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Review

Surgical

Surgical management of colorectal liver metastases

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Abstract

Introduction

Colorectal cancer is the fourth most common malignancy and the second most common cause of cancer related death in the United States. In patients with colorectal liver metastases who are candidates for resection, surgical resection provides optimal clinical outcomes and the only chance for cure. As such, this article will review current knowledge in the surgical management of colorectal liver metastases.

Discussion

Surgical resection has been shown to be the most effective treatment for colorectal liver metastases. As such, evaluation for resectability is of the utmost importance during initial work-up. Improved chemotherapeutic regimens in addition to recent advances in the surgical techniques, such as staged resections, portal venous embolism, ablation and minimally invasive surgery have expanded the indications for resection while reducing the morbidity and mortality of hepatic resections and improving survival rates. Repeat hepatectomy for resectable recurrence has also been shown to improve survival. In addition, select patients with extrahepatic disease may benefit from an aggressive surgical approach.

Conclusion

A multidisciplinary approach centred around surgical resection is safe and the most effective treatment for colorectal liver metastases. As chemotherapeutic and surgical techniques continue to improve, the definition of resectability continues to expand. Absolute contraindications to resection include inability to leave the patient with a future functional liver remnant (FLR) greater than 20-25% in a normal liver and 40% in a chemotherapy-injured liver, and the inability of the patient to tolerate surgery due to medical comorbidities or poor functional status.

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Introduction

In the United States, colorectal cancer is the fourth most common malignancy with approximately 140,000 new cases diagnosed per year and is the second most common cause of cancer-related deaths with about 50,000 deaths per year[1]. Colorectal metastases occur by hematogenous spread via the portal vein, and consequently the liver is the most common site for blood borne colorectal metastases[2].

Approximately 20% of patients present with synchronous metastases with another 30% ultimately developing metachronous metastases[3,4]. Of these, 40% have metastases isolated to the liver. Unfortunately, only approximately 20-25% of patients with liver metastases are candidates for curative resection[5]. Therapy for colorectal liver metastases continues to evolve. The median survival for untreated stage 4 colorectal cancer is 5-12 months[4,6,7,8].

With systemic chemotherapy, median survival increases to 20-22 months[9]. Surgical resection with negative margins results in median survival of 42-62 months with a 5 year survival of 37-58% and a 10 year survival of 15-25%[10,11,12,13,14,15,16,17].

Given the current evidence, hepatic resection has become standard of care for colorectal liver metastases. As liver surgery has become safer with improvement in techniques as well as experience, indications for resection have expanded. Techniques such as staged resections, portal venous embolism, and ablative technologies have allowed previously unresectable patients to undergo resection. In addition, modern chemotherapy converts approximately 15% of previously unresectable patients to resection. This article will review current knowledge in the surgical management of colorectal liver metastases.

Discussion

Resectability

As with any surgical procedure, selecting which patients will benefit the most from surgery is key to successful outcomes. Multiple clinical risk scores using known prognostic factors have been developed in an attempt to address appropriate patient selection1[5,18]. While these do help to stratify risk, they do not help in the decision of which patients to exclude from resection.

There are many factors to consider when determining resectability. The definition of resectability has evolved over time. Classically, bilobar metastases, inability to obtain margins of at least one centimeter, four or more metastases, and extrahepatic disease were contraindications to resection.

However this data was based on small numbers of patients in the 1980's, from an era with poor imaging and staging modalities, as well as less effective chemotherapy. Numerous studies have subsequently demonstrated that none of these factors by themselves are contraindications to surgery.

With the application of parenchymal sparing liver surgery using non-anatomic wedge resections and anatomic partial hepatectomies, bilobar metastases are no longer a contraindication to surgery. Bilobar resections can be safely performed with resection of up to 75-80% of normal liver.

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Patients treated with chemotherapy often have chemotherapy-associated liver injury (steatosis, irinotecan-associated steatohepatitis, and oxaliplatin-associated sinusoidal obstruction syndrome) may safely undergo resection of approximately 60% of the liver. Patients with Childs a cirrhosis may tolerate 30-40% resection. Resection of more than this amount can result in irreversible liver failure. Due to a lack of education regarding modern surgical therapy, some primary care physicians and medical oncologists continue to believe that bilobar metastases are a contraindication to resection and defer referral to a surgical oncologist.

The inability to achieve surgical margins of at least 1 centimeter was traditionally thought to be a relative or absolute contraindication to resection[19].

