Surgery for colorectal liver metastases: expanding the boundaries but where have all the patients gone

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Aim: To review and discuss the current strategies and controversies in the surgical management of colorectal cancer liver metastases.

Methods: An analysis of indications, contraindications and scoring systems and concepts for expanding the indications for resection are discussed. The findings and discussion are related to our own experience, especially with radiofrequency assisted liver resection for colorectal cancer liver metastases.

Results: Resection is the only management strategy that can potentially cure the patient. Certain controversies still exist, such as contraindications for surgery, timing of treatment of synchronous metastases, significance of extra-hepatic disease etc. Strategies that can improve respectability are discussed. Parenchyma oriented, tissue sparing surgery facilitates reresection should it become necessary.

Conclusion: The management of colorectal cancer liver metastases is still a confusing issue for general oncologists and general surgeons. A multidisciplinary approach that tailors the management strategy to the individual patient is the only option that provides optimal results for patients with advanced disease.

Key words: surgery, liver metastases, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer in the Western World, following lung and stomach cancer. It ranks second as cause of cancer death, with a cumulative lifetime risk of approximately 5% and an incident rate of 50/100,000. Almost one million new cases occur worldwide annually and approximately 500,000 people will die from CRC every year.1,2

Liver metastases are the main cause of death in patients with CRC cancer and 20% of patients that die from metastatic CRC have metastases limited to the liver only.3,4 Without any treatment, the median survival after the detection of liver metastases of CRC is approximately 9 months, depending on the extent of the disease at time of diagnosis.5 Survival in untreated patients is dismal and in a large series it is 31% at one year, 7.9% at two years, 2.6% at three years, 0.9 at four years.5 Five year survival is anecdotal and there are no 10 year survivors.4

Already, at the time of diagnosis of the CRC, 15-25% of the patients will have detectable liver metastases. Another 35-45% of patients will develop liver metastases during the course of their disease.6 In the group of patients with advanced CRC 20 – 30% have liver only metastases.7 Curative resection is possible in less than 25% of those patients that have metastases confined to the liver only, which translates to 5 – 10% of the patients that develop CRC cancer.8 Unfortunately some 20-50% of patient will develop liver metastases within 3 years following resection of the primary tumor.8,9 In approximately 50% of these patients metastatic disease is confined to the liver only.8,9

Hepatic resection for CRC metastases is the standard of care and the only potentially curative treatment strategy. Contemporary operative mortality rates are as low as 1–2%.10,11 Five year survival rates following liver resection for CRC metastases, in the majority of large series, range between 25-51%.12,18 Some studies that have long-term follow-up have demonstrated 10 year survival rates of 22-24%.15,19,20 Several authors have reported survival periods in excess of 20 years following hepatic resection for CRC metastases.8,20 Such good therapeutical results are unique to hepatic resection for CRC metastases only.

Chemotherapy alone, whether delivered systemically or regionally, rarely results in prolonged survival. New chemotherapeutic agents have provided better results. Nevertheless, chemotherapy at best can prolong survival but cannot cure the patient. Randomized trials comparing hepatic resection, chemotherapy and best supportive care, in patients with potentially resectable liver metastases, are unethical and have not been published. It has been argued that patients with resectable CRC liver metastases are a
strictly selected group of patients and that respectability is an independent prognostic factor and that, since randomized trials are non-existent, the role of surgery is difficult to assess. It should be recognized that numerous single institution reports have demonstrated long-term survival and there are no other treatment options that have shown a survival plateau. New, more potent and more expensive, chemotherapeutic agents (eg. oxaliplatin and irinotecan etc.) are capable of inducing tumor downsizing, and prolonging survival in nonoperable disease. New, more effective chemotherapeutic agents have made it possible that an additional 10-20% of patients, initially deemed as unresectable and treated for palliative intent, undergo curative resection. Long-term survival rates for these patients are comparable to survival rates of primarily resected patients.

Management of CRC liver metastases is multidisciplinary. The role of surgery is crucial and the surgeon should have an aggressive, balanced approach, utilizing all technological innovations in order to expand the frontiers of surgical therapy for CRC liver metastases.

Only a minority of patients (10-15%) with CRC liver metastases are considered candidates for hepatic resection. The number of patients eligible for resection can be increased by improving: a. patient selection and prognostic criteria, b. surgical technique and c. management strategies. New concepts and techniques will be discussed in this paper

Surgery for CRC has greatly improved. The number of operations per year has increased and more and more surgeons and institutions are engaged in the management of patients with CRC. Hepatic surgery has become safe and efficient and it has reached boundaries that were unimaginable a decade ago. The number of hepatic resections done for CRC metastases per year is slow to increase. If statistics and figures are correct, the number of hepatic resections for CRC metastases should increase significantly every year. This did not happen. Does this reflect the traditional belief that surgery can do little for these patients? One must ask the question: where have all the patients gone?

