Regional Hepatic Therapies for Colorectal Hepatic Metastases

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ABSTRACT

The modern era of hepatic resection began with the first published report on "formal" right hemi-hepatectomy by Jean Louis Lortat–Jacob in France in 1952.[1] Advanced imaging has enabled improved patient selection for potentially curative resection.[2] Dramatic clinical and technical innovations over the last several decades have resulted in >50% five-year survival for patients undergoing resection; however, only about 25% patients with colorectal hepatic metastases (CRHM) will be candidates for operation.[3] Given this modest rate of resectability, most patients will require a combination of systemic and local non-surgical therapies

In this patient population, besides systemic chemotherapy, treatment modalities collectively termed "regional hepatic therapies (RHT)" may be employed. RHT include trans-arterial chemotherapy, hepatic artery infusion (HAI) pumps, trans-arterial radio-embolization (TARE) with Yttrium-90 (Y-90) and thermal tumor ablation using radiofrequency ablation (RFA) or microwave ablation (MWA). [4]

In this review, we introduce RHT and discuss their utility in the modern day.

KEYWORDS: systemic chemotherapy; hepatic resection; hepatic artery infusion; trans-arterial embolization; thermal tumor ablation

INTRODUCTION

Surgical resection is the gold standard for the potential curative treatment of CRHM, but optimal patient selection continues to evolve. While there are few generally accepted guidelines, the consensus is that absolute contraindications to resection include: extensive extrahepatic disease, involvement of more than 70% or six segments of liver, tumor involvement of major hepatic artery, major bile ducts or main portal veins or co-morbidities preventing surgery.[4] Barring these contraindications, operative resection in the management of colorectal hepatic metastases should be routinely considered and evaluation by experienced hepatic surgeons is the standard of care.

For patients with resectable CRHM, there must be the potential to achieve complete resection with negative margins without evidence of extrahepatic disease, which is essential for survival.[5] Patients with borderline resectable disease may not be initially deemed operable due to inadequate liver reserve, high risk of positive margin, or prior metastatic disease that is no longer visible. These patients along with patients with advanced surgically untreatable liver dominant disease will benefit from systemic therapy and non-operative regional treatment adjuncts.[6-7] In some patients these non-surgical therapies may also improve resectability.

There is a wealth of historical data suggesting the utility and effectiveness of hepatic resection in colorectal liver metastases. Collectively, over time, multiple studies reviewing surgical resection outcome for CRHM have demonstrated overall survival with reproducible five-year survival metrics above 50%.[8-12]

SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy is an important treatment modality that can be used as adjuvant to resection, in a neoadjuvant manner for potentially resectable, and as primary therapy for unresectable CRHM.

Prior the FOLFOX era (2008), the chemotherapy agent most often employed was 5-Flourouracil (5-FU). In the preceding 20 years to FOLFOX, the extent of progress had been the advancement from 5-FU + Levamisole to 5 FU + Leucovorin. Rapidly after the introduction of FOLFOX the advent of specific anti-angiogenic therapies led to the now explosive era of targeted/immunotherapies.[13-16] These modern chemotherapy ± immunotherapy regimens have demonstrated remarkably improved outcomes for resectable and non-resectable CRHM, and median survival with 5-FU based regimens has dramatically improved with time.[17-18]

Conceptually, patients that can undergo curative resection and patients that are only candidates for systemic chemotherapy, represent the treatment extremes of this population. Most patients will be in-between, and it is for these patients RHT have the potential utility.

REGIONAL HEPATIC THERAPIES

Regional hepatic therapies (RHT) can be broadly organized into nonarterial, arterial, and ablative modalities.

Non-arterial modalities include radiosurgery and intense modulated radiation therapy (IMRT) or image-guided radiation therapy (IGRT). Arterial regional hepatic therapies include non-embolic treatment such as the hepatic artery infusion pumps (HAI) or embolic treatment such as Y-90 trans-arterial radioembolization (TARE). Thermal ablative modalities include hot-thermal modalities such as RFA and MWA or cold-thermal modality such as cryoablation (not discussed, due to limited modern use).

Fundamental to arterial-based approaches was the description in the 1970s that tumors in the liver >3mm derive their blood supply from the hepatic artery and not the portal vein.[19] Thus, increased delivery and concentration of chemotherapy is achieved by arterial infusion compared to systemic venous infusion and this is the principle for hepatic artery infusion pumps.

