



Current Trends in the Surgical Management of Colorectal Cancer Liver Metastases

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Abstract

Purpose of Review Cancers of colorectal origin are the second leading cause of cancer-related deaths in the USA, and with the improvements in chemotherapy and other therapeutic modalities, there are more options for the management of metastatic disease. The liver is the most common site of colorectal metastasis, and treating the disease to the liver may lead to prolonged survival and possible cure. Our understanding of tumor biology and the refinement of surgical techniques have resulted in significantly improved outcomes. The treatment of colorectal liver metastasis is complex and thus requires a multidisciplinary approach.

Recent Findings There is increasing body of literature that points towards more aggressively selective and personalized surgical treatment of colorectal cancer liver metastases. New techniques like hepatic artery infusion, liver chemoperfusion, operative and transcatheter liver ablation with microwave, radiofrequency or irreversible electroporation have resulted in significantly improved outcomes.

Summary There is significant progress in the surgical management of liver metastasis of colorectal origin, with improved outcomes in patients that otherwise would be candidates only for palliative chemotherapy. More and exciting research is underway in order to appreciate the impact of newer techniques.

Keywords Colorectal metastases · Hepatectomy · Ablation

Introduction

Liver metastases pose a therapeutic challenge in the treatment of colorectal cancer (CRC), which is the third most common cancer and second leading cause of cancer-related deaths in the USA, with an estimated 140,000 new cases and 51,000 deaths in 2018 [1]. About 21% of patients with CRC will present with distant metastases, and despite the favorable outcomes for localized and regional disease (89.8% and 71.1% 5-year survival respectively), the 5-year survival for metastatic disease is about 14% [2]. However, 50% of the patients with metastatic disease have liver only disease that may be amenable to therapeutic intervention. Historically, chemotherapy

had been the mainstay of treatment of colorectal liver metastases, but in the past few years, it has been shown that resection or application of any other therapeutic modality (hepatic artery infusion pump, liver chemoperfusion, tumor ablation with radiofrequency/microwaves/cryoablation, tumor embolization, chemoembolization, radioembolization, and stereotactic body radiotherapy (SBRT)) confers significant survival advantage. Liver resection has shown the best results, with 34–49% 5-year and 17–34% 10-year survival [3, 4, 5]. In this review, we will elaborate on recent advances in the field of treatment of CRC liver metastasis.

Surgical Treatment Options: √

Modern chemotherapy has resulted in improved response rates, thus allowing patients who were otherwise unresectable an option for liver-directed therapy. These liver-directed therapies include surgical options (metastasectomies, hepatic artery infusion pump, liver chemoperfusion, and ablative techniques, such as radiofrequency ablation, microwave ablation,

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irreversible electroporation, and cryoablation), and non-surgical options (chemoembolization, radioembolization, and radiotherapy with stereotactic body radiotherapy (SBRT)). It is obvious that a single technique or a combination of techniques may be used for the optimal result, thus the need for a multidisciplinary team approach.

Resection

Since the 1980s, it was understood that resection of liver metastases from colorectal cancer was able to improve patients outcomes. Initial studies reported that patients, who had their liver metastases resected, were able to achieve 5-year survival of up to 38% [6, 7]. Unfortunately, at that time, liver resection was neither widespread nor popular, because of the associated high morbidity and a mortality that was up to 13% in the 70s and 5% in the 80s. The improvement of anesthetic drugs (Propofol was approved for use in 1989) along with advancement in imaging for preoperative planning, including the evolution of CT liver volumetrics for the calculation of the future liver remnant volume (the algorithm was first described in 1986 [8]), has made liver surgery safer. Furthermore, development of enhanced surgical techniques and the need for negative margin resections [9], parenchyma-sparing resections, low central venous pressure surgery [10], advanced parenchyma transection techniques [11], two-stage hepatic resections, liver partition, and portal vein ligation for staged hepatectomy (ALPPS) [12, 13]), have improved surgical outcomes.

The addition of neoadjuvant (conversion) chemotherapy, in the sense of converting unresectable cases to resectable [14], has expanded the pool of potential surgical candidates and helped achieve R0 resection rates up to 60% [15]. For purposes of downstaging, apart from conversion systemic chemotherapy, liver-directed chemotherapy with hepatic arterial infusional chemotherapy has shown promising results, albeit it is not widely available [16]. With all these advances in cancer care, it is not surprising that the median overall survival for patients with colorectal liver metastasis has more than doubled from 14.2 months, in patient diagnosed between 1990 and 1997, to 29.3 months in patients that were diagnosed between 2004 and 2006 [17].

