World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v3.i1.1

World J Gastrointest Oncol 2011 January 15; 3(1): 1-9
ISSN 1948-5204 (online)

EDITORIAL

Surgical treatment of hepatic metastases from colorectal cancer

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Received: August 20, 2010 Revised: December 9, 2010
Accepted: December 16, 2010
Published online: January 15, 2011

Abstract

Colorectal carcinoma is one of the most frequent cancers in Western societies with an incidence of around 700 per million people. About half of the patients develop metastases from the primary tumor and liver is the primary metastatic site. Improved survival rates after hepatectomy for metastatic colorectal cancer have been reported in the last few years and these may be the result of a variety of factors, such as advances in systemic chemotherapy, radiographic imaging techniques that permit more accurate determination of the extent and location of the metastatic burden, local ablation methods, and in surgical techniques of hepatic resection. These have led to a more aggressive approach towards liver metastatic disease, resulting in longer survival. The goal of this paper is to review the role of various forms of surgery in the treatment of hepatic metastases from colorectal cancer.

Key words: Hepatic metastases; Colorectal cancer; Liver resection

Peer reviewers: Oliver Stoeltzing, MD, Associate Professor, Department of Surgery and Surgical Oncology, Johannes Gutenberg University Hospital, Langenbeckstr. 1, Mainz 55131, Germany; Yo-ichi Yamashita, MD, PhD, Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Senda-machi 1-9-6, Naka-ku, Hiroshima 730-8619, Japan

Tsoulfas G, Pramateftakis MG, Kanellos I. Surgical treatment of hepatic metastases from colorectal cancer. *World J Gastrointest Oncol* 2011; 3(1): 1-9 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i1/1.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i1.1

INTRODUCTION

Every year there are approximately 125 000 new cases of colon cancer in the U.S. Fifteen percent of these patients will have liver metastases at the time of diagnosis, and another 50% will develop liver metastatic disease during the course of their disease[1]. Recent advances in adjuvant therapy after the colon resection offer the promise of a decrease in the number of cases with metastatic disease[2]. Just as important for patients with metastatic liver disease, newer chemotherapeutic agents such as irinotecan and oxaliplatin, as well as new targeted agents such as cetuximab and bevacizumab (Vascular endothelial growth factor, or VEGF, antibody) added to current protocols, have improved response rates and survival[3-7]. Unfortunately, even with these combinations, the two-year survival is at best 40% for patients with metastatic disease.

These findings make surgical treatment the cornerstone of the therapeutic approach to this disease, as it has been demonstrated that curative resection of liver metastases increases survival, with 5-year survival rates of 30%-40%[1,8,9]. Although only 10%-25% of patients with liver metastatic disease are candidates for surgical resection, a combined therapeutic approach has shown the most promise, especially since it has been possible to convert around 15% of patients previously considered unresectable and achieve survival rates similar to those for patients deemed resectable from the outset[10].

DEFINING RESECTABLE DISEASE

The concept of is what is considered resectable disease has evolved significantly over time. Originally, it was felt that patients with more than three metastatic liver lesions or with bilobar disease were not appropriate for resection. However, more recent studies have shown that even in patients with poor prognostic signs, 5-year survival can be achieved after curative liver resection[11-13]. Different studies have attempted to provide risk scores based on a variety of prognostic features including age, number of metastases, size of the largest lesion, carcino-embryonic antigen (CEA) level, primary tumor stage, positive tumor resection margins, disease-free interval, positive lymph nodes from the primary[11-13]. Of these, the clinical risk score (CRS) as proposed by Fong *et al*[11] has been used most widely. This scoring system has been validated by independent databases, and has been demonstrated to be useful not only in predicting recurrence, but also in predicting yield for diagnostic tests such as laparoscopy and positron emission tomography (PET)[11,14-16]. Others have attempted to improve on previous predictive scoring systems with the use of a normogram, whereby rather than counting risk factors the specific value for each factor is taken into consideration[17]. This makes the prediction more specific to the individual patient, and thus potentially more accurate. However, there is not universal agreement, as there have been arguments that on one hand some of the prediction scoring systems are based on factors that are not always associated with survival on multivariate analysis, and on the other hand that the normogram prognosis is based on data that can be inherently misleading because it is limited to estimation of initial risk around the time of surgery[18]. As a result, Nathan *et al*[18] have proposed the use of conditional survival as a dynamic assessment of survival probability. Conditional survival is defined as the probability that is calculated after a given length of survival and includes only individuals who have survived for a pre-defined time. In other words, if a patient survives for a certain period of time after surgery, the probability of surviving for an additional period of time changes, because the patient has already demonstrated a propensity to survive[19]. There is, however, common agreement between all these studies that although poor characteristics will definitely decrease survival, 5-year survival was still better compared to those patients with liver metastatic disease who had not undergone resection. As a result, none of these series suggested that patients with poor prognostic signs should not undergo surgery.

