Review

Liver resection for colorectal cancer liver metastases

Kashwa Jamin

Department of Surgery, Homerton University Hospital, UK

ABSTRACT

Surgery is the only potentially curative treatment of colorectal cancer liver metastases. Important change in the surgical treatment of colorectal cancer liver metastases took place in the last two decades. Due to advancement in diagnostic methods more patients can be surgically treated in the earlier phase of disease and advancement in surgical technique and the development of new surgical instruments enabled safer complex resections with minimal blood loss. Because of complex liver vascular supply, thorough knowledge of inner hepatic anatomy is of utmost importance for performing resections. Indications for liver resection in patients with colorectal cancer metastases underwent fundamental changes so today the number, size and distribution of metastases in the liver are no longer important. The only contraindication for liver resection is the inability to preserve sufficient volume of functional liver parenchyma after resection that enables more patients to undergo potentially curative surgical treatment. In patients with initially inoperable liver metastases there are other methods for destruction of liver metastases, such as radiofrequency ablation or high-intensity focused ultrasound, and regenerative capability of the liver enables repeated surgical procedures with five year survival that reaches 40%. Bleeding during liver resection, that was a major problem in the past, has been nowadays reduced to minimum with techniques such as reducing central venous pressure, new devices for liver resection and the usage of local hemostatics.

KEYWORDS: colorectal cancer; secondary liver tumors; liver resection

Correspondence to: Jamin Kashwa, MD, Department of Surgery, Homerton University Hospital, UK, e-mail: jamin.kashwa@gmail.com

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INTRODUCTION

Colorectal cancer is the second most common malignancy in both men and women. Although the incidence and mortality is increasing, the mortality is increasing slower in incidence, which is at least in part due to the advancement of Health Care for these patients (1). Because of its biological and anatomical specificities, liver is the most common site of metastasis from colorectal cancer (2). All the portal venous blood passes through the, you will either represents the basic and the first filter for all the substances absorbed in the digestive system and the blood which is also true for cancer cells that spread through the bloodstream from the primary site.

At the moment of diagnosis of the primary colorectal cancer, liver metastasis can be diagnosed in approximately 30% of patients and are called synchronous metastasis. In another 30% of patients metastases are diagnosed during postoperative follow-up (3). Finally, only 1/3 patients with primary colorectal cancer will never develop metastases. Metastasis diagnosed during the postoperative follow-up, that is more than 12 months after surgery are called metachronous metastases.

The aim of surgical treatment of colorectal cancer liver metastases is to achieve curative resection (R0), which is possible in approximately 30 to 40% of patients(4). However, after potentially curative resection liver metastases reoccur in about

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a 60 to 70% of patients (5). Average survival after curative operation is 30 to 45 months, while 20 to 50% of operated patients live five years after surgery. In patients with relapse of metastatic disease in the liver it is possible to perform repeated resections and five year survival ranges from 16 to 25%. Besides surgery, as the primary method of treatment, other modalities can be used such as radiofrequency ablation, transarterial chemoembolization and microwave therapy (5).

INDICATIONS FOR RESECTION

Surgery is the gold standard of treatment of patients with colorectal cancer liver metastasis. Patients with untreated metastasis from colorectal cancer have a median survival of only 12 months (6-8), while surgery can achieve five year survival of up to 40%. Surgical resection is therefore considered as the only potentially curative modality of treatment of patients with colorectal cancer liver metastasis.

In recent years there has been a substantial change in criteria for resectability of colorectal cancer liver metastasis. While former criteria were based on the extent of necessary section, today's criteria are based on the volume of residual liver parenchyma.

It has been considered for long time that the presence of colorectal cancer metastasis in the liver represents a systemic disease that is not treatable with surgical methods. However, studies conducted in the late 20th century clearly showed that five year survival after surgery can be as high as 30% (Table 1).