Preoperative Considerations

Patient selection is paramount for any surgical procedure, and in order to be able to achieve optimal results safely, tumor resectability and patient fitness have to be established. Because of improved perioperative services and minimally invasive procedures, treatment for metastatic colorectal cancer, including liver resection, can be safely offered in older patients although careful preoperative planning with a multidisciplinary approach is strongly recommended [18].

Due to the early poor results, patients with more than 4 liver metastases were not advised to undergo resection [19, 20], but newer data have demonstrated that the number of liver lesions does not preclude resectability, since median survival may reach up to 50 months in patients with 4 or fewer liver lesions, but can be up to 32 months for patient with multiple metastases [21], with 5-year survival range between 23 and 51% [22–25].

The question of resectability becomes less of a technical and more of a biological issue in the presence of extrahepatic disease. Similarly to disease confined to the liver, resection of liver metastasis in the presence of extrahepatic disease had initially shown poor results, to the extent it was contraindicated [26–28]. However, with improved understanding of the biology of the disease, and careful preoperative planning, such that all the disease can be excised, some patients may be candidates for therapeutic resection. Patients with two specific areas of extrahepatic colorectal metastases: peritoneal cavity and lungs are also potential surgical candidates. Attempts of resection of both hepatic and extrahepatic disease, regardless of the area of extrahepatic disease involvement (peritoneum, lung, local recurrence, distal and hepatic lymph nodes, ovaries, striatus muscle, adrenal, small bowel, surgical wound, pancreas), have shown promising results as a proof of principle for solitary or very low-volume lesions, with 5-year survival 28% for extrahepatic disease vs 34% liver only disease [29]. With the advent of peritoneal cytoreduction and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for the treatment of peritoneal carcinomatosis, more studies are currently conducted to answer the question about the concurrent resection of liver and intraperitoneal colorectal metastases, but the ongoing results from case series and retrospective studies so far are encouraging, showing that, in principle, resectable low-volume hepatic disease in patients with peritoneal carcinomatosis from colorectal primary lesions should not be considered an absolute contraindication for CRS/HIPEC procedures. Although the survival benefit for patients with both liver involvement and peritoneal carcinomatosis is less prominent than the benefit for patients with liver disease alone, the median overall survival for these patients with resectable disease both in the liver and peritoneum can extend from 21.1 to 32.5 months, making such efforts meaningful [30–33]. Apparently, more prospective randomized studies will be required on this topic, but the results so far have been promising.

Similar results are observed in carefully selected patients with concomitant liver and lung colorectal metastases: With resection of disease at both liver and lung, with either order of resection (lung first, or liver first), the overall disease-specific survival can be up to 31% in 5 years and 19% in 10 years [34]. However, resection of liver lesions in the presence of subcentimeter lung lesions does not seem to impact the 3-year disease-specific survival (70% in the presence of subcentimeter lung

nodule vs. 83% in the absence of suncentimeter lung nodule; $p = 0.46$) [35].

In terms of predicting long-term survival, several models have been proposed [36, 37], taking into account parameters like age, size of largest metastasis, CEA level; nodal status and stage of the primary tumor; disease-free interval; number of liver nodules; and resection margin, of primary, but their validation has been controversial [38]. Lately, there is an increasing body of literature that focuses on the biological features of the colorectal metastasis to the liver: it seems that patients with Kras and Braf mutations have a strong association with worse prognosis, which provides a good indicator in the selection of patients for resection of metastatic disease [39, 40].

Technical Considerations

Open resection is the current golden standard for colorectal liver metastasectomy, which can be achieved either through a midline or a right subcostal/hockey stick incision. Modern imaging modalities are very good in identifying extrahepatic disease, although it is not uncommon that some small extrahepatic disease may evade the detection threshold of preoperative imaging, although it has been shown that a diagnostic laparoscopy prior to the planned hepatectomy has a yield of 5% and the sensitivity 75% [41].