The indications have changed over time to the extent that currently a surgical resection would be considered beneficial if it is possible after resection to achive an R0 resection, leave behind at least two contiguous segments and functional liver volume > 20%. As it will be discussed later, even extra-hepatic metastatic disease is not necessarily a contraindication and more patients are being considered for resection[20]. Advances that have played a central role in this include preoperative portal vein embolization to induce hypertrophy of the residual non-diseased part of the liver, better vascular clamping techniques, controlled anatomic resection, the use of radiofrequency and microwave ablation for small lesions that may remain in the portion of the liver left behind after a resection, and more recently the use of image-guided liver surgery[21-26].

ROLE OF CHEMOTHERAPY

The targeted use of chemotherapy regimens, such as 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) has been critical in increasing resectability to the level of 10% to 35%[27-30]. Comparisons have been somewhat difficult because of the different ways that unresectability is perceived or defined. Some studies include number of lesions or bilobar disease, whereas others look at more technical issues, such as involvement of all three hepatic veins, both portal veins, or the retrohepatic vena cava, or that resection would leave less than two segments or an inadequate liver reserve. Even with these limitations, there is definitely a role for neoadjuvant treatment in moving from unresectable disease to surgical cure.

A variety of large studies, such as the recent European Organization for Research and Treatment of Cancer (EORTC) Intergroup trial 40983 and a study of 1600 patients undergoing hepatic resection for colorectal cancer from Memorial Sloan-Kettering, have demonstrated an improvement in progression-free and overall survival[31,32]. This is especially evident in the most recent studies, and appears to be a combination of improved quality of targeted chemotherapy agents, with better patient selection, based on the response to chemotherapy[33].

There is less unanimity on the use of chemotherapy prior to resection of lesions initially defined as resectable. Arguments in favor include the decrease in tumor size, the potential control of micrometastatic disease, the assessment of the activity of chemotherapy, improved chemotherapy tolerance, and a potential marker for the success of liver surgery[11-13,34]. Arguments against preoperative chemotherapy use in resectable patients include liver toxicity (chemotherapy-associated steatohepatitis or CASH), risk of progression or growth at other sites, selection of resistant clones and the fact that response may make the surgery more difficult[35-37]. Overall, the prevailing opinion appears to be that, unless the lesions are metachronous and of borderline resectability, they should be resected first with chemotherapy to follow[38].

ROLE OF IMMUNOTHERAPY

Another promising avenue for adjuvant treatment of colorectal liver metastases is the use of immunotherapy, based on exploiting the rich network of liver immunity. An unknown proportion of microscopic tumor cell deposits in the liver are precursors of the development of clinically established metastases. In addition there is the tumorigenic effect of surgical intervention, possibly related to the production by healing tissues of growth factors, angiogenesis mediators, inflammatory cytokines and chemokines[39,40].

In the liver, as a consequence of intrinsic tumor pathways or chronic inflammation, dendritic cells and macrophages with altered stimulating activity, together with regulatory T cells and myeloid-suppressor cells, expand *in vivo* and exert potent inhibitory effects on anti-tumor immunity[41]. If innate liver immunity could be triggered by antibodies to control growth of metastatic tumor deposits into the liver, activation of adaptive immunity through the administration of a cancer vaccine could offer the additional advantage of inducing a protective immunological memory for long-term and systemic disease control. Promise has been shown by an anti-tumor vaccine composed of heat shock protein 96 extracted from liver metastases, whose use led to significantly reduced recurrence rate and prolonged survival in colorectal cancer patients mounting a CD8-mediated tumor-specific response[42,43]. Cancer vaccines could be administered in combination with antibodies to achieve more aggressive immune-mediated tumor control. The timing of such treatments, in relation to surgery, needs to be further investigated, in order to achieve the maximum benefit for the patients.