These studies represented a change in development of liver surgery, and enabled broadening of indications for liver resection in metastatic liver disease from colorectal cancer. Formerly, the criteria for resection of colorectal cancer liver metastasis were based on the number and distribution of metastases in the liver (3 to 4 metastases, unilobar distribution of metastases), the size of tumor, mandatory tumor resection margin of 1 cm and the absence of extra hepatic disease. However, the analysis of survival of patients in whom the resection of both liver metastases and lung metastases was performed also showed high five year survival reaching up to 30% (Table 2).

Based on these results, it is today considered that surgical resection of colorectal cancer liver metastasis is contraindicated only in the following cases: inability to achieve radical (R0) resection, including the resectability of extra hepatic disease and the inability to preserve sufficient functional residual volume of the liver after resection.

Today's criteria are therefore focused on the volume of the liver remaining to offer surgery. Sufficient function residual volume of the liver is approximately 20% of health and liver, 30 to 60% of liver volume in the liver damaged by chemotherapy, steatosis or hepatitis (10), and approximately 40-70% in patients with liver cirrhosis (11). It is considered that eight grams of healthy functional liver parenchyma for every kilogram of body mass is sufficient to protect from liver failure (12). The required of residual volume can be assessed radiologically according to the known volume of certain parts of the liver, or using biochemical tests based on the speed of lidocaine metabolism.

It is also necessary to preoperatively assess the possibility of achieving R0 resection. Liver resection is indicated also in patients with extra hepatic disease as long as these extra hepatic metastasis are amenable to resection, such as lung metastasis or solitary metastasis in adrenal glands. Contraindication for resection of liver metastasis is the inability to preserve sufficient functional liver volume either due to the extent of surgery or the extent of liver fibrosis (12, 13).

Prognostic index

Thanks to careful selection of patients with liver metastasis, improvements in the preoperative diagnostics and more common use of neoadjuvant and adjuvant chemotherapy, the survival of patients with colorectal cancer liver metastasis has been significantly improved (14).

Table 1. Results of surgical treatment of colorectal cancer liver metastases.

Author	Year	Number of patients	Five year survival
Iwatsuki (9)	1986	60	35%
Scheele	1991	219	39%
Gayowski	1994	204	32%
Fong	1999	1001	37%

Table 2. Results of surgical treatment of colorectal cancer liver metastasis and lung metastases.

Author	Year	Number of patients	Five year survival
McAfee	1992	139	31%
Okumura	1996	39	33%
Ambiru	1998	25	43%
Murata	1998	30	44%
Regnard	1998	43	11%
Robinson	1999	25	43%
Kobayashi	1999	47	31%

Several studies determined that the factors associated with prognosis after liver resection for colorectal cancer liver metastasis. These factors include positive resection margin, presence of extra hepatic metastasis, metastasis in lymph nodes, synchronous metastasis, multiple metastasis, liver metastasis over 5 cm as well as CEA levels over 200 ng/ml (15).

Today, liver resection is performed even after the recurrence of metastases in the liver, that also increases survival. Mortality and morbidity after recurrent resections is almost equal to the mortality and morbidity of the first resection. Median survival after repeated resections is 32 to 46 months, and five year survival can reach over 30%. In patients in whom the largest metastasis is smaller than five centimeters, the prognosis is significantly better (16).

ONCOLOGICAL PRINCIPLES OF LIVER RESECTION

Resection margin

In oncological surgery in general, and also in liver surgery, the great care is taken to achieve negative resection margin. During the past decades there has been a lot of discussion regarding the necessary extent of resection margin.

In 1980s, when liver surgery began to significantly improve, it was considered that resection margin must be greater than 1 cm. Inability to achieve resection margin of one centimeter was considered a contraindication for surgical resection (17).

However, Pawlik et al. Demonstrated in their study that there is no difference in survival dependent on the extent of resection margin and concluded that the inability to achieve resection margin of 1 cm should not be a contraindication for surgery. Pawlik analyzed patients according to resection margin (1-4 mm, 5-9 mm i >10 mm), and concluded that there was no statistical difference in survival between these 3 groups of patients (18).