**PROGNOSTIC EVALUATION, PATIENT SELECTION AND RECENT ADVANCES IN CONTRAINDICATIONS TO HEPATIC RESECTION FOR CRC METASTASES**

The safety of hepatic resection has improved. More surgeons and more institutions embark upon hepatic resection for CRC metastases. The subgroup of patients eligible for potentially curative resection has increased. Nevertheless, the proportion of resectable patients has not been accurately defined and most authors quote data originating from large series sometimes extending more than two decades back in time when selection criteria were different. Hepatic resection for CRC metastases is done with curative intent, but, nevertheless, the majority of patients will develop recurrent disease after surgery. In some 20% of operated patients metastatic disease will be detected within 6 months after the operation. This raises the question of whether: a. the operation was not done according to oncological standards or b. the indication for surgery was wrong. The significance of prognostic factors is twofold: a. outcome prognosis and b. surgical candidate selection. A clearly defined and easily applicable prognostic scoring system based on routine clinical parameters would enhance optimal patient selection or enable stratification of patients in clinical trials. Very strong negative prognostic factors might become absolute or relative contraindications for surgery.

The first scoring system was introduced by Nordlinger and colleagues 10 years ago. The scoring system was based on data derived from 1568 patients operated for curative intent in a French Multicenter Study. Two and 5-year survival rates were 64% and 28%, and they were affected by: age; size of largest metastasis or CEA level; stage of the primary tumor; disease free interval; number of liver nodules; and resection margin. Giving one point to each factor, the population was divided into three risk groups with different 2-year survival rates: They divided all the patients into three groups according to the risk of poor outcome: a. low (0-2 points - 79%), b. intermediate (3-4 points - 60%) and c. high (5-7 points -43%).

Ohlsson et al. reported their 25 year experience from Sweden in the surgical management of CRC liver metastases. They demonstrated that five factors were independently significant: grade of liver tumor, extra hepatic metastases, intra-operative blood transfusion and the preoperative CEA level and whether the operation was performed in the earlier 15-year period versus the later 5-year period. They reported that when there are extra-hepatic metastases, satelitosis, poorly differentiated liver metastases or positive resection margins none of the patients survived for 5 years.

Fong and colleagues from the Memorial Sloan-Kettering Cancer Center proposed a clinical pre-operative risk scoring system based on 1001 operated patients between 1985 and 1998. Five clinical parameters were selected: a. primary tumor nodal status, b. disease free interval from the primary to liver metastases <12 months, number of hepatic tumors >1, preoperative CEA level 200 ng/ml, and size of the largest hepatic tumor >5cm. Each criterion was assigned 1 point. The total score was highly predictive of outcome. The 5-year survival rate for patients with zero points was 60%, and for those with 5 points only 14%. The liver resection margin status and presence of extra-hepatic lesions was not included into this single institution scoring system because these two most influential single factors were considered contraindications for operation. Belghiti stresses that the widespread indiscriminate use of such scoring systems can result in patients with scores of 3 – 5 being denied operation, especially if a difficult operation is predicted. For such high-risk patients some authors have introduced the "biologic test of time". Patients are referred to neoadjuvant chemotherapy trials and if there is a response they are referred to hepatic resection. The five-year survival of 10-20% that can be achieved in this group of patients is definitely superior to the less than 5% for non-operated patients.
Several authors have published other risk scoring systems based on the analysis of preoperative factors: Iwatsuki, Cady, Hughes, Scheele, Gayowski, Jamison etc. Most systems are multifactorial and relatively complicated for routine use. It seems that patient sex and site of the primary tumor do not influence the outcome. Nordlinger points out that in stage I and II primary colorectal cancers the five-year survival rate is 70% and only 33% for stage III cancers. An analysis of most scoring systems reveals that prognosis seems better with metachronous metastases, when there are fewer than 4 lesions and when the lesions are small. The involvement of one or both lobes does not influence the outcome. The CEA level is strongly correlated with recurrence-free survival. It looks like the type of resection does not influence prognosis if a clear margin is achieved but the total number of metastases does. Blood transfusion could be associated with adverse outcome and postoperative morbidity, but it may reflect the operative technique, operator experience and technical difficulties and course of the procedure determined by the number, size and distribution of the liver metastases.