PREOPERATIVE PREPARATION AND INTRAOPERATIVE PLAN

During early efforts to manage metastatic liver disease from colorectal cancer, it was not unusual to find as many as 40% of patients to be unresectable during surgery, mainly because of difficulties in properly assessing the location and number of metastatic lesions[44]. A patient discovered to have metastatic liver disease from colorectal cancer should undergo a thorough radiological workup. Contrast computed tomography (CT) scans of the abdomen have detection rates for hepatic metastases of 68%-91% (70% for lesions > 1 cm), and this has long replaced ultrasonography as the preferred imaging modality[45]. However, the sensitivity and specificity of CT liver scans will vary, depending on the equipment and contrast enhancement methods used. Magnetic resonance imaging (MRI) is now being used as alternative for assessing the liver. A recent meta-analysis comparing sensitivity estimates of various imaging modalities for detection of colorectal metastases showed that F-18 fluorodeoxyglucose (FDG) PET had significantly higher sensitivity on a per patient basis but not on a per lesion basis, compared with other modalities[46]. Sensitivity estimates for MRI imaging with contrast agent were significantly superior to those of helical CT with 45 g of iodine or less. PET may, however, miss small hepatic lesions and its performance can be affected by concurrent administration of chemotherapy. Using CT and/or a PET scan can be critical to either exclude the patient from resection, or at least to have a plan for addressing the different sites of metastatic disease.

Studies should ideally be performed either in or under the guidance of a liver surgery unit, and should address the question of whether a biopsy should be performed. There is evidence that percutaneous biopsy of liver tumors may be associated with extrahepatic dissemination of tumors and result in decreased potential survival, even when resection of the metastatic disease is undertaken[47,48]. Laparoscopy may identify occult metastatic disease and prevent unnecessary laparotomy in some patients with potentially curable hepatic metastases, although it may be used more selectively in patients with low risk of tumor[49,50].

Radiological studies can offer valuable information in determining the resectability of lesions preoperatively. Specifically, a triple phase CT with volumetry can be used to identify the location and vascular supply of the lesions and serve as a road map, as well as giving an estimate of whether a resection would leave behind an adequate liver remnant. Ideally, in an otherwise healthy liver, there should be a remnant of at least 20%-30%. If that is not the case, then preoperative portal vein embolization can be used to induce hypertrophy of the non-diseased part of the liver that would remain behind. This would lead to an increase of 10%-30% in the liver volume within 6-8 wk[51].

The use of intraoperative ultrasound during surgery is almost essential, both to identify the the location of known lesions in relation to the surrounding vessels, as well as to look for other lesions that may not have been detected preoperatively. This is one area where technology is increasingly becoming an integral part of surgical progress, as here are certain advanced computer-generated models that allow an image-guided approach to the resection of these lesions, even in real time[25,26,52]. They provide 3D visualization of anatomical structures in the operating room and the real-time tracking of therapeutic delivery tools. The combined advantage of precise therapeutic planning and volumetric analysis, allows the surgeon to determine the optimal path of therapeutic delivery (ablation trajectory guidance) and the plane of transection in the cases of resection. In this way liver tumors embedded deep in the parenchyma can be localized and approached with accuracy and safety.

LAPAROSCOPIC RESECTION

Since the first laparoscopic liver resection was reported in 1992, the number has increased significantly, now numbering several thousands. Technology has played a critical role in allowing the expansion of laparoscopic surgery in the treatment of colorectal liver metastases. The combination of laparoscopic surgical ultrasonic aspirators and ultrasonic shears, as well as endovascular staplers and a variety of haemostatic agents offer the laparoscopic liver surgeon a variety of choices. The technique offers the advantages over open surgery of reduced postoperative pain, less operative morbidity, shorter hospital stay, and faster recovery[53,54].

In one study, 85 patients underwent open liver resection *vs* 55 undergoing laparoscopic resection, with a very similar mix of types of resection[55]. In relation to short- and medium-term survival, mortality, morbidity, resection margins, local recurrence or port-site metastases, the laparoscopic approach was safer and more effective than open resection. In another multicenter, international series of laparoscopic resection for colorectal carcinoma metasta-

ses there were no perioperative deaths and a complication rate of 12% among 109 patients[56]. The series included a significant number of major resections (45% were more than 3 segments) and negative margins were achieved in 94% of patients, with overall survival at 1-, 3- and 5-years of 88%, 69% and 50% respectively.

The original concern with laparoscopic liver resection was regarding the risk of bleeding and the possibility of increased local recurrence, as a result of either inadequate margins or port-site recurrence. On the other hand, it might be argued that the laparoscopic approach, as a more controlled approach, may lead to a reduced pro-tumorigenic effect from surgical intervention, possibly related to decreased production of pro-inflammatory cytokines and chemokines, as well as growth and angiogenesis factors[57]. Either way, the fears of an inadequate oncological resection with laparoscopy have not been realized, perhaps partly because the definition of what we consider an R0 approach may be evolving. Conventionally, an R0 resection has been considered as having a disease-free margin of more than 1 cm, and has been associated with better long-term outcome. However, recent data suggest that smaller margins may be acceptable and curative hepatectomies with a margin of less than 1 cm have been reported[58,59]. Just as important in avoiding such complications, is the routine use of laparoscopic ultrasound to achieve adequate disease-free margins, as well as use of impermeable retrieval bags, attention to port-site placement and the use of an intraoperative no-touch technique.