Scheele et al. demonstrated that tumor differentiation, presence of synchronous metastasis, positive lymph nodes and tumor size were associated with worse prognosis. In R0 resections, resection margin less than 1 cm was not associated with worse prognosis and it is today a generally considered that for colorectal cancer liver metastasis recession it is adequate to achieve negative resection margin, while the extent of resection margin does not significantly improve five year survival (19). Therefore, the rule of 1 cm that was established in 1980s is no longer valid and the inability to achieve resection margin of at least 1 cm is no longer a contraindication for resection of colorectal cancer liver metastasis.

Treatment of unresectable metastases

Certain techniques can be employed in patients with inoperable metastasis that can render those metastasis operable. These methods include portal vein embolization or ligation, two-stage liver resections, resections combined with ablation and tumor volume reduction using preoperative chemotherapy.

Portal venous ligation or embolization can be used in patients in whom it is estimated that postoperative functional liver volume will be too small. Portal venous embolization was first performed in 1982 by Makuuchi and colleagues. Portal embolization is performed by selective cannulation of the main branch of portal vein. Portal vein embolization causes redistribution of blood into the collateral lobe causing its hypertrophy as well as atrophy of the embolized lobe. Instead of embolization it is also possible to perform ligation of the main branch of portal vein (20, 21). The mortality of two portal vein embolization is sporadic and the

complications are seen up to 18% (22, 23).

Hypertrophy of the contralateral lobe, that usually occurs within a month, results in a sufficient residual volume of the liver. However in patients with multiple bilobar metastases, portal venous embolization can lead to quicker growth of metastases in the contralateral lobe. In these cases, two-stage resection is often employed. During the first surgery, metastasis are removed from one lobe of the liver and embolization or legation of the main branch of the portal vein for the contralateral lobe is performed. After liver hypertrophy, the second surgeries performed that includes the removal of residual metastases.

Postoperative mortality (7%) and morbidity (59%) after second century is still greater than after first surgery (0% i 20%)(24). Still, in spite of high morbidity, 3 year survival after such procedure is approximately 35% (22).

Timing of liver resection

Untreated patients with colorectal cancer liver metastasis have very poor prognosis. Former standards of surgical treatment included delayed resection of synchronous metastases after a period of 3 to 4 months (4). This approach enabled better evaluation of the progression of disease and selection of patients with better prognosis and slower growing tumors. Resection of colorectal cancer liver metastases after the resection of primary tumor avoids one extended surgical procedure, and time between two surgeries enables better selection of patients as well as selection of patients with inoperable extrahepatic disease. However from the oncological standpoint, such an approach is questionable. The advancement of surgical techniques rendered liver resections safe (4). Also, initially operable isolated metastases may become inoperable due to the invasion of the adjacent structures or the occurrence of "secondary metastases", which can be avoided by single stage surgery.

TECHNIQUES OF LIVER SURGERY

From the technical side liver resection represents a special challenge because this organ contains a complex of biliary and vascular structures. The knowledge of hepatic anatomy is therefore essential for safe liver surgery. Liver resection itself can be divided to the resection of liver parenchyma and resection of vascular and biliary structures.

Anterior approach

In the case of a large metastasis in the right lobe, classical mobilization of the right lobe may be difficult and there is a danger of the lesion to the diaphragm and lungs. Also, larger right lobe is difficult to rotate, and even if rotation is possible it may cause pressure to the v. cava, causing inflow reduction and subsequent drop in blood pressure. Furthermore, forceful manipulation with the liver during mobilization may push malignant cells into the bloodstream which represents the risk for further systemic spread of malignant disease and endangers the concept of oncology radical surgery that requires minimal manipulation with the tumor (25). It is therefore often impossible to fully mobilize the right lobe in cases of large metastasis. In these cases it is possible to perform liver resection even without the mobilization of the right lobe.

In recent years the technique of our team approach demonstrated sufficient safety. In this technique, intraoperative ultrasound is often used to confirm the location of the medial liver vein. The decision itself starts with the section on the ventral side of the liver, just to the right of the middle liver vein that must be preserved in order to secure blood outflow from the fourth segment that functionally belongs to the left lobe. Only after the dissection of parenchyma the ligation of the right portal vein is performed.

Some studies demonstrated that the level of tumor mRNA in blood is significantly greater during classical mobilization of the liver as compared to the anterior approach and is considered as a significant prognostic factor (25).