In terms of the presence of primary disease along with the liver metastasis of colorectal origin (synchronous liver metastasis), there are three operative options: either staged procedures, with hepatectomy first and primary tumor second, or the opposite, with primary tumor first and hepatectomy second, and lastly, as a single-stage operation. Although a staged operation can be favored in many cases (rectal cancer—to allow for neoadjuvant chemoradiation for the rectal primary [42], small future liver remnant—to allow for time for the future liver remnant to grow [12], downstaging neoadjuvant chemotherapy to allow for a smaller liver resection [14]), a single-stage operation seems to be gaining favor among both patients and surgeons [43]. In terms of short-term outcomes, there are no significant differences among the three operative approaches [44], so the treatment may be tailored to each patient individually for the best desired outcome [45].

The advent of minimally invasive techniques in surgery has also influenced liver surgery. Since the Louisville Statement in 2008, which involves guidelines for laparoscopic liver surgery drafted by an expert panel [46], laparoscopic liver resections have been increasingly performed. Although there is a lack of randomized clinical trials, evidence from case series, or case-control studies show that laparoscopic surgery in resecting synchronous colorectal liver metastasis has not proven to be inferior to the open approach, having comparable postoperative time, morbidity, and long-term oncologic outcomes (overall and disease-free survival) [47–49].

Using the robotic platform and the newest technology, more and more surgeons are performing complex hepatobiliary operations, including major hepatectomies. The robotic technique combines the benefits of laparoscopic minimally invasive surgery (less intraoperative blood loss, decreased postoperative pain, smaller wounds with similar long-term outcomes) with the greater visualization, using high-definition 3D, binocular vision with high magnification, enhanced dexterity, and greater precision that the robotic arms allow, having almost 360° degrees of movement [50]. Many centers are reporting feasibility of performing even the most complex liver resections robotically, with improvement in short-term outcomes compared with laparoscopic or open technique [51, 52, 53, 54]. Since the robotic approach is still developing, being relatively new, there are no data regarding long-term outcomes, and more studies are required to validate it in comparison with laparoscopic and open approaches.

Hepatic Artery Infusion

The application of conversion chemotherapy has widened the patient selection criteria for resection of hepatic colorectal metastases. Hepatic artery infusion is a novel and effective way to deliver high-dose chemotherapy directly to the liver, while avoiding the burden of systemic chemotherapy side effects. Implantable arterial infusion pump systems were described in the early 1970s [55] and were first used for cancer treatment in 1980 [56]. Since then, several prospective randomized trials showed a higher response rate in the patients with liver metastases of colorectal cancer that received hepatic artery infusion therapy, compared with systemic chemotherapy [57, 58]. The response rate was so significant (73%) that many patients (47%) with extensive liver disease were able to have liver resection, with 3-year survival of 80% compared with 26% for those who could not undergo resection [59]. Importantly, in a single center's experience, with 2368 consecutive patients who underwent complete resection of colorectal liver metastases, the patients who had received hepatic artery infusion therapy versus the ones who had not, had median overall survival 67 months versus 44 months, respectively, and overall survival 38% versus 23.8% in 10 years, respectively [60]. These data were confirmed with another center that reported median overall survival for patients with unresectable colorectal liver metastases, 32.8 months in patients who received hepatic artery chemotherapy with systemic chemotherapy compared with 15.3 months with systemic chemotherapy alone [61]. Additionally, the hepatic artery infusion chemotherapy for unresectable colorectal liver metastases showed better overall survival compared with selective internal radiation therapy with Yttrium-90 radioembolization, with overall survival 31.2 months versus 16.3 months, respectively [62].

Based on these impressive results, it is only natural to combine the short-term beneficial outcomes of the minimally invasive liver surgery with the long-term outcomes of the hepatic artery infusion pumps. Many investigators reported initially laparoscopic [63–65] and subsequently robotic [66–68] intrahepatic arterial pump placements, that are feasible and safe, with conversion to open rate 17% for the robotic, versus 67% for the laparoscopic cases.

Liver Chemoperfusion

Isolated hepatic perfusion for unresectable liver metastases has emerged as a second-line surgical option for patients who have failed other treatment modalities. It involves the intraoperative isolation and control of the liver inflow (hepatic artery via the gastroduodenal artery) and outflow (hepatic veins via the suprahepatic and infrahepatic vena cava), and the establishment of a venovenous bypass (typically femoral-jugular) via a pump. Subsequently, heated chemotherapy is infused through the liver and gets collected through the already controlled hepatic vena cava, whereas the blood return from the lower body is secured through the femoral-jugular bypass. The largest series of 120 patients with unresectable colorectal liver metastases, using melphalan, tumor necrosis factor (TNF) or both as the perfusate, had an objective response rate of 61%, with median overall survival 17.4 months [69]. In a phase I trial of 12 patients with unresectable colorectal liver metastases, using fixed-dose oxaliplatin with escalating 5-FU doses, and a median follow-up of 24 months, the median overall survival was not reached for that time [70]. Efforts have been made to minimize the invasiveness of the technique, using a percutaneous system [71], but more clinical trials are warranted to validate this modality.