Laparoscopic liver resection for colorectal liver metastases has shown great promise and has the potential to become the mainstay of treatment. However, enthusiasm about this surgical technique should be tempered as we do not have yet any long-term outcomes.

SYNCHRONOUS METASTASES

Synchronous liver metastases are commonly defined as liver metastases occurring within 12 mo of the colon primary. The optimal timing for their surgical resection is challenging. The original paradigm of staged resection (colon primary first with the liver metastatic resection 2 to 3 mo later), has begun to change and good results have been achieved with simultaneous resection[60,61]. A study of 230 patients (70 undergoing simultaneous resection and 130 staged) revealed no difference in morbidity and mortality, but a significantly shorter hospital stay for the group undergoing simultaneous resection[62]. However, the combined strategy can only be offered to less than half of the patients[63,64]. The major limitation is that major liver resections, when combined with a simultaneous resection of the primary tumor are associated with increased mortality and morbidity rates of 8% and 36% respectively[65,66]. Based on these findings some have argued in favor of an alternative reverse strategy where preoperative chemotherapy is followed by resection of the colorectal liver metastases and then by resection of the colorectal primary during a second operation[67,68]. This has been proposed for patients with advanced colorectal liver metastatic disease and an asymptomatic primary tumor, where delay in the treatment of the liver disease could lead to an unresectable situation.

In general, all three approaches, the classic, the combined and the reverse, have shown similar outcomes in terms of overall survival, perioperative mortality and morbidity. These strategies should not be seen as competitive, but rather as complementing each other with the extent of disease influencing the choice and sequence of treatment. If the strategy is tailored to the different hepatic and colorectal disease burdens in each patient, then the optimal result can be achieved.

EXTRAHEPATIC DISEASE

An aggressive multidisciplinary approach has gained significant ground and leads to long term survival in cases of serial metastasectomy of hepatic and pulmonary metastases from colon cancer. Studies have reported 5-year survivals of 51%, from an aggressive approach where every time a metastatic lesion is identified, it is resected[69-71]. Given the selection bias of these studies, the reported favorable outcomes could be expected in fit patients with limited and resectable liver and lung tumors, and without other extrahepatic disease. The technical approach, particularly the sequencing of resections, can be individualized according to the surgeons' preferences and the extent of the disease in the different organs. Alternatively, the procedures can be staged if an extensive resection is required for the liver.

The promising results in the treatment of synchronous liver and lung colorectal metastatic disease, have led to a more aggressive approach towards other types of extrahepatic disease. Specifically, in cases where portal lymph node involvement was identified, this was found to be a poor prognostic factor, but not an absolute contraindication[72-74]. When there is suspicion of portal lymph node metastases preoperatively, a selective approach to resection should be undertaken. The location of the lymph nodes appears to be important, and patients with celiac or retroperitoneal lymph node disease should not be resected, whilst patients with true portal disease should. Even in patients with peritoneal disease there have been some voices arguing in favor of surgical resection, provided the peritoneal metastases are isolated[75,76]. These retrospective studies have shown improved survival with the combination of cytoreductive surgery and intraperitoneal chemotherapy. Nevertheless, this combination should be considered as a major operation with significant complications, and should be viewed with caution.

A prudent strategy in cases of portal lymph node involvement or peritoneal implantation is the use of preoperative chemotherapy as a way to evaluate the biological behavior of the disease. If there is a prolonged, stable period after the chemotherapy, then resection might be of benefit.

A ROLE FOR LIVER TRANSPLANTATION?

Previous cases of liver transplantation for colorectal can-

cer liver metastases have led to long-term survival and even cure in some cases[77,78]. This is not surprising since liver transplantation for liver-only metastatic disease is by definition an R0 resection and, as such, acceptable from an oncological perspective. However, given organ shortages, the outcome has to be comparable to other indications for liver transplantation. The fact that overall survival following liver transplantation has dramatically improved and that patients with hepatic metastatic disease of colorectal origin present less of a technical challenge, given the lack of cirrhosis and portal hypertension, these patients should be considered relatively low-risk for liver transplantation. In addition, the use of a class of immunosuppressive medications, the mTOR inhibitors, has shown clinical effect and stabilization of disease for a variety of cancers, in their role as antiproliferative agents[79-81].

Based on these considerations, a group from Norway, taking advantage of the surplus of donor organs in that country, initiated a study where 16 patients underwent liver transplantation for isolated hepatic metastatic colorectal disease[82]. Although 2-year survival was 94% with an excellent quality of life, there was a high recurrence rate of 63%. These preliminary data seem promising although, it is too early to tell whether this will prove to be a beneficial strategy. Specifically, it is important to evaluate the 5-year survival in order to see whether it is comparable to other indications for liver transplantation, thereby so as to justifying the use of a limited organ supply. In addition, selection criteria for the candidates need to be refined to be able to decrease the high recurrence rate.

COMBINATION THERAPY

Part of the recent aggressive approach to colorectal liver metastatic disease is the use of several treatment modalities in combination, in an effort to deal with more advanced disease. In a series of 224 patients, where a very high number had multiple (five or more), bilateral liver lesions, treatment consisted of a combination of hepatic arterial chemotherapy, cryotherapy and resection[83-85]. This led to 1-, 3-, and 5-year survival rates of 87%, 43% and 23% respectively in this high risk group of patients. The surgeon and the medical team have a wide armamentarium in their hands and it is up to them to find the right treatment modality for each patient.

ABLATIVE THERAPY

A special mention should be made regarding the role of ablative therapy in the treatment of liver metastatic disease from colorectal cancer, and especially that of radiofrequency ablation (RFA). As experience with RFA has increased over the last several years, there has been an effort to comprehensively evaluate the results. A Clinical Evidence Review regarding RFA of hepatic metastases from colorectal cancer, published by The American Society of Clinical Oncology in 2009, suggested that, based on the existing evidence, overall survival was better for hepatic resection than for RFA, especially for patients with resectable tumors without extrahepatic disease[86]. RFA investigators reported a wide variability in the 5-year survival rate (14% to 55%) and local tumor recurrence rate (3.6% to 60%). The reported mortality rate was low (0% to 2%), and the rate of major complications was commonly reported to be 6% to 9%. In another systematic review of the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases, the authors found that comparative studies indicated significantly improved overall survival after RFA *vs* chemotherapy alone, RFA plus chemotherapy *vs* RFA alone and up-front RFA *vs* RFA following second-line chemotherapy[87]. These findings support the suggestion that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected patients, but not as an alternative to resection.

FOLLOW-UP AND RECURRENCE AFTER LIVER RESECTION

Recurrence can occur in as many as 60% of patients following liver resection of colorectal metastatic disease, with the most frequent site of recurrence being the liver. In approximately 20% of these patients the liver may be the only site of recurrence and as a result these patients may be suitable for re-resection[88]. The vast majority of these recurrences occur in the first two years and for that reason frequent surveillance with CT is critical for early detection. This becomes even more important if we consider that the reported morbidity and mortality rates, as well as overall survival rates after re-resection, are similar to those reported for the initial hepatectomy, despite the potentially greater technical difficulty[87-89]. In the current cost-conscious environment, the fact that intensive 3-monthly CT surveillance detects recurrence that is amenable to further resection in a considerable number of patients, leads to significantly better survival for these patients with a reasonable cost per life-year gained[90].

USE OF MULTIDISCIPLINARY TEAMS

A key factor in achieving a successful outcome for patients with hepatic metastases from colorectal cancer is the close cooperation between the colorectal and the hepatobiliary team. Both of these should include specialist surgeons, in addition to an oncologist, gastroenterologist, diagnostic and interventional radiologist, histopathologist and clinical nurse specialist. The goal is to achieve a multidisciplinary input, as well as to develop protocols that will be the cornerstone of developing a "best practices" approach. The improved outcomes that we are witnessing in the management of liver metastatic lesions from colorectal cancer are most likely to be the result of this concerted effort, in addition to a possible volume effect.

CONCLUSION

Surgery is the cornerstone of any successful therapeu-

tic approach to patients with hepatic metastases from colorectal cancer. However, with the significant progress in areas such as chemotherapy and local, ablative treatments among others, we have been able to expand the definition of what is resectable in the treatment of colorectal liver metastatic disease and to be able to talk about 5-year survivals in cases, where it was previously unthinkable. There have been reports of 10- and 15-year survivals of 24% and 21% respectively[91]. In a review from the Memorial Sloan Kettering Cancer Center of 612 consecutive patients with colorectal liver metastases, there were 102 10-year survivors. They serve as proof of the importance of surgery in allowing us to talk about curing this disease, as chemotherapy regimens during most of that earlier period were not very helpful[92]. With all the new weapons currently in the surgeon's armamentarium, the future certainly looks even brighter. In order to be able to continue down this path, there is a need for an ongoing collaborative collection of data with the use of various protocols and multicenter trials.

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