There have been numerous studies as well as a meta-analysis to address this issue. A primary determinant of outcome is achieving a negative microscopic resection margin. In a study of 557 patients, 45 patients with positive margins had a 5-year survival of 17% compared to 64% in those with negative margins1[6].

Patients with microscopic margins <1 cm showed no difference in survival compared to those with margins >1cm. Another study demonstrated a markedly improved median survival in patients with microscopically negative margins compared to those with a microscopically positive margin (46 months vs. 24 months)[13].

A meta-analysis demonstrated a statistically significant 5-year survival difference in patients with surgical margins > 1cm compared to < 1cm, 46% vs. 38%, respectively[20]. It is important to note that the 5-yr survival is excellent, and that there may be other biologic or anatomic factors which are unaccounted for in this meta-analysis. Our practice is to obtain 1cm margins when possible, but the data clearly indicates that a microscopically negative margin is adequate for resection of colorectal liver metastases.

Early reports suggested that patients with 4 or more metastases did not derive benefit from surgery. A study comparing 48 patients with ≥4 tumours to 425 patients with 1-3 tumours who underwent R0 resection demonstrated no difference in survival. Additional single institution studies have shown 5 year overall survival ranging from 28-51% after resection of ≥4 tumours[21,22,23]. Currently, the presence of ≥4 liver metastases is not a contraindication to surgery.

The presence of extrahepatic disease has been a well-accepted contraindication to liver resection. Advances in surgical techniques with improvements in morbidity as well as the use of more effective chemotherapy has prompted several centres to operate on patients with liver metastases and concomitant resectable extrahepatic disease.

Commonly resected extrahepatic sites include lung, periportal lymph nodes, and peritoneal metastases. These patients have a lower 5-year survival rate of 28% compared to those without extrahepatic disease (55%) in one study assessing 186 of 840 patients with extrahepatic disease[24].

Because of the poor prognosis in patients with both intra- and extrahepatic disease, these patients should be treated with chemotherapy initially. Those who progress on chemotherapy will not benefit from surgery, whereas those with stable or responsive disease can be considered for surgery by a multidisciplinary oncology team.

The decision regarding resectability requires the clinical judgment of an experienced hepatobiliary surgical oncologist. In the current era, the primary determinant of resectability is the ability to perform an R0 resection while leaving behind a large enough functional liver remnant (FLR) to avoid postoperative liver failure.

Expanding Resectability

Because of the improvements in survival after surgery and the advances in the safety of liver resection, there are novel strategies to expand the pool of resectable patients. These include a combination approach using resection and ablative techniques, portal vein embolization (PVE), 2-stage hepatectomy, and Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS).

PVE utilizes the regenerative capabilities of the liver. This is a strategy employed when the expected FLR would be inadequate in patients who require an extended resection, particularly in those with any degree of liver dysfunction. The technique involves percutaneous embolization of the portal vein ipsilateral to the tumour, leading to hypertrophy of the contralateral lobe which constitutes the postoperative FLR. The FLR typically increases by 10-20%. The patient should undergo cross-sectional imaging 4-6 weeks after PVE to assess hypertrophy. Lack of hypertrophy selects those patients whose liver would not tolerate a major resection. In addition, chemotherapy can be continued while the liver is undergoing hypertrophy[25].

Liver resection remains the standard of care for resectable disease, but the adjunctive use of ablative techniques can expand the eligibility for liver-directed therapy[26]. The most commonly utilized techniques are radiofrequency ablation and microwave ablation, both of which use thermal energy to destroy cancer cells. This is a useful approach when treating bilobar lesions with large lesions in one hemiliver, and small lesions in the contralateral hemiliver.

Lesions measuring 3 cm or less and those which are not abutting major vascular structures demonstrate the lowest local recurrence rates. Large vascular structures act as a heat sink, potentially leading to incomplete ablation of adjacent tumour. With improving technology, larger lesions can be treated with ablation. Lesions near the hepatic hilum should not be

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ablated due to the high risk of biliary injury causing central biliary stricturing.

Two-stage hepatectomy also utilizes the regenerative capabilities of the liver. This is a strategy used in patients with extensive bilateral metastases which cannot be extirpated with either resection or a combination of resection and ablation in one operative setting due to low postoperative FLR. At the first stage, resection and/or ablation is performed of lesions from the least affected lobe or enough lesions to allow the second resection to be potentially curative. The remnant liver is then allowed to regenerate while the remaining tumor is controlled with systemic chemotherapy. PVE or portal vein ligation can be used to further enhance the hypertrophy of the FLR. The second stage clears the remaining disease. Two stage hepatectomies have resulted in 5 year survival up to 42%[27,28].