Next, trans-arterial radioembolization with yttrium 90 utilizes the arterial route to deliver targeted brachytherapy and internal tumor embolization.[20] CRHM are vascularized in peripheral neo-angiogenic arcades with central necrosis, thus traditional embolization ± chemotherapy is of limited use. Additionally, the known susceptibility of hepatic parenchyma to radiation requires a focused and defined delivery of radiation to tumor while sparing normal parenchyma.

Last, hot-thermal ablation relies on heat induction by electromagnetic resonance to achieve protein denaturation progressing to tumor coagulative necrosis.[21] Radiofrequency ablation (RFA) and Microwave ablation (MWA) are generally grouped together; however, the mechanism for the heat generation is distinct and RFA is more susceptible to incomplete tumor destruction due to energy loss to nearby structures causing a "heat-sink". MWA ablation is the newer modality and likely due to the efficiency in heat delivery has become the more commonly used modality.[22]

Hepatic Artery Infusion (HAI)

HAI pumps are subdermally implanted specialized infusion pumps that deliver chemotherapy through a surgically placed catheter passing retrograde from the gastroduodenal artery to the proper hepatic arterial circulation. In this way, HAI takes advantage of both liver metabolism and tumor blood supply.[23] The liver metabolizes certain drugs in a "first pass" effect, i.e. 5-FU to floxuridine.[24] This leads to high intrahepatic concentrations with minimal systemic toxicity, which makes drugs with short half-lives such as Floxuridine (FUDR) useful. 5-FU specifically demonstrated up to 99% extraction by the liver during first-pass metabolism.[25]

HAI has various roles; it can be used for initially unresectable colorectal hepatic metastases to potentially convert to resectability, as adjuvant liver-directed therapy post liver resection or as liver directed therapy in combination with systemic therapy for unresectable otherwise untreatable disease.

In a prospective phase II study, 33 of 64 (52%) patients were reported to have conversion to resection after receiving hepatic artery infusion FUDR with modern systemic chemotherapy.[26] Conversion to resection was associated with long-term survival, with a five-year OS for resected disease at 63.3% compared with 12.5% for patients who did not undergo resection.[26] Overall, studies support the use of HAI to increase the number of patients who are eligible for resection, which is associated with longer survival.

HAI can also be used as an adjuvant therapy after liver resection. A retrospective study of 125 patients treated between 2000 and 2005 with adjuvant HAI with FUDR and concurrent systemic chemotherapy including 5-FU plus oxaliplatin or irinotecan found that patients who received HAI with FUDR with systemic chemotherapy demonstrated improved OS and hepatic PFS compared with those who received systemic therapy alone.[27] The strongest evidence for adjuvant HAI is from the Memorial Sloan Kettering Cancer Center (MSKCC) group who reported results from 2,368 patients with consecutive colorectal hepatic metastases resections who received modern systemic chemotherapy, 785 of which also had adjuvant HAI with FUDR. Despite a higher disease burden, patients who received combined therapy had a longer median OS of 67 months compared with 44 months for those who were treated with adjuvant systemic chemotherapy alone ($p < 0.01$).[28] This survival benefit persisted as the ten-year OS was 38.0% in the HAI/systemic therapy group compared with 23.8% in the systemic therapy–alone group.

In 2006, a multi-institutional study of HAI was reported by the Cancer and Leukemia Group B for patients with unresectable otherwise untreatable colorectal hepatic metastases. A total of 135 patients with hepatic metastases were randomly assigned to receive HAI FUDR/leucovorin/dexamethasone compared with 5-FU/leucovorin. OS was favored with HAI with FUDR at 24.4 months versus 20.0 months for systemic therapy ($p = .0034$).[29]

It is worth noting that there is strong literature going back to the early 1990s for the survival benefit of HAI.[30] However, in the era of 5-FU there remain few specialized centers with dedicated HAI programs. There has been renewed interest in this modality in the last few years as modern systemic agents have been proven effective. As more centers adopt HAI programs the use of this treatment option will become increasingly common. Established centers continue to demonstrate viability of this approach with robust clinical studies, but an individualized approach will be necessary as not all centers may have HAI programs at their disposal. When available, HAI should be considered for patients with CRHM.

