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TOPIC HIGHLIGHT

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Role of surgery in colorectal cancer liver metastases

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Abstract

Colorectal carcinoma (CRC) is the third most common cancer, and approximately 35%-55% of patients with CRC will develop hepatic metastases during the course of their disease. Surgical resection represents the only chance of long-term survival. The goal of surgery should be to resect all metastases with negative histological margins while preserving sufficient functional hepatic parenchyma. Although resection remains the only chance of long-term survival, management strategies should be tailored for each case. For patients with extensive metastatic disease who would otherwise be unresectable, the combination of advances in medical therapy, such as systemic chemotherapy (CTX), and the improvement in surgical techniques for metastatic disease, have enhanced prognosis with prolongation of the median survival rate and cure. The use of portal vein embolization and preoperative CTX may also increase the number of patients suitable for surgical treatment. Despite current treatment options, many patients still experience a recurrence after hepatic resection. More active systemic CTX agents are being used increasingly as adjuvant therapy either before or after surgery. Local tumor ablative therapies, such as microwave coagulation therapy and radiofrequency ablation therapy, should be considered as an adjunct to hepatic resection, in which resection cannot deal with all of the tumor lesions. Formulation of an individualized plan, which combines surgery with systemic CTX, is a necessary task of the multidisciplinary team. The aim of this paper is to discuss different approaches for patients that are treated due to CRC liver metastasis.

Key words: Colorectal cancer; Metastasis; Liver; Prognosis

Core tip: In patients with colorectal liver metastases, surgical resection is the treatment of choice. This paper aimed to discuss the goals of surgery, which should be to resect all metastases with negative histological margins while preserving sufficient functional hepatic parenchyma. The paper also discusses treatment options for patients with extensive metastatic disease who would otherwise be unresectable, such as systemic chemotherapy, radiofrequency ablation and preoperative portal vein embolization combined with surgery.

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INTRODUCTION

Colorectal carcinoma (CRC) is the third most common cancer and the liver is the most common site of colorectal metastasis, of which 15%-20% of patients will be candidates for hepatectomy[1,2]. Approximately one-third of

patients will develop liver metastases within three years after diagnosis[3]. The most common route of dissemination is hematogenous *via* the portal circulation[4,5].

Surgical resection is the current treatment of choice for colorectal cancer metastases isolated to the liver, and has been proven to be the only potentially curative therapy[6,7]. The combination of advances in medical therapy, such as systemic chemotherapy (CTX), and the function of surgery for metastatic disease, have enhanced prognosis with prolongation of the median survival rate and cure[8].

The 5-year survival rates after surgical resection are reported to be as high as 71% for solitary CRC liver metastasis (CRLM)[9]. Using the multidisciplinary approach of surgical resection combined with CTX and portal vein embolization, however, has increased the 3-year survival rate to 60%-86%[3,10].

INDICATIONS FOR RESECTION

The resectability of CRLM includes R0 resection, which includes the sparing of at least two adjacent liver segments having an independent inflow, outflow and biliary drainage. The remnant liver should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients, respectively, and can be predicted precisely by computerised tomography (CT) or magnetic resonance imaging (MRI) in a preoperative setting[11].

CRLM may be classified into three groups according to resectability: (1) Group one: At presentation the liver lesion(s) are clearly resectable; (2) Group two: At presentation, the liver lesion(s) are unresectable but potentially exchangeable to resection after primary CTX, known as conversion CTX; and (3) Group three: At presentation the liver lesion(s) are unresectable and are likely to remain so even with effective CTX[12].

OncoSurge system

The possibility of resection of all liver metastases with negative margins greater than 1 cm and a residual healthy liver volume greater than 20% defines the OncoSurge system. The performance status and the percentage of the remaining healthy liver create the prognostic factors.

The extraliver metastases (hilar lymph nodes, lung, ovary, and/or adrenal metastases) are not contraindications against performing surgery. Currently, approximately 20% of the patients with CRLM can be resected with an estimated 5-year survival of 50%[13]. Advanced age was once perceived as a relative contraindication, but liver resections are now routinely performed for patients in their 70s and 80s[14].

The 2010 guidelines for the treatment of colorectal cancer published by the Japanese Society of Cancer of the Colon and Rectum (JSCCR) list five conditions as criteria indicative for the resection of CRLM: (1) the patient is capable of tolerating surgery; (2) the primary tumor has been controlled or can be controlled; (3) the metastatic liver tumor can be completely resected; (4) there are no extra liver metastases or they can be controlled; and (5) the function of the remaining liver will be adequate[15,16].

In recent years, a number of procedures aimed at improving the rate of surgical resection have been developed. As safety and long-term cancer-related outcomes develop, indications for liver resection have been enhanced correspondingly.