Methods of parenchymal dissection

The oldest and method of the resection of liver parenchyma is so-called "finger fracture" method. In this technique liver parenchyma is gently crushed between fingers and vascular and biliary structures are then selectively ligated and dissected (26). More modern devices for parenchymal resection are ultrasonic dissector (CUSA) (27) i and water jet dissector (28). Ultrasonic dissector contains a high frequency vibrating tip that breaks the liver parenchyma as well as the aspirator that aspirates and removes broken the liver tissue. High frequency vibrations of this device do not damage blood vessels and biliary structures that can be selectively ligated (27).

As opposed to the ultrasound dissector that has a high price, water jet dissector washes liver parenchyma with a high pressure water, also without causing the damage to blood vessels or biliary structures that also need selective ligation as well as

is the case with ultrasound dissector (28).

These modern devices and methods significantly improved liver resection. However, because of well vascularized liver parenchyma, selective ligation of blood vessels and biliary structures can significantly prolong the operation.

Coagulation methods of liver transection

As opposed to previously mentioned methods and devices for liver dissection, today there are available devices that enable simultaneous dissection of liver parenchyma, as well as coagulation of blood vessels and biliary structures up to 7 mm in diameter (29).

High frequency monopolar current is the oldest method for coagulation of blood vessels (30). During the use of monopolar instruments, high frequency current passes through the body, that does not disturb normal neural signals regardless of the voltage. Electrical circle is closed between the instrument used for coagulation and so-called neutral electrode that has a high surface contact with the body. Since the amount of heat that has developed by passing the electric current through the body is inversely proportional to the surface of the current, larger surface of the neutral electrode avoids the occurrence of high temperatures that can damage and the tissue. Therefore, the tip of instruments used for coagulation is small, resulting in a high temperatures that leads to dissection of tissues, but also often leads to necrosis (31). During the use of monopolar instruments the current passes through the body from one electrode to another on the path of smaller resistance so that the path of the current is not always easy to predict. This method therefore causes local heating and damage of tissues and possible sparking increases the risk of damage to the internal organs (32).

Instruments for bipolar coagulation reduce the risk of thermal lesion because these instruments contain two electrodes so that the passage of electric current between electrodes can be precisely controlled. Conventional bipolar electro-surgical technology is there for safer than the use of monopolar energy because the passage of electric current between two electrodes reduces the risk of thermal lesion. Bipolar coagulation enables the surgeon to work with weaker currents that reduces the influence on other organs (30).

LigaSure is an example of the instrument that uses bipolar electrodes for tissue coagulation with added pressure during coagulation (29). This combination of precise bipolar coagulation produced by high frequency low voltage current and tissue pressure leads to denaturation of collagen and elastin in the walls of blood vessels that increases the safety of vessel sealing (33). Most instruments that use this technology utilize tissue resistance feedback information to regulate the dose of applied energy (34). Because of the system of feedback information, lower energy can be applied and some studies showed that these instruments cause less tissue damage as compared to conventional bipolar devices (35).

TECHNIQUES FOR REDUCING INTRAOPERATIVE HEMORRHAGE

Bleeding during liver resection represents one of the major technical surgical problems. Since the liver is extremely vascularized organ, it is the bleeding that caused a major concern for surgeons in the past. Today there are several methods that are used to control hemorrhage during liver resection, and these methods are often combined.

Control of central venous pressure

Control of central venous pressure represents extremely important method to reduce intraoperative hemorrhage during liver resection. Venous outflow of the liver is comprised of three major liver veins that flow into the inferior vena cava on a short segment between the diaphragm and that the liver surface. This area is located at the back of the liver and therefore it is necessary to mobilize the liver in order to control venous outflow from the liver. Lesions in this area during major resections may result in fatal hemorrhage. By lowering the central venous pressure to values between 0 and 2 cm of water significantly reduces hemorrhage from liver veins and makes the resection much easier (36).