Transarterial Radioembolization (TARE)

TARE is a catheter-based intra-arterial technique that focally delivers a high radiation dose using β-radiator Yittrium-90 (Y-90) into hepatic tumors; this results in tumor necrosis and fibrosis. TARE should be considered for patients with

colorectal hepatic metastases with liver-limited disease that have failed to respond to systemic chemotherapeutic options or are not candidates for resection. The Y-90 TARE concept dates to the 1970s when Y-90 TARE was initially used to salvage patients with CRHM being treated with HAIP that had progressed though HAIP therapy. Since then, TARE was shown to be beneficial in conjunction with systemic chemotherapy in the pre-FOLFOX era. In a phase III randomized controlled clinical trial of 44 patients with chemorefractory disease who were treated with 5-FU or TARE/5-FU, patients who received the combined TARE/5-FU demonstrated longer time to tumor progression (median, 4.5 months vs. 2.1 months; p = .03) and longer time to liver progression (median, 5.5 months vs. 2.1 months; p = .003).[20]

In the modern era of FOLFOX, the use of TARE for patients with treatment-naïve colorectal hepatic metastases has been evaluated in three large randomized controlled trials. In the SIRFLOX trial, van Hazel et al, randomly assigned 530 patients with treatment-naïve disease to FOLFOX versus TARE/FOLFOX with or without bevacizumab.[31] Although TARE/FOLFOX did not improve PFS (median, 10.7 months vs. 10.2 months; p = .43), median liver PFS was longer in the TARE trial arm (20.5 months vs. 12.6 months; p = .002). The combined results of the three phase III trials, SIRFLOX, FOXFIRE, and FOXFIRE Global, which evaluated the effectiveness of TARE/FOLFOX as first-line treatment for 1,103 patients with treatment-naïve colorectal liver metastases, did not note prolonged OS compared with FOLFOX alone (median OS, 22.6 months vs. 23.3 months; p = .61).[32] However, subgroup analyses suggested that selected patients might benefit from TARE. These analyses highlight the necessity for optimized patient selection to maximize the clinical effectiveness of TARE and to provide individualized treatment schemes.

Thermal Ablation

Thermal tumor ablation techniques (RFA/MWA) induce tumor cell death through frictional heating resulting in protein denaturation and coagulation necrosis. Ablation can be considered for patients with CRHM that are deemed unresectable or as a combined approach with resection. It is preferred for patients with less than three lesions, each with a diameter less than 3 cm.[33] While it may be offered independently, it can also be utilized alongside surgical resection in patients with small or low volume metastatic burden isolated to the liver. Ablation may be done in the open, laparoscopic or image-guided percutaneous setting. Percutaneous ablation with image guidance is most frequently performed for patients with recurrence after hepatectomy. In all cases where thermal ablation is planned, all metastatic disease sites must be feasible and accessible for ablation with encompassed treatment margins. The choice of laparoscopic versus percutaneous image guided thermal ablation depends on practical factors related to tumor size and location for accessibility.

Several studies have been published over the last two decades demonstrating the effectiveness and safety of thermal ablation for CRHM. One phase II trial randomly assigned 119 patients with CRHM to systemic therapy versus radiofrequency ablation plus systemic therapy with or without surgical resection. Longer OS was reported for the combination treatment (HR, 0.58; 95% CI, 0.38–0.88; p = .01).[34] Associated five-year OS rates were 43.1% versus 30.3%, with a median OS of 45.6 months versus 40.5 months. Wang et al, described excellent outcomes in 115 patients with CRHM who underwent percutaneous ultrasound-guided microwave ablation; three-year OS was 78.7% and the three-year recurrence rate was 59.3%.[35]

Both RFA and MWA show comparable technical success rates, outcomes, and safety in patients with CRHM.[36] However, MWA demonstrates a technical advantage over RFA because of a reduced heat-sink effect.[37]

SUMMARY

Surgical hepatic resection with clear margins has been and remains the gold standard for the potentially curative treatment of CRHM. However, modest rates of surgical resectability require a multidisciplinary team approach employing systemic chemotherapy and the various regional hepatic therapies.

There is a consistent theme to this disease; there is no one independent "magic bullet". While resection is the gold standard for potential cure there is still the need for adjuvant systemic chemotherapy ± immunotherapy. The recurring theme is that a combination of modalities is required to achieve the best possible outcome. Considering the well-documented historical experiences with combined modalities, the evidence is clear that treatment must be individualized and that patients need to have a care team that is aware and knowledgeable in the various options that are available.

A care team must have expertise in the total assessment of the patient to inclusively and collaboratively recommend treatment. Modern treatment strategy necessitates a patient-centered approach to fully optimize clinical options and outcomes.

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Disclosures

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