PREOPERATIVE EVALUATION

A staging system was proposed by the European Colorectal Metastases Treatment Group system that divides the CRLM into 4 groups. These include M0: no metastases; M1a: resectable liver metastases; M1b: potentially resectable liver metastases; and M1c: liver metastases that are unlikely to ever be resectable. For both M1a resectable patients and M1b patients who qualify as resectable after systemic treatment, resection offers the possibility of a cure. For the M1c group, the possibility of resection should not be excluded and should be based on each case individually[17].

Multidetector helical CT scans have increased the sensitivity of detecting CRLM to 70%-90% as its resolution has improved[18]. The resected and residual liver volumes can be calculated without difficulty, by tracing the liver regions on transverse CT images and by liver resection simulation using a dedicated 3-D image analysis software[19].

When MRI using contrast agents is compared with the CT scan, no distinctive advantage has been obtained[20]. In the detection of extraliver disease, preoperative staging techniques, such as ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning or laparoscopic staging, has been shown to be effective[21,22]. Using these techniques, the overall management plan maybe modified in up to 20%-25% of patients[11,23]. Sensitivity has been shown to increase from 75% to 89% when CT and FDG-PET are combined, and is considered the gold standard[24].

In patients receiving neoadjuvant CTX, steatohepatitis or liver damage caused by sinusoidal injury may occur. A physician should be aware of the possible side effects caused by CTX. Liver disorders have been found to be associated with an increase in the incidence of perioperative complications of liver resection and of surgical mortality[25,26]. For the purpose of detecting CTX-associated liver disorders, the indocyanine green (ICG) test has been widely used[27]. Pathological confirmation *via* preoperative biopsy should be avoided, as it may cause tumor seeding and has adverse effects on both survival and local control[28].

PROGNOSTIC FACTORS AFTER LIVER RESECTION

The microscopic status of the resected margin is the most important prognostic factor for overall survival, and incomplete tumor removal is often damaging to the

overall long-term outcome. The presence of a positive margin increases recurrence rates, and reduces overall and disease-free survival[11]. The effect on prognosis with extraliver spread has also been shown to be detrimental; however, some research has proven the opposite[29].

A number of factors have been identified in the literature with regards to prognosis after liver resection. The most common factors include: liver portal lymph node metastasis, number of metastases, a positive resection margin, the presence or absence of extraliver metastasis, and synchronicity/metachronicity. Other primary tumor factors consist of the degree of differentiation, depth of wall invasion and positive lymph node metastasis. Metastatic lesion factors, however, include > 4 individual tumors, degree of differentiation (poorly differentiated), and maximum tumor diameter; one surgical factor is a resection margin of < 10 mm; and background factors include high carcinoembryonic antigen (CEA) before hepatectomy and disease-free duration of < 1 year[29,30].

Another important factor effecting prognosis for a patient undergoing liver resection is the response to CTX[31]. A study by Adam *et al*[32] showed that if tumor progression continued whilst receiving CTX (oxaliplatin or irinotecan-based) this was independently associated with decreased survival rate in patients with an objective response, stabilization and progression of a 5-year survival rate of 37%, 30% and 8%, respectively.

Other prognostic factors that remain a subject of debate are the spread to lymph nodes by the original CRC and the maximum size of metastases [29]. Another factor investigated was the interval between the CRC operation and detection of CRLM; while some studies support this[30,33], others contradict it as a predictive factor[34,35]. The difference between synchronously and metachronously presenting metastases has also been investigated and the majority of studies have shown that it lacks prognostic value[29]. Studies have also failed to show bilobar spread as a prognostic factor[29,33,35].

LIVER RESECTION PROCEDURES

The process of resection has proven to be very safe, with an operative mortality < 5%. Recovery is rapid, with a median hospital stay of 5-7 d for minor liver resection and 7-10 d for major resection[6].

Studies have shown that the type of resection, whether anatomical or non-anatomical, is of no consequence, as long as negative histological margins can be accomplished[36]. However, a cautionary note is that during resection, the liver must be preserved as much as possible. The use of non-anatomical resection has certain advantages, such as lower blood loss and shorter duration of hospitalization[37]. If radical resection can be achieved, a better prognosis than that of non-curative resection cases can be expected, even for patients with multiple CRLMs[38]. One of the most important determinants of surgical procedure is the location of the tumor. The difference between surgical procedures for hepatocellular carcinoma and CRLM is that in hepatocellular carcinoma, the tumors can often be peeled off even if they seem to be closely attached to the liver vein or Glisson's sheath. However, in CRLM, forced peeling may cause local recurrence because of the high propensity for infiltration. When metastatic lesions are attached to major vessels, the vessels have to be sacrificed, even if the size of the metastatic lesions is small, sometimes necessitating liver segmentectomy, hemi-hepatectomy, or reconstruction of the liver and portal veins[26,39].

Approaches to CRLM surgery vary from country to country. In western countries, a more common procedure is simple hemi-hepatectomy, usually because of normal liver function, because it confers sufficient tolerance to surgery, and its technical ease. In contrast, in Japan, non-anatomic partial resection is more commonly used, even in patients with multiple tumors; the purpose is to leave as much residual liver volume as possible[26]. When multiple metastatic lesions occur in one lobe of the liver and/or when infiltration is observed in the major Glisson's sheath, liver segmentectomy or hemi-hepatectomy, is required. When the residual liver volume is estimated to be insufficient, preoperative portal vein embolization should be considered[26], and is advised in patients where the degree of surgical resection will result in a liver volume of less than 25%-40%, which is less than the optimal functional liver to prevent postoperative liver failure[11]. This treatment increases the expected residual liver volume by approximately 20%-40% in 2-4 wk[40,41].

Criteria for the residual liver volume may vary depending on what is considered acceptable in terms of surgical mortality and complication rates, and 20% residual liver volume is considered to be sufficient in some facilities[42]. In patients who were otherwise considered unresectable, a 2-stage hepatectomy procedure, with or without portal vein occlusion, has been shown to allow a curative resection in up to 20% of patients. However, approximately 20%-30% of these patients will not complete the 2nd-stage resection because of disease progression[43]. Since the preliminary description of 2-stage hepatectomy, this new surgical strategy has confirmed its effectiveness in improving the resectability rate of patients with multiple bilateral liver metastases not resectable by single hepatectomy[44,45].

The two-staged hepatectomy utilizing PVE alongside CTX allows for a major colorectal resection with minor wedge resection in the first stage and major hepatectomy in the second stage[10]. Although this procedure has been shown to be successful, a major downside of the 2-stage procedure is that there is a 30% dropout rate because of disease progression of the disease after the 1st-stage hepatectomy. A potential explanation for early disease progression has been investigated in some experimental studies, which showed that both liver resection and portal vein occlusion result in an increased expression of growth factors and residual CRLM[43].

In recent years, the choice of resection procedure has been determined by considering the areas of congestion

caused by resection of the major liver veins. When the expected residual liver volume is less than the required volume, reconstruction of the liver vein is taken into consideration[26,46].

SIMULTANEOUS COLO-RECTAL AND LIVER RESECTION FOR SYNCHRONOUS METASTASES

There are two strategies with respect to the timing of liver resection for synchronous CRLM. One of these methods is resection at the same time as the primary tumor is removed; this is termed as synchronous resection. The second is performed 2-3 mo after removal of the primary tumor and the resection is performed if curative liver resection is possible, termed as metachronous resection[16]. The choice of method is debatable. If the primary CRC has been removed, a delay in resection of synchronous secondaries is justified by the need to recover from the primary resection, or if the patients have comorbidities that require optimization of medical condition. If the patient has synchronous primary and metastatic disease that can be safely removed in the same operation, a combined resection is justified[47].

In a study from the Memorial Sloan-Kettering Cancer Center, total hospital stay and blood loss were reduced in the simultaneous resection group, with no sacrifice in mortality or complications. The outcomes of the patients undergoing major liver resections were also clearly superior to the patients with a sequential operation[47].

Reddy *et al*[48] reported on the experience of simultaneous resections, and demonstrated that combining minor liver resection with resection of the colorectal primary shortened total hospitalization without compromising safety.

On the other hand Lambert *et al*[49] stated that there was no difference in survival rates between patients undergoing synchronous and metachronous resections, and that secondary metastases tend not to occur after removal of the primary tumor. They concluded that metachronous resection should be performed, and synchronous resection should only be recommended if there is a possibility that metastatic lesions may grow during the waiting period and become harder to resect. Some studies have shown an increase in mortality when the primary has been combined with major hepatectomy, with operative mortality as high as 17%[50].

TREATMENT OF UNRESECTABLE LIVER METASTASES

Conversion CTX is administered to patients with initially unresectable disease, with the intention of downsizing the tumor burden, and, ultimately, considering resection in the pre-operative setting. Downsizing of CRLM has numerous advantages, such that small metastases can disappear in one lobe allowing resection of metastases in the opposite lobe; major vascular pedicles of the liver may become tumor-free; and large lesions may become accessible to ablative techniques, when they shrink to less than 3 cm in diameter[12].

A study by Adam *et al*[51] showed in a case series of 1104 patients with initially unresectable liver metastases that the 5-year survival rate of the resected patient (12%) following primary CT was 33%, which approached the 5-year survival rate of resectable patients in the same period (equal to 48%). Particularly impressive is the ability of regional CTX to convert unresectable patients to resectable. Studies have shown that chemotherapeutic regimens can downstage 15%-50% of patients from unresectable to resectable. The optimal regimen is currently under debate, as is the optimal period for which to be on downstaging therapy before resection. Some authors may argue that resection should be performed as soon as lesions become resectable, whereas others would argue between maximum response (usually 4 mo) and first subsequent progression, which is usually 9 mo[6]. Clavien *et al*[52] reported a conversion rate of nearly 30% for regional liver arterial infusional (HAI) floxuridine (FUDR), whereas Kemeny *et al*[53] reported a rate of > 50% for a regimen combining HAI FUDR with systemic FOLFOX.

In clinical trials using FOLFOX and FOLFIRI, the response rate for unresectable liver metastatic lesions exceeded 50%, with rates of 43%-81% reported with the addition of the molecular targeted drug bevacizumab or the anti-epidermal growth factor receptor (EGFR), antibodies cetuximab or panitumumab[16]. Azoulay *et al*[54] showed that, although the required residual liver volume after liver resection is > 25% for a healthy liver, this rises to > 40% when high-volume anticancer agents have been administered preoperatively.

EXTRALIVER DISEASE

Although patients with previously unresectable CRLM may now become candidates for resection following tumor downsizing after treatment with neo-adjuvant CTX[55], extraliver disease (EHD) has been considered by most to be a contraindication for hepatectomy. On the other hand, with improved treatment responses observed, there are increasing reports that suggest that long-term survival rates are being obtained in patients with CRLM with EHD after surgical resection[51,56].

A review of the literature by Chua *et al*[57] evaluated 22 studies that included 1142 patients with CRLM and concomitant EHD, they concluded that resection of CRLM with EHD is a safe surgical option with median mortality rates of less than 1% and a median post operative complication of 28%. The results appeared to be similar with patients undergoing liver resection for isolated CRLM alone. However, resection of CRLM with more than one site of EHD do not benefit from this radical approach. Therefore, it would be important to perform surgery only for patients with single site extraliver metastases. Adam

et al[58] reported the extraliver disease features of patients undergoing liver resection and concomitant surgery for CRLM with EHD, of which 39% of patients with lung metastases, 89% of patients with lymph node metastases and 92% with peritoneal metastases had complete resection. The low rate of complete resection of lung metastases was the result of pulmonary metastasectomy often being performed as sequential treatment after liver resection and during this interval, 68% of patients developed evidence of disease progression.

The review by Chua *et al*[57] stated that studies have shown patients with lung metastases have the most favorable survival outcome when compared with patients with lymph node and peritoneal metastases. Nevertheless, the median 3-year survival rate in patients with lymph node or peritoneal metastases was still in excess of 28%. They concluded that poorer survival rates of patients who had lymph node or peritoneal metastases whose resection was performed at the time of liver resection compared with a sequential approach for lung metastases could be explained by the self selection of favorable responders to undergo pulmonary metastasectomy and the exclusion of patients whose disease progressed[57]. Another factor is the location of the abdominal lymph node metastases, which should be considered when selecting patients for resecting lymph node. Pulitanò *et al*[59] reported that EHD with porto-caval lymph node had a 27% 5-year survival rate compared to 7% in patients with aorto-caval lymph node metastases. In the series reported by Adam *et al*[58] there were no 5-year survivors observed in the case of celiac or para-aortic lymph nodes compared with a 25% 5-year survival rate observed in patients with only pedicular lymph nodes. From these two large studies, the spread of nodal metastatic disease from the porto-caval lymph nodes along the hepatoduodenal ligament towards the celiac axis and the retroperitoneal nodes impact survival negatively. Performing an extended lymphadenectomy in patients with advanced nodal metastasis beyond the porto-caval lymph nodes does not seem to improve survival[59].

ADJUVANT SYSTEMIC CTX

The goals of adjuvant CTX after liver resection are to prevent recurrence in the residual liver and to treat latent extraliver metastases[16]. Surgery enables complete resection of the tumor and CTX allows for targeting micrometastatic disease. This was observed in a study by de Haas *et al*[60] that compared R0 and R1 resections. They showed a higher recurrence rate in patients with R1 resections, but similar overall survival amongst patients with R0 and R1 resection owing to the concurrent treatment with effective CTX.

Standard treatment for CRLM prior to the year 2000 was based on palliative CT using single-agent 5FU (or fluoropyrimidine drugs) combined with folinic acid (LV), which had a response rate of approximately 20%. Initial randomized studies confirmed that a regimen based on 5FU/LV, improved median survival rates of patients with metastatic disease from 8 to 12 mo[61]. However, in the attempt to improve