There are several ways to achieve low venous pressure. One day before surgery the input of liquids is controlled in order to reduce volume overload. Author induction into anesthesia and intubation, it is useful to place the catheter into the right atrium for precise measurements of central venous pressure. This catheter can also be used for rapid restoration of volume and blood in the case of significant intraoperative hemorrhage. During liver resection the infusions of electrolytes should be avoided. If these methods can not reduce central venous pressure, nitrates can be given. After the resections finished, it is necessary to increase central venous pressure in order to detect possible bleeding sites. Since the venous pressure in the liver is low, minimal compression can stop the bleeding and the increase in central venous pressure after dissection

is valuable to detect open blood vessels (36).

Although this method is technically simple, it can represent a great challenge to the anesthesiologist especially in patients of older age or in patients with cardiac diseases who have a low tolerance to hypovolemia or hypervolemia (37).

Partial vascular occlusion and total vascular exclusion

Blood enters the liver through the portal vein and common hepatic artery that are contained in hepatoduodenal ligament. Stopping the blood inflow in the liver effectively reduces the bleeding during liver resection. Because it is easily accessible during surgery the occlusion of portal vein and common hepatic artery is the simplest and oldest method to control bleeding from liver. This method was first introduced by Pringle and is therefore called the Pringle maneuver (38).

The occlusion of blood inflow into the liver may have negative consequences for the liver itself and even cause of liver failure. Therefore, the Pringle maneuver must be used with caution. It has been demonstrated that the application of Pringle maneuver in healthy liver will not have negative effects of the liver even if it lasts over one hour. However, in damaged and cirrhotic liver, negative effects of Pringle maneuver is much more pronounced so in patients with liver cirrhosis the Pringle maneuver should be avoided (39).

One of the methods to reduce the negative effect of Pringle maneuver on the liver is so-called liver preconditioning. This procedure consists of short term application of Pringle maneuver and subsequent restoration of blood flow.

In everyday practice, longer duration of Pringle maneuver is seldom applied, and series of 15 minutes occlusion with 10 minutes of blood flow restoration are more frequently used.

With modern techniques of liver resection the surgery can be performed much faster so that Pringle maneuver lasting longer than 15 or 30 minutes is very infrequent even for extensive resections (40).

During central liver resection there is a danger of significant bleeding from major hepatic arteries as well as a retrohepatic veins. In order to reduce the risk of uncontrolled bleeding in these cases it is possible to use total vascular occlusion. This method completely stops both inflow and outflow of the blood to the liver. The method consists of a Pringle maneuver to prevent blood inflow to the liver while the control of the major hepatic veins, because of their anatomical position, is most effectively achieved by the occlusion of the inferior vena cava in its suprahepatic and infrahepatic portion. This method simultaneously controls also direct retrohepatic veins that drain the blood directly into the inferior vena cava (41). Total vascular occlusion can control bleeding from the liver entirely, regardless whether it's the bleeding from the branch of liver artery or portal vein, and also controls retrograde bleeding from liver veins and direct hepatic veins. During local vascular exclusion it is necessary to avoid negative effects of liver ischemia (41).

Local hemostatics

Sometimes, after liver resection, there is a small arterial or venous bleeding, or small biliary leak (42). In these cases the application of local hemostatics is of great help as they effectively stop these minor bleedings and prevent the formation of subphrenic hematoma that many develop into an abscess. Today there are several types of local hemostatics. The simplest local hemostatic is a surgical gauze. As a foreign body, it activates the coagulation system and stops the bleeding. However, if coagulation factors have already been depleted, which can happen in extensive bleeding, it is sometimes necessary to leave the surgical gauze in the abdomen as a tamponade. The gauze is left in place until the coagulation system normalizes, but no more than 48 hours, to prevent the formation of abscess.

Today there are many kinds of local hemostatics other than surgical gauze. Some of them are made of cellulose that can be dissolved and is therefore not required to be removed, but strong activities the system of coagulation. There also hemostatics that contain animal or human coagulation factors (fibrinogen and thrombin) that may be impacted into cellulose or are applied as a liquid form (so-called fibrin glue). These hemostatics are extremely effective in stopping more pronounced bleedings or in cases when coagulation factors have been depleted (43).

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