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• REVIEW •

Current treatment for liver metastases from colorectal cancer

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Abstract

The liver is the commonest site of distant metastasis of colorectal cancer and nearly half of the patients with colorectal cancer ultimately develop liver involved during the course of their diseases. Surgery is the only therapy that offers the possibility of cure for patients with hepatic metastatic diseases. Five-year survival rates after resection of all detectable liver metastases can be up to 40 %. Unfortunately, only 25 % of patients with colorectal liver metastases are candidates for liver resection, while the others are not amenable to surgical resection. Regional therapies such as radiofrequency ablation and cryotherapy may be offered to patients with isolated unresectable metastases but no extrahepatic diseases. Hepatic artery catheter chemotherapy and chemoembolization and portal vein embolization are often used for the patients with extensive liver metastases but without extrahepatic diseases, which are not suitable for regional ablation. For the patients with metastatic colorectal cancer beyond the liver, systemic chemotherapy is a more appropriate choice. Immunotherapy is also a good option when other therapies are used in combination to enhance the efficacy. Selective internal radiation therapy is a new radiation method which can be used in patients given other routine therapies without effects.

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INTRODUCTION

Colorectal cancer is one of the commonest solid tumors in human beings and is responsible for approximately 10 percent of the cancer death in Western world[1-5]. The incidence of colorectal cancer is also increased recently in China[6-8]. The liver is the commonest site of distant metastasis in this disease and nearly half of the patients with colorectal cancer ultimately develop liver involved during the course of their diseases. Treatment of primary colorectal cancer with surgical resection, combined with chemotherapy and radiotherapy in some cases, is effective in many patients. But, about 10-25 % patients had liver metastases at the time of primary diagnosis and another 20-25 % patients developed metachronous liver metastases[9-12].

Death of colorectal cancer is often a result of liver metastases. Over half patients died from their metastatic liver diseases. Surgical resection of distant metastases in colorectal cancer can produce long-term survival and cure in some selected patients. Surgery is the only therapy that offers any possibility of cure for the patients with hepatic metastatic diseases. The five-year survival rates after resection of all detectable liver metastases can reach up to 40 %. Unfortunately, only 25 % of the patients with colorectal liver metastases are candidates for liver resection, while the others are not amenable to surgical resection. Chemotherapy and some newer therapies are expected to raise the survival time for the unresectable colorectal liver metastases[13-15].

This article reviews the natural history of colorectal cancer liver metastases, pretreatment assessment of patients, surgical resection of liver metastases, systemic and hepatic artery chemotherapy (hepatic artery infusion, HAC, HAI), hepatic artery chemoembolization, portal vein embolization, immunotherapy and selective intra-artery radiation therapy (SIRT), and other regional therapies, including cryotherapy, radiofrequency ablation (RFA).

NATURAL HISTORY

Understanding the natural history of colorectal cancer is useful to assess the value of various treatments. About 60 % patients who underwent curative surgery for colorectal cancer will develop local, regional, or distant recurrence. Nearly 85 % of tumors recurrence are detected within 2.5 years after resection of primary colorectal cancer, and the remaining 15 % are detected within the next 2.5 years. Median survival for these patients was found to be between 5 and 9 months[16,17]. However, the majority of patients in former studies had advanced diseases diagnosed without modern imaging techniques. Several previous studies have retrospectively determined the survival of patients with potentially resectable colorectal cancer liver metastases that left untreated. It was found that a 0 % five-year survival for patients with untreated but potentially resectable liver metastases compared with a 28 % five-year survival for operated patients with resected liver metastases[18]. Another study found that patients untreated but potentially resectable liver metastases had a mean survival of 21.3 months[19]. Other study found patients with an untreated single liver metastasis had a median survival of 19 months, with no patients surviving 5 years, while patients with a resected single liver metastasis had a median survival of 36 months with 25 % of patients surviving five years[20]. It is well known that resection of colorectal cancer liver metastases improves long-term survival.

PRETREATMENT ASSESSMENT

Synchronous liver metastases from colorectal cancer may be detected before operation or during operation. Suspicious liver lesions should be biopsied and send to freezing pathology during the operation. Metachronous liver metastases may be found after the operation of colorectal cancer by physical examination, blood test, and radiological imaging. Further evaluation of patients with colorectal cancer liver metastases depends on the available treatment procedures. If the patients are not suitable to operation, confirmation of the presence of metastatic lesions by ultrasound and CT scan is sufficient, no

matter of number and size of the lesions. If patients are candidates for surgical resection of liver metastases, a series of examinations should be done to determine the liver function and general condition to tolerate liver resection, to delineate exactly the anatomy of the lesions including the number, size and relationship with vessels and bile ducts, and to exclude the presence of extraheapatic disease.