A new modification of the 2-stage approach is ALPPS[29]. This involves resection and/or ablation of lesions in one hemiliver, portal vein ligation of the contralateral side, and in-situ splitting of the liver parenchyma. Cross-sectional imaging is performed a week later to assess for hypertrophy of the FLR, and the patient is taken for the second stage surgery within 2 weeks of the first stage during the same hospitalization.

Despite R0 liver resection, there is an 80% cancer recurrence rate with approximately 40% of recurrences occurring in the liver. When recurrences are isolated to the liver, re-resection with second, and even a third hepatectomies can be considered as morbidity, mortality as well as 5 year survival rates are similar to primary hepatectomies[30,31,32,33].

Chemotherapy

Chemotherapy for patients with isolated unresectable colorectal liver metastases can convert 10-20% of patients to resectability. Five-year overall survival rates of 30-40% can be achieved after surgery, comparable to resection in patients who are resectable at presentation[21, 34,35,36]. As such, patients with initially unresectable disease who have an excellent response to chemotherapy should be re-evaluated by a hepatobiliary surgeon.

In patients with resectable metastases at presentation, chemotherapy can be used in a "neoadjuvant" approach. Perioperative chemotherapy has been compared to no chemotherapy in a prospective randomized trial.

Chemotherapy improved progression free survival without a statistically significant difference in overall survival, but the use of preoperative chemotherapy increased post-operative morbidity[37]. Given the potential for liver toxicity with standard chemotherapeutics used in colorectal cancer (steatohepatitis with irinotecan, sinusoidal obstruction syndrome with oxaliplatin, and steatosis with 5-FU), decisions regarding neoadjuvant chemotherapy are best made by a multidisciplinary tumour board.

Operative Considerations

The optimal timing of resection for the primary colorectal cancer and synchronous liver metastases is debated in the literature.

Simultaneous resection avoids the morbidity of a second surgery. Some studies have shown no difference in morbidity and mortality while others have shown that synchronous resections have a higher mortality rate than staged resections[38,39]. An accepted approach is to perform staged resections in cases which would require an extensive liver resection such as hemihepatectomy in addition to a complex colorectal resection. Other combinations can be performed simultaneously, but clinical judgment is critical in these cases.

Minimizing blood loss is a joint effort between anaesthesiologists and surgeons. The anaesthesiologist helps maintain a low central venous pressure to minimize hepatic venous bleeding during liver parenchymal transection. From a surgical perspective, techniques such as clamping the porta hepatis, use of intra-operative ultrasound, energy devices, and surgical staplers can reduce blood loss.

The use of minimally invasive techniques for the treatment of colorectal liver metastases is increasing. Currently, there have been no randomized controlled trials comparing open to laparoscopic liver resections. A matched comparative study by Castaing et al. showed no difference in length of hospital stay, overall complication rates, and long-term oncologic outcomes. These results suggest that complication rates and oncologic outcomes are related to the extent of liver resection and tumour biology, respectively, rather than the approach to resection[40].

Conclusion

The definition of resectability for colorectal liver metastases has changed over time. Factors such as bilobar metastases, inability to obtain margins of at least one centimetre, four or more metastases, and extrahepatic disease should not be used to exclude patients from surgical resection. In the current era, the primary determinant of resectability is the ability to perform an R0 resection while leaving behind a large enough FLR to avoid postoperative liver failure.

The eligibility for resection has been expanded by the combination approach using resection and ablative techniques, PVE, 2-stage hepatectomy, and ALPPS. These approaches may allow for resection in patients with extensive disease and limited hepatic reserve.

Although surgery is not absolutely contraindicated in patients with resectable extrahepatic disease, these patients must be well selected based on tumor biology. Chemotherapy can convert a number of patients from unresectable to resectable. Neoadjuvant chemotherapy is not

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mandatory for resectable patients. With the changing definition of resectability and the increasing arsenal of techniques available, it is critical that patients be evaluated at the time of diagnosis by a surgeon with expertise in hepatic resection.

Given the complexity of this clinical problem, a multidisciplinary team approach is necessary to determine optimal treatment.

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