Ablative Techniques

Initial data regarding resection versus any other tumor destructive technique for the treatment of hepatic colorectal metastases has been in favor of resection, as far as it concerns durable long-term outcomes: In a series of 418 patients, the ones who had undergone resection had 65% 4-year overall survival, versus 36% of the ones that received radiofrequency ablation combined with resection and 22% of the ones with radiofrequency ablation only. At 5 years, only patients that had undergone resection survived at 58% [72]. Similarly, a more recent study demonstrated that resection of colorectal liver metastases was superior than resection plus radiofrequency ablation, with median and 5-year overall survival 75.3 months and 58.7% for resection versus 41.8 months and 37.2% for resection plus radiofrequency ablation [73]. However, when the patients were stratified according to risk factors

that were independently associated with decreased overall survival (namely, female gender, primary tumor nodal metastases, right-sided primary tumor, KRAS mutation, CEA ≥ 30 ng/mL, and number of ablative lesion ≥ 3), patients who had low risk (0–1 risk factors) and received resection with radiofrequency ablation had 52.7% 5-year overall survival, comparable with the resection only group, whereas none of the high-risk patients (2–3 risk factors) survive for 5 years. In that case, it is evident that it is the biology, apart from the therapeutic modality, that drives survival in such patients.

More recently though, there is an increased body of literature that claims equal results to resection for colorectal metastases, especially for tumors < 3 cm [74–78]. Additionally, although radiofrequency ablation is the most widely used technique, both operatively and percutaneously, there is increasing interest to microwave ablation, as this technique is less susceptible to the “heat-sink” phenomenon, especially next to large high flowing vessels. Furthermore, there is less charring, causing less heat dissipation, which helps ablate larger areas in less time. Currently, there is only one clinical randomized trial comparing microwave tumor ablation of multiple hepatic metastases from colorectal carcinoma (2–9 tumors) to resection, which showed no statistically significant difference (median survival 27 months in the microwave ablation group versus 25 months to the resection [79]; however, this study included patients that had large tumors (up to 8 cm) and up to 10 lesions. There is an ongoing clinical trial, the Colorectal Liver metastases: Surgery versus thermal ablation (COLLISION), a phase III single-blind prospective randomized controlled trial, for lesion < 3 cm, the results of which may change the field of treatment colorectal liver metastases [80].

Cryoablation has been used in thermal destruction of multiple solid malignancies, including colorectal liver metastases, with comparable with resection reported long-term outcomes, when combined with hepatic resection [81, 82]. When combined with resection, cryoablation has also been used to provide a “handle” to the resection of the frozen tumor, for better maneuverability of the liver parenchyma.

Irreversible electroporation (Nanoknife™) is a non-thermal ablation technique that is causing irreversible damage to the cell membrane with the application of short bursts of electric current, thus causing irreversible permeabilization of the phospholipid cellular membrane, which leads to cell death [83]. The technique is feasible and safe in treating hepatic metastases of colorectal origin [84]; however, no long-term outcomes exist so far. Based on the success of the technique in other solid malignancies [85], it seems that there may be another tool in our armamentarium for successfully treating colorectal metastases to the liver.

Conclusions

In summary, there is significant progress in the surgical management of liver metastasis of colorectal origin. Resection, either simultaneously with the primary tumor, or staged, currently has the best prognosis, and with the improvement in technique and perioperative care, it can be offered to a larger subset of the patient population. However, newer modalities involving regional liver therapy (hepatic artery infusion pump, liver chemoperfusion, tumor ablation with radiofrequency or microwaves), or a combination of any number of modalities available, have improved outcomes in patients that otherwise would be candidates only for palliative chemotherapy. More and exciting research is underway in order to appreciate the impact of newer techniques.

Compliance with Ethical Standards

Conflict of Interest Georgios V. Georgakis and Iliya Goldberg each declare no potential conflicts of interest.

Aaron R. Sasson has received personal fees from Novartis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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