Candidates for surgical resection of colorectal cancer liver metastases should be under a detailed history and physical examination, hematology test, liver function test, chest X-ray, and abdominal and pelvic CT scans. Patients should undergo colonoscopy to rule out the recurrence of the original primary colorectal cancer or development of a second primary colorectal cancer, if they had not already done within the past 6 months. A range of imaging techniques, including transabdominal ultrasound, CT scan, CT arterioportography (CTAP), magnetic resonance imaging(MRI), and positron emission tomography (PET) can provide information of liver metastases and extrahepatic diseases[21]. Transabdominal ultrasound examination of liver correctly identifies around 52-58 % of patients who had liver metastases. Ultrasound may be most appropriately used because it is cheapest and readily available. But transabdominal ultrasound plays no role in the preoperative evaluation of potential liver resection candidates[22-24]. Abdominal CT scan is mostly used for the assessment of liver metastases, in which images are usually hypoattenuated relative to normal liver. The use of intravenous contrast increases the detectability of liver metastases because normal liver is perfused primarily by portal vein and liver metastases are perfused mostly by hepatic artery. Hypoattenuated liver metastases are more easily recognized following the intravenous contrast on CT scan during the portal venous phase. The sensitivity of helical CT of liver metastases was 80 %[25,26]. We often used more sensitive CT arterioportography (CTAP) which is an invasive method to investigate the metastatic liver lesions. We firstly placed a catheter into the superior mesenteric artery and then captured the liver CT images during the arterial and portal venous phase following contrast injection. The overall sensitivity for detection of liver metastases helical CTAP exceeded 90 %. But, perfusion abnormalities and pseudolesions were frequently observed with CTAP, thereby significantly reducing the specificity of this technique[27-29]. Magnetic resonance imaging (MRI) is increasingly utilized for the diagnosis and characterization of liver lesions, particularly the liver-specific contrast agents and dynamic scanning have been incorporated. One liver-specific contrast agent, manganese-pyridoxal diphosphate (Mn-DPDP), is a paramagnetic agent taken up preferentially by hepatocytes and excreted in the bile. The popularity of MRI is also due to its non-invasiveness in some centers[30,31]. PET is a newer technique which can scan the whole body. It is mainly used to rule out the potential extrahepatic diseases which could not be identified by other methods before operation[32,33].

Laparoscopy is usually used for preoperative evaluation of metastatic liver diseases. Laparoscopy with laparoscopic ultrasound may be the most sensitive imaging technique for detection of liver metastases. Laparoscopy can prevent laparotomy in some unresectable cases with liver metastases which were judged resectable preoperatively by conventional imaging studies[34]. But it is still an invasive procedure which need general anesthesia. Therefore, laparoscopy was not routinely used unless the resectablity of the lesions was not determined by other methods.

SURGERY

Patients without extrahepatic diseases and with good liver function and general condition are candidates for surgical resection, while all liver metastases can be resected with at least 1 cm tumor-free margin. Up to 75 % of the liver can be removed if the liver function is normal. Recognition of the segmental basis of liver anatomy led to the evolution of the segment-based resection. This has had a particular influence on surgery for colorectal metastases because it allows excision of bilateral or multiple liver lesions that might previously have been deemed unresectable. Staged resection is another means and may be useful for bulky bilateral lesions. In fact, one or more segmental resections can often spare more normal liver than a major resection or allow resection of metastases not encompassed by a traditional major resection[35-39].

The surgical resection of liver metastases from colorectal cancer first involves an exploratory laparotomy through a right subcostal incision. The abdominal cavity is explored for signs of extrahepatic disease, and suspicious areas are biopsied. The liver is fully mobilized by dissection of its supporting ligaments and palpated to identify lesions. Intraoperative ultrasound is used at this point to identify nonpalpable lesions and delineate vascular anatomy. No matter traditional liver resection or segmental resection is performed, the goal of the operation is complete removal of all metastases with at least a 1cm tumor-free margin. Although there are various methods of dividing hepatic parenchyma, I prefer using ultrasonic surgical aspirator in normal liver and a combination of ultrasonic surgical aspirator and clamp fracture in cirrhotic liver. Small vessels are controlled with electrocautery or hemoclips, and large vessels are controlled with sutures. An argon beam coagulator can also be used to achieve hemostasis in resection margin[40-42].