A simple to use scoring system would be very welcome. A prognostic scoring system that has a minimal number of predictive factors and is easy to use was proposed by Makucchi. This system is based on the analyses of 369 operated patients from 1980 to 2002 with curative intent. Lymph node metastases in the hepatic nodes was the single independent factor with the highest risk, followed by number of lymph nodes around the primary tumor and the CEA values. Put into perspective, the prognostic system is based on the sum of points. A total of 0-3 lymph nodes around the primary cancer were worth 0 points, 4 or more lymph nodes were worth 1 point. CEA levels <50 ng/ml were worth 0 points and levels >50 ng/ml were worth 1 point. Stage 1 (52% five-year survival) had a sum of 0 points. Stage 2 (39% five-year survival) had a sum of 1 point. Stage 3 (9% five-year survival) had a sum of 2 points. Patients with positive hepatic nodes were classified into Stage 4 and had no 5 year survival. This staging system is effective only if complete removal of hepatic or extra-hepatic metastases is accomplished and if repeat hepatectomy for hepatic recurrence is performed without delay.

The size of the tumor free resection margin has been thoroughly debated but no clear consensus has been reached. In a multi-institutional retrospective study including more than 1500 patients Nordlinger found that five-year survival was greater than 30% when the resection margin was larger than 1 cm and only 15% when the resection margin was less than 1%, and 0% when the resection margin was positive. A tumor free resection margin of at least 1 cm was considered best for avoiding recurrence, but several studies have demonstrated that smaller margins did not affect survival. Kokudo suggests that micrometastases around liver tumors are not common, and most are confined to the immediate vicinity of the tumor border. He proposes a surgical resection margin of 2mm as a clinically acceptable minimum require-
metastases in the liver only. Interestingly, this study demonstrated that the total number of metastatic lesions has a stronger negative prognostic value after complete resection of the metastases as compared to their site. The problem of hepato-portal (HP) lymph node involvement and prediction of outcome has recently been elucidated by Jaeck et al. In a prospective study they classified HP lymph nodes into two distinct groups: a. lymph nodes limited to the hepatoduodenal ligament and retro-pancreatic area and b. lymph nodes around the common hepatic artery and celiac axis. The first observation was in accordance with previous studies that lymph node involvement was a poor prognostic factor. The 3-year survival was 19% vs. 62% (p<0.001). A break-down analyses revealed that prognosis for patients in the first group was significantly better than prognosis for patients in the second group. Patients with lymph nodes in the hepatoduodenal ligament and retropancreatic area had a 3-year survival of 38% vs. 0% (p<0.001) for patients with lymph nodes around the common hepatic artery and celiac axis.

The once considered absolute or relative contraindications for hepatic resection in the management of patients with CRC metastases have been challenged. Large, prospective, randomized, well-controlled trials are clearly necessary to confirm these new challenges. It is imperative that evidence-based guidelines be compiled. Hao is correct in assuming that "the current discussion on prognostic factors and contraindications is at a stage as it was for colorectal secondaries some 20 years ago". Presently the only absolute contraindication accepted worldwide is the inability to remove all the lesions while leaving sufficient functional liver parenchyma (30-40%), regardless of the number, size, distribution and site of the metastases.

SURGICAL TECHNIQUES AND MANAGEMENT STRATEGIES.

Preoperative work-up of potential candidates for hepatic resection for CRC metastases is the same as for other indications for hepatic resection. The American Society of Anesthesiology (ASA) score needs to be determined preoperatively. Special attention is focused on the cardiocirculatory status of the patient because. Clamping procedures (inflow and outflow) may need to be done either on an elective or emergent basis, and these procedures, especially in the setting of marginal liver function, can be deleterious. Hemodynamic disturbances induced by clamping are poorly tolerated in patients with altered cardiovascular function and these procedures are always associated with some degree of reperfusion liver injury. The coagulation profile of the potential candidate needs to be assessed. The best available imaging modalities need to be utilized. Fine needle aspiration is unnecessary and it has been demonstrated that it can decrease long-term survival. Radiological staging (volumetric) is vital to determine the feasibility of hepatic resection. Advanced diagnostic imaging defines the extent of intra-hepatic and extra-hepatic disease. Both CT, NMR and MRCP can accurately define the number and size of the metastases as well as their relationship to major blood vessels and bile duct. A prospective study recently demonstrated that PET/CT has similar value to contrast-enhanced CT for CRC liver metastases. Consensus has not been reached concerning the timing of the surgical liver resection for CRC metastases and the CRC primary tumor in the group of patients with synchronous metastases. Increased mortality for simultaneous resection has been reported by some authors. The "biologic test of time" has been suggested to evaluate the biologic features of the tumor. Other authors believe "delayed" hepatic resection for CRC metastases improves
outcome. In many reports the survival rates, peri-operative mortality and post-operative morbidity are comparable for simultaneous resection of liver CRC metastases and delayed resection. A simultaneous resection is usually associated with right colon primaries and when there is only one metastasis in the liver that can be done as wedge or small atypical liver resection. Analysis of patients in different subgroups according to the location of the primary tumor and extent of hepatic resection did not reveal a particular group which is at an unacceptable risk when performing simultaneous colon and liver resection. Simultaneous resection is safe, efficient and the patient does not need a second laparotomy. The psychological and economic advantage for the patient is obvious. Nevertheless, the controversy is not really solved, there are no clear-cut indications and contraindications for performing simultaneous resection. The reason is twofold: a. most of the studies done were done at referral centers and b. the studies are retrospective. The question remains: who is to do the resection? Obviously the surgeon is a very significant independent variable for outcome prediction. The decision should be made by the operating surgeon, based on his expertise, experience and available facilities.

The feasibility of repeated liver resection for recurrent CRC liver metastases has greatly improved survival. The liver is the most common site of recurrence and might be the only site of recurrence in about one third of those who recur. Repeated hepatectomy for recurrence is becoming more frequent due to early detection, new chemotherapeutic agents, accumulating experience with liver parenchyma sparing resections and due to the use of new powered instruments. Prognostic factors and surgical goals that apply to the initial liver resection for CRC metastases apply to repeat hepatectomies as well. It has been demonstrated that repeat hepatectomies are safe. Second and even third hepatectomies have similar mortality, post-operative morbidity and impact on survival compared to the first hepatic resection.

The technique of liver resection has improved during the past decade. Segmental liver anatomy, introduced in the first half of the past century, marked a turning point in liver surgery. Unfortunately, all benefits of segmental anatomy could not be fully utilized in liver resection until intra-operative ultrasound was introduced in the '80-ties of the past century. The use of intra-operative ultrasound and the Glissonian approach made segment oriented liver resection safe and feasible. Liver surgery was essentially oriented to managing the pedicles and hepatic veins, achieving demarcation and subsequent tissue transection.

Blood loss during tissue transection was reduced by introducing low CVP anesthesia, inflow and outflow occlusion and an array of instruments used for tissue transection (e.g. the CUSA, the harmonic scalpel, the water jet dissector, the argon beam, staplers etc.). In order to minimize the adverse effect of reperfusion injury, several modifications of the classic hepatic pedicle clamping procedure (Pringle's maneuver) have been developed. Clamping can be continuous or intermittent and with or without preconditioning. Clamping can be selective: hemihepatic, hemihepatic with clamping of the ipsilateral hepatic vein and segmental vascular clamping. For large metastases encroaching the retro-hepatic vein total vascular exclusion (HVE) is possible (Conventional hepatic vascular exclusion and HVE with preserved caval flow). Selective infrahepatic IVC clamping as a salvage procedure has been described. For managing difficult liver resection specific procedures have been described like the "anterior approach" and the "hanging maneuver".

The axiom: wedge resections and anatomical segmentectomy is most commonly indicated for peripheral liver lesions has been challenged. This concept was based on a few retrospective reports that wedge resection more frequently yields positive margins than anatomical resection. Others demonstrated that there was no difference in survival rate according to type of liver resection. Kokudo demonstrated that CRC liver metastases can grow crossing intersegmental planes, without infiltrating the parenchyma and with minimal lateral spread. Based on such observations Kokudo concludes that anatomic resection for CRC liver metastases is neither necessary nor beneficial and that analogy with operations for HCC is not accurate. In another paper Kokudo concludes that there is no significant difference in survival between anatomical major resection and non-anatomical limited resection for CRC liver metastases. In unilobar single or double metastases major hepatectomy unnecessary in 80.4%. In 90% pts. ipsilateral recurrence can undergo second hepatectomy with 5 yr. survival 58.3%. Nevertheless, major anatomical resection for CRC liver metastases is done in 24.0% - 83.3% of patients and it is ethically difficult to do a prospective randomized study. Since the chances after hepatic resection for CRC metastases for intrahepatic recurrence are the same all over the liver it is wise to do tissue sparing liver resection.
Radiofrequency (RF) assisted liver resection is a new concept for performing parenchyma sparing liver resection for CRC liver metastases. Liver tissue adjacent to the exposed tip of the electrode is heated by radiofrequency induced ionic agitation causing tissue coagulation and collagen restructuring. The liver tissue is "welded" and the blood vessels and bile ducts are permanently occluded at the cut surface. The coagulated liver is cut with a surgical knife without blood loss. This procedure was first described by Weber and Habib\(^6\) as the "two circle technique" and later modified by Milicevic and Bulajic\(^6\) and reported as the "sequential coagulate-cut technique". The significance of the RF assisted technique is that liver resection is now "parenchyma oriented" and not "pedicle oriented". Segment demarcation lines for tissue transection are not necessary because it is possible to cut parts of segments without additional hemostasis. This has made the removal of multiple CRC liver metastases safe and possible with minimal tissue loss, regardless of site and size. Tissue sparing liver resection for CRC metastases is important, because if at the initial operation a minimal quantity of functional liver parenchyma is removed repeated resections, if necessary, can be done safely. Tissue transection with the Tyco Cool Tip\(^5\) electrode is presented in Fig.1. The remnant liver after removal of multiple CRC metastases is presented in Fig. 2 and after removal of a large CRC metastasis in Fig. 3.

Methods for improving respectability have been developed. New potent chemotherapeutical agents can "down-size" unresectable metastases to resectable metastases.\(^7\) Portal vein embolization (PVE) can induce homolateral atrophy of the liver to be resected and contralateral compensatory hyperthropy of the remnant liver.\(^7\)

This increases the respectability of patients with CRC liver metastases that have an insufficient calculated mass of remnant liver and the safety of the procedure itself. The "two stage hepatectomy procedure combined with PVE" is used for initially unresectable patients with multiple and bilobar CRC metastases. In the first-stage one hemiliver is completely cleared of CRC metastases by hepatic resection or RF ablation. A subsequent PVE to the contralateral hemiliver is performed to induce atrophy and hypertrophy of the cleared hemiliver. Finally a second-stage liver resection to remove the metastases-involved liver will be performed. The 5-year survival is comparable to patients that have had initial resection of CRC liver metastases.\(^7\)

Liver resection is the only potential curative therapy for CRC liver metastases. It is safe and more and more patients CRC liver metastases are eligible for liver resection. If the statistics are correct we should be seeing and operating more and more patients. The increase in the number of operated patients is negligible. Where have all the patients gone?

**CONCLUSION**

The concepts of liver resection for CRC metastases have changed dramatically during the past 20 years. Risk scoring systems have made patient selection for resection more accurate. The only absolute contraindications are an unfit patient, inability to do a R0 resection and when the anticipated liver remnant after resection is less than 40% of the liver mass. Advanced surgical techniques make it possible to safely remove CRC metastases from all sites within the liver. RF assisted liver resection is an interesting concept introducing tissue oriented resection and tissue sparing procedures. Re-resection is safe and has a similar effect on long-term survival as the initial liver resection for CRC metastases. New potent chemotherapeutical agents, PVE and two-stage procedures have increased the number of patients eligible for resection. Management of CRC liver metastases can be efficient only if it is done by a multidisciplinary team according to evidence based treatment modalities.
Cilj: Sagledati i prodiskutovati trenutne strategine i kon-
trouverze hirur{kog le~enja metastaza kolorektalnog karcinoma.

Metod: Analiza i razmatranje indikacija, kontraindi-
kacija i skoring sistema; koncept pro{irenih indikacija za
resekciju. Rezultati i diskusija se odnose na sopstveno
iskustvo posebno sa RF asistiranim resekcijama metastaza
kolorektalnog karcinoma.

Rezultati: Resekcija je jedina strate{ka opcija koja po-
tencijalno mo'e izle~iti bolesnika. Odredjene kontroverze
i dalje postoje, kao {to su kontraindikacije za hirur{ko
le~enje, vreme le~enja sinhronih metastaza, zna~aj ekstra-
hepati~ne propagacije bolesti itd. Strategije koje mogu
pove}ati resektabilnost su takodje navedene. Hirur{ki
pristup koji {tedi parenhim jetre omogu}ava naknadnu
reresekciju ukoliko je ona neophodna.

Zaklju~ak: Le~enje metastaza kolorektalnog karcinoma
je i dalje izvor konfuzije za op{te hirurge i onkologe. Mul-
tidisciplinaran pristup prilagodjen svakom obolelom jed-
inina je opcija koja daje optimalne rezultate za bolesnike sa
uznapredovalom bole{}u.

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