 12.2016,
Houston, TX 77030, USA
e-mail: eabdalla@mdanderson.org

Chemotherapy

There is uniform agreement that chemotherapy, which converts patients with unresectable disease to resectable,

is of value, and that subsequently resected patients benefit from resection.[2] Although not all agree that chemotherapy should be given to patients before resection of *resectable* CLM, significant data support the utility of chemotherapy in this setting. Firstly, progression of extensive disease (four or more CLM) predicts poor outcome from liver resection even if resection remains feasible.[2] Furthermore, comparison of patients who underwent similar workup and imaging revealed a significantly reduced likelihood of nontherapeutic laparotomy because of unsuspected disease among those treated with chemotherapy prior to laparotomy vs. those who went directly to surgery.[3] Importantly, the EORTC Phase III prospective, randomized trial of perioperative FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) demonstrated that the nontherapeutic laparotomy rate was only 5% in the group that received chemotherapy vs. 11% nontherapeutic laparotomy in the no chemotherapy group, proving this hypothesis.[4] Furthermore, the population studied in the prospective trial included patients with very limited disease—more than half had solitary CLM, two thirds had metachronous disease, and the tumors were small. Thus, it is important to understand that the population which benefits from preoperative chemotherapy (in terms of selection for resection), includes patients with limited disease.

Treatment of Patients with Extensive or Bilateral Disease

Discussion of patients with bilateral disease permits discussion of several key elements of liver surgery for CLM. Such patients generally require major resection of disease on one side of the liver, with minor (wedge) resection(s) on the contralateral side. Furthermore, those with extensive disease often require an approach to increase the volume and function of a small liver remnant. Thus, issues of wedge vs. anatomic resection, minimal margin resection, and liver enhancement (portal vein embolization) are addressed as these patients are considered.

Anatomic vs. Nonanatomic Resection and Resection Margins

Careful study of nonanatomic vs. anatomic resection for CLM shows that as long as the margin of resection is free of disease, the two different surgical approaches are oncologically equivalent.[5] No differences in overall survival, recurrence-free survival, recurrence at the cut edge of liver (marginal recurrence), intra- or extrahepatic recurrence can be shown. Similarly, when large cohorts are studied, it is clear that the width of the negative margin for CLM has no impact on overall survival, disease-free survival, recurrence at the cut edge of the liver, or overall recurrence patterns.[6] Patients with a positive margin (tumor within 1 mm of the cut edge of the specimen after resection) have an increased risk of local recurrence and decreased overall survival compared to those with a negative margin (>1 mm); however, those with a margin ≥10 mm do no better than those with a 1–4-mm margin. Thus, a negative margin is a negative margin, and wedge resection and anatomic resection are oncologically equivalent.

Portal Vein Embolization

The definition of resectable CLM focuses on complete resection leaving an adequate liver remnant. Consensus has been reached, based on objective data, as to the adequate remnant, specifically >20% in patients with normal liver, >30% in patients with liver damage, e.g., from very extensive chemotherapy, and >40% in patients with well-compensated cirrhosis[1] (Fig. 1). Prior to extensive resection (e.g., extended right hepatectomy), systematic liver volumetry is used to assess the volume of the liver remnant before resection, as this volume predicts postresection liver function. If that volume is inadequate, preoperative portal vein embolization (PVE) should be considered. PVE is generally performed percutaneously by the interventional radiologist who accesses the portal branches under ultrasonographic guidance, and then occludes the portal branches within the liver to be resected. As a result, portal blood flows solely to the future liver remnant (FLR, or liver that will remain after resection), inducing hypertrophy. This liver growth or degree of hypertrophy (DH) of the FLR in response to PVE has been shown to increase both the volume and function of the remnant, and to decrease the risk for major complications, hepatic insufficiency, and death from liver failure postresection.[7] Of importance is the volumetric response to PVE. In patients with normal liver who undergo resection leaving an FLR≤ 20% or with a DH≤5%, complications, liver insufficiency, and death are significantly more common than in patients with FLR>20% and DH>5%[7] (Table 1). Among patients with cirrhosis, the needed DH appears to be greater; in a small series, all patients with a DH≤10% died postresection vs. no deaths in those with DH>10%.[8] Thus, PVE directly increases the volume and function of the liver remnant, and analysis of volumetric data post-PVE allows preoperative estimation of postoperative risk for complications and death.

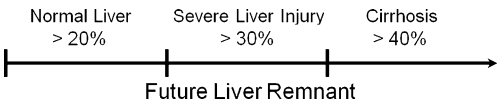

Fig. 1 Minimum FLR volume needed for safe hepatic resection in patients with normal liver, intermediate liver disease, or cirrhotic liver. Adapted from Zorzi D et al., Br J Surg 2007; 94: 274–286, with permission

Table 1 Short-term clinical outcome by standardized future liver remnant, degree of hypertrophy, and combined criteria following portal vein embolization and extended hepatectomy

Normal liver	FLR≤20% or DH≤5%	FLR>20% and DH>5%	*P*
Major complication (%)	47	14	0.01
Hepatic insufficiency (%)	20	1.9	0.03
Death within 90 days (%)	13	0	0.049

No deaths occurred when FLR volume target volume >20% was reached and DH after portal vein embolization was >5%. Modified from Ribero D et al., British Journal of Surgery 2007; 94: 1386–1394, with permission

Potential concerns regarding PVE in patients with CLM generally surround fear that embolization might induce growth not only of liver but also of tumors. Other concerns include the fear that chemotherapy, especially chemotherapy with agents such as bevacizumab, which block the action of vascular endothelial growth factor, might also impair liver regeneration after PVE. Both of these problems can be avoided. Firstly, if all tumor-bearing liver is embolized (e.g., in the case of the need for extended right hepatectomy, embolization of the right liver and segment IV), the median (and mean) change in tumor size pre-PVE vs. post-PVE is 0.0 cm.[7] Furthermore, it has been shown that there is no difference in DH post-PVE in patients with no chemotherapy vs. chemotherapy alone vs. chemotherapy with bevacizumab[9] (Fig. 2). Thus, attention to the details of embolization allows surgery, chemotherapy, and embolization to be combined effectively.

Surgery, Chemotherapy, and PVE

Combining all these data, a measured approach to patients with extensive disease, such as multiple, bilateral CLM can be devised. Such patients have advanced disease of uncertain biology, are likely to benefit from systemic chemotherapy, require extensive resection, and generally undergo a combination of wedge and anatomic resections as follows.[10] Following initial staging, chemotherapy is the first treatment step. Only patients with a decrease in tumor size and who do not develop new lesions on treatment at repeat staging are considered for the next therapeutic step, first-stage liver resection. First-stage resection includes laparotomy and wedge or minor resection clearing the FLR of metastatic disease. Typically, this includes wedge resections in the lateral liver, in preparation for future extended right hepatectomy, but may rather include wedges in posterior liver in preparation for extended left hepatectomy, or many combinations focused on developing a disease-free remnant. Recovery from the first-stage resection is an important assessment of the patient before moving to future steps. Patients with a now disease-free FLR are considered for PVE based on volumetry and consideration of the degree of underlying liver disease determined at first-stage surgery. Restaging typically occurs, further allowing tailored treatment (some will require chemotherapy because of progression of in situ disease between stages, and others will not). Those who undergo PVE are again restaged, and DH is assessed. If FLR volume, DH, staging, and recovery from first-stage surgery are acceptable, then second-stage major resection is performed to clear remaining disease. Patients with intact primary tumors generally undergo resection of the primary at the first stage, but emerging data suggest that the primary, which responds to chemotherapy, is rarely a problem and can be addressed after surgical treatment of the liver metastases with excellent oncologic outcomes.[11,12] Between two thirds and three quarters of patients who undergo first-stage resection will proceed to complete all stages of treatment, leading to a remarkable 86% 3-year overall survival in this cohort with extensive disease (median seven tumors per patient).[10] Thus, selection using chemotherapy, surgery, and when indicated, PVE, allows even patients with extensive disease to be selected for therapy enabling remarkable long-term survival.

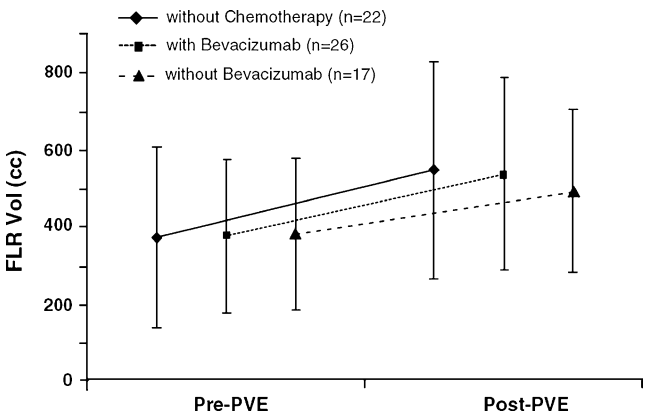

Fig. 2 Changes in absolute future liver remnant volume after portal vein embolization are not impacted by the use of chemotherapy with or without bevacizumab. *FLR Vol* future liver remnant volume, *PVE* portal vein embolization. Values are mean ± standard deviation. From Zorzi D et al., Ann Surg Oncol, 2008; Oct;15(10):2765–72

Conclusion

The limits of resection continue to expand, yet outcomes continue to improve. Chemotherapy is an important element, which improves survival in stage IV colorectal cancer, and can be combined with surgery to improve outcomes even further. Tailored approaches to patients include major (anatomic) resection, minor (wedge) resection, liver volumetry, and PVE with assessment of volume change after PVE (DH>5% in normal liver and DH>10%

in cirrhotic liver predict good outcome). Step-by-step approaches combining these elements allow even patients with extensive and bilateral disease to be properly selected for surgical therapy with excellent short- and long-term outcomes. Until laboratory, pathologic, biologic, or genetic studies can tell us which patients will benefit most from surgical and other treatments, careful application of proven diagnostic and therapeutic approaches to patients with advanced disease will continue to allow surgeons to deliver tailored, patient-centered treatment in a multidisciplinary way.

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