Vascular occlusion techniques, particularly the Pringle maneuver, have had a major impact in minimizing blood loss and reducing the morbidity associated with liver resection. Selective vascular occlusion has been popularly accepted in segment resection in patients with limited liver function. Total vascular exclusion has become widely accepted as a means of minimizing blood loss when we operated on difficult lesions. Although few surgeons use total vascular exclusion routinely, it is a technique that facilitates excision of lesions involving the vena cava or those lying near the junction of the hepatic veins and the vena cava. Some lesions which were previously been thought unresectable can now be resected with the reconstructed segments of hepatic inflow or outflow vascular structure. Replacement of hepatic vein and vena cava with autologous vein and prosthetic grafts respectively had been fasciliated by the use of total vascular exclusion and a number of techniques of liver transplantation. The use of venovenous bypass in combination with *in situ* hypothermic perfusion and *ex situ* resection and autotransplantation, have both been important additions to the liver surgeons[43,44].

The operative mortality for major liver resections has declined with improved operative techniques and postoperative care, but still significant. Operative mortality ranged from 0 % to 7 %. The causes of death include hemorrhage, sepsis, and liver failure. The Morbidity of liver resection was between 22-39 %, and the causes of morbidity included hemorrhage, biliary leak or fistula, liver failure, abscess around liver, wound infection, and pneumonia. Median survival ranged from 28 to 46 months. The five-year survival was between 24 % and 38 %[45-48].

How many lesions are too many in colorectal cancer liver metastases underlying liver resections? Many surgeons consider four or more tumors in the liver to be a contraindication for surgical resection before. But more and more authors think that the number was not a limitation in liver resection of colorectal cancer liver metastases with the use of new techniques. The follow-up showed that there was no significant difference in the mortality, morbidity and five-year survival between patients whose lesions more than four and those less than four[49].

RADIOFREQUENCY ABLATION (RFA)

The so-called RF thermal ablation works by converting RF waves into heat. A high-frequency alternating current (100 to 500 kHz), mostly 460kHz, passes from an uninsulated electrode tip into the surrounding tissues and causes ionic vibration as the ions attempt to follow the change in the direction of the rapidly alternating current. This ionic vibration causes frictional heating of the tissues surrounding the electrode, rather than the heat being generated from the probe itself. The goal of RFA is to achieve local temperatures to make tissue destruction occur[50-55]. Tissue heating also drives extracellular and intracellular water out of the tissue and results in further destruction of the tissue due to coagulative necrosis. Besides these, different studies have shown that hyperthermia can cause accelerated emigration and migration of peripheral blood mononuclear cells, activation of effect cells, induction and secretion of cytokines, expression of heat shock proteins, and increased induction of apoptosis[56-58].

Most of the early reports on the use of RFA for colorectal cancer liver metastases came from Rossi in Italy. In 1996, they reported their results with percutaneous RFA in 50 patients, of whom 11 patients had 13 metastases ranging from 1 to 9 cm in diameter. Monopolar and bipolar needles were utilized and multiple probe insertions and treatment sessions were performed. There were no associated complications or deaths. Of the 11 patients with metastases, two underwent subsequent surgical resection, one of them had complete tumor necrosis by histopathologic examination. At a median follow-up of 22.6 months, 10 (90 %) of 11 patients were alive, two (18 %) had a local recurrence and seven (64 %) had persistent or distant disease. Only one (9 %) patient, therefore, was alive without disease. These studies suggested that although RFA was effective in preventing local recurrence of metastases, it may not affect the progressive course of the cancer[59].

Wood TF reported 231 tumors in 84 patients treated with 91 RFA procedures. The majority of the patients had metastatic lesions (213 lesions in 73 patients). RFA was given in 51 of the 91 treatments alone. The other 40 included RFA combined with surgical resection, cryoablation, and hepatic artery infusion of chemotherapy. Of the 91 RFA treatments, 39 were ablated at laparotomy, 27 by laparoscopy and 25 percutaneously. Tumors ranged in size from 0.3 to 9.0 cm. Three deaths occured, one (1 %) of which was directly related to the RFA procedure. Ten patients underwent a second RFA procedure (sequential ablations). It is due to progressive (seven patients), and recurrent (three patients) lesions. A third RFA procedure for large was performed in one patient. At a median follow-up of 9 months (range 1-27 months), 15 (18 %) patients had developed a local recurrence. Of the remaining 69 patients, 34 were alive without disease, 14 were alive with disease, and 21 died. New hepatic tumors or extrahepatic diseases occured in 35 patients. The average hospital stay was 3.6 days[60].

Although RFA has a lot of advantages in the treatment of metastatic liver tumors, it still has a few disadvantages and complications. These complications included symptomatic pleural effusion, fever, pain, subcutaneous hematoma, subcapsular liver hematoma, and ventricular fibrillation. The severe complication is treatment-related death. Interms of the methods related to tumors, the outcome of RF thermal abalation involves the skill of a surgeon performing the procedure. Exact placement of the ablation needles requires considerable skill and some degree of guess work by the radiologist and surgeon, who may be the most experienced in interventional procedures. Recurrence at the treatment margin may result from an inability to adequately kill the tumor the hepatic parenchyma adjacent to the treated tumors. The abundant portal venous blood flow present in normal hepatic parenchyma acts as a heat pump, which makes the creation of thermal injury in normal liver more difficult than that it is in liver tumors. RF also caused skin burn in percutaneous procedures, hemorrhage, diaphragmatic necrosis, hepatic abscess, hepatic artery injuries, bile duct injuries, renal failure, coagulopathy and liver failure, which were severe and eventually fatal[61-64].

Although long-term observations are not available, RFA will definitely give the surgeon a helpful hand and bring the patients a better prognosis. But, RFA is unlikely to be curative for most patients, it can relieve the symptoms of patients and improve the quality of life of patients. RFA has been shown to be safer and better tolerated as compared with other ablative techniques, such as cryotherapy, laser ablation and microwave ablation. RFA has been associated with fewer local recurrence. RFA for unresectable liver tumors provides a relatively safe, highly effective method to control local disease in some liver metastatic patients who are not candidates for liver resection. RFA also showed some better respect in combination with surgical resection, hepatic artery chemotherapy. The most interesting feature of RFA is the minimal-invasiveness with zero mortality rate, significantly lower complications, reduced costs and hospital days compared with surgery and other therapies. Furthermore, in combination with other procedures, RFA will improve the survival of patients with colorectal cancer liver metastases[65,66].

CRYOTHERAPY

Cryotherapy has been mostly used as a regional therapy all over the world for a long time[67,68]. Hepatic cryotherapy involves the freezing and thawing of liver tumors by means of a cryoprobe inserted into the tumors. During freeze/thaw cycles, intracellular and extracellular ice formation occurs in an area termed "the iceball", leading to tumor destruction. Hepatic cryotherapy is generally reserved for patients with liver metastases from colorectal cancer in whom one or more lesions are not surgically resectable. Some centers offer liver cryotherapy as an alternative to surgical resection[69-71]. Cryotherapy can treat multiple lesions and salvages more uninvolved liver parenchyma than surgical resection. Cryotherapy may also be used to treat tumors intimately associated with major vessels. But, major vessels may serve as "heat-sinks" and prevent adequate freezing of immediately adjacent tumors. Hepatic inflow occlusion may reduce the incidence of inadequate freezing of tumors adjacent to large blood vessels. Cryotherapy can also treat patients who are left with a positive surgical margin after hepatic resection which is called "edge cryotherapy". Cryotherapy can also be used in patients in whom underlying illness or hepatic insufficiency precludes surgical resection[72-74].

Hepatic cryotherapy is performed by making an abdominal incision, followed by exploration of the abdomen to search for extrahepatic metastases. Intraoperative ultrasound is used to identify and assess intrahepatic lesions[75,76]. For superficial lesions, a cryoprobe can be placed into the center of the lesion under direct vision. For deeper lesions, the probe can be inserted into the center of the tumor under ultrasound guidance. Sometimes two or three probes may be used for large lesions. Freezing is continued until the iceball is at least 1 cm beyond the tumor. Two or three cycles should be performed or combine freezing with occlusion of hepatic inflow to increase tumor destructive ice ball and negative edge of ice ball in some lesions. It can also be done percutaneously under the guide of ultrasound and CT scan[77].

The complications of cryotherapy include subsequent hemorrhage of cracking frozen liver, bile collection, biliary fistula, right-sided pleural effusion, liver abscess, thrombocytopenia, myoglobinuria, arrhythmia, acute renal failure, and cryoshock due to multi-organ failure with DIC.

Overall morbidity rates range from 6 % to 29 %. Mortality rates range from 0 % to 8 %, with an overall mortality rate of 1.6 %. Median survival ranged from 8 to 43 months. New or improved liquid nitrogen delivery systems and together with intraoperative ultrasound have led to significant advances in cryotherapy over the past few years and its feasibility and safety are now well accepted. Although long-term survival following hepatic cryotherapy for liver metastases from colorectal cancer is unclear, hepatic cryotherapy is still an option for patients who are not candidates for surgical resection but enough to cryoablation of all lesions. Cryotherapy is also an important supplement of surgical resection and benefitial to the patients with liver metastasis from colorectal cancer when combined with surgery[78,79].

HEPATIC ARTERY CHEMOTHERAPY

Following resection of liver metastases from colorectal cancer, recurrence will occur in 60-70 % of patients, most commonly in the liver, so effective postoperative adjuvant treatment is also required, during which chemotherapy is the main method. Chemotherapy is also required in unresectable liver metastases to sustain the survival rate[80-83]. However, the optimum regimen and route of delivery should be clarified. As most drugs have a steep dose-dependent curve, it is a basic pharmacokinetic principle that if drug delivery is increased to tumors, the response rates can be elevated. An alternative approach to liver metastases is therefore, to deliver the drug intra-arterially[84,85]. Hepatic artery catheter chemotherapy has been a therapeutic possibility for unresectable liver metastases for many years. The rational for hepatic artery catheter chemotherapy is based on the fact that liver metastases over 1 cm derive most their blood supply from hepatic artery. The other rational is the high first pass hepatic extraction of the drug used for this approach. Both factors cause high local drug concentrations with reduced systemic toxicity and allow relatively higher dosages as compared with intravenous treatment[86,87].

Some studies compared intra-arterial chemotherapy with conventional systemic chemotherapy and showed consistently higher response rates in patients receiving intra-arterial chemotherapy[88]. In the United Kingdom, patients were randomized to receive intra-arterial chemotherapy through a totally implantable infusion device; patients were given systemic chemotherapy in other group. Survival was significantly longer in the intra-arterial group (median survival 405 days compared with 226 days). The intra-arterial group also had a better quality of life than those received systemic chemotherapy[89]. Other studies showed that the response rate was 43 % in the intra-arterial group compared with 9 % in the systemic chemotherapy group. Furthermore, the intra-arterial group showed a significant increase in the one-year survival (64 % *vs* 44 %) and two-year survival (23 % *vs* 13 %). Other studies also showed a higher response rates in intra-arterial chemotherapy than in systemic chemotherapy[90].

In all studies, 5-FU and FUDR were chosen for the arterial route of administration. As 84-99 % of FUDR is extracted by the liver on first pass, it seemed logical to use FUDR to achieve the dual objective of high levels within the tumor and low plasma levels, thereby increasing the probability of the tumor' s response while minimizing the systemic toxicity[91]. But 55 % of patients using FUDR in the UK and French studies developed extra-hepatic progress, suggesting that these patients may have had occult extra-hepatic disease at the time of entry into the trial or during the intra-arterial chemotherapy. The lower plasma level of drugs has been misplaced, while 5-FU, which has a higher plasma level than FUDR, should be preferred. Although there are some complications in HAC, it is still a feasible method for liver metastases from colorectal cancer. Most complications was related to the technique of surgery and care of patients[92].

Comparison of intra-arterial with systemic chemotherapy is an important topic that has not been resolved adequately. Some groups were unable to detect any difference in recurrence of hepatic colorectal metastases after liver resection among groups treated with systemic, intra-arterial or intra-portal chemotherapy. There are a lot of new agents such as Xeloda, currently being assessed as adjuvant treatment for both primary colorectal cancer and following resection of metastatic liver lesions[93-102].

HEPATIC ARTERY CHEMOEMBOLIZATION

Hepatic artery chemoembolizaton (HACE) was developed to treat unresectable non-disseminated liver tumors[103,104]. Although HACE has not shown any benefit on survival, it increased the response rate compared with systemic administration of cytotoxic agents. HACE has been studied mostly in the treatment of hepatocellular carcinoma, which was also used in colorectal cancer liver metastases for some clinical trails[105]. Preoperative HACE has been proposed as a possible means of decreasing perioperative tumor dissemination, but only in a small number of patients. Some centers reported that HACE in patients with borderline resectable tumors caused sufficient tumor shrinkage to allow resection. Routine HACE produced no survival benefit on patients with resectable tumors. It was only used in unresectable tumors as an adjacent treatment[106,107].

PORTAL VEIN EMBOLIZATION

Preoperative portal vein embolization induced hypertrophy in the normal liver which will be remnant and decreased the likelihood of liver insufficiency occurring after extensive liver resection[108,109]. It has not only mostly used in cholangiocarcinoma but sometimes used in liver metastases from colorectal cancer. Portal vein embolization may be performed either by percutaneous ultrasonographically guided puncture of a portal vein radical or by operative exposure of an ileocolic vein to access portal vein. It can not only be performed in the right portal vein to allow the left side hypertrophy in those who will receive right hepatectomy, but also in left portal vein to allow the right side hypertrophy in those who will receive extend left hepatectomy. Portal vein embolization was well tolerated and produced a less severe systemic reaction than intra-arterial chemoembolization[110-113].

IMMUNOTHERAPY

Immunotherapy is mainly used in advanced diseases which have failed to respond to conventional therapy. Levamisole, a non-specific immune stimulate, was used in adjunctive treatment with 5-FU as a immune modulator[114]. More exploration of different combinations may provide new adjuvant regimens. Some scientists have recently reported a phase I-II clinical trial of neoadjuvant immonotherapy with interlukin 2 before hepatectomy for liver metastases from colorectal cancer in 19 patients. Pretreatment with interleukin 2 prevented the postoperative immunodepression seen in the control patients[115,116]. Clinical trials have also shown that the monoclonal antibody 17-1A was effective in increasing the survival following resection of Dukes C primary colorectal tumors. It can also be used as an adjuvant treatment before or after liver resection for liver metastases from colorectal cancer[88,117-119].

RADIOTHERAPY

Traditional external beam irradiation has found little place in

the management of liver tumors because of the particularly radiosensitive nature of normal liver tissues, which limits the total dosage to 30-35 Gy[120-122]. Selective internal radiation therapy (SIRT) is a new modality that may be valuable in colorectal cancer liver metastatic patients which was not suitable to resection, RFA and cryotherapy. SIRT is a technique that allows high average doses of radiation of 200-300Gy to liver tumors with minimal serious effects on the non-tumorous liver. The treatment entails delivery of usually a single dose of ^{90}Yttrium microspheres into the hepatic artery, which by virtue of the almost exclusive arterial supply to liver tumors compared with the predominant portal supply to normal liver, resulting in selective tumor uptake and irradiation. ^{90}Yttrium is a particularly suitable isotope for medical use in this situation. As a pure beta emitter, it is simpler to handle and use than gamma or mixed beta and gamma emitters such as^{131}iodine[123,124]. In addition, its half-life of 2.7 days and maximum penetration in soft tissues of 11 mm both are suitable for the purpose. The microphereres do not degrade and are of a size of 29-35 μm that means they are trapped in the arteriolar capillaries. To avoid the potential radiation pneumonitis and pancreatitis and ulcaration of stomach and duodenum caused by inadvertent perfusion. The placement of a hepatic artery port is particularly important in terms of safety and efficacy. The high rate of response and encouraging survival from SIRT have been reported for hepatocellular and liver metastases from colorectal cancer[125,126].

CONCLUSION

Patients with liver metastases from colorectal cancer that are potentially resectable should be evaluated by experienced surgeons and radiologists, because surgical resection remains best treatment for long-term survival, although a minority of patients are amenable to the resection. Patients who are not suitable to surgical resection and who have no extrahepatic disease can be considered for regional therapies such as RFA and cryotherapy. Patients with extensive liver metastases, Hepatic artery catheter chemotherapy and chemoembolization can be considered as an alternative to systemic chemotherapy. Portal vein embolization may be combined in the treatment of patients with huge metastases. SIRT should be used for patients without extrahepatic metastases who failed in the treatment with 5-FU and other cytotoxic agents prefer. Systemic chemotherapy should be administered in patients with extrahepatic diseases. Immunotherapy can only be used to amplify the efficacy of antitumor cytotoxic agents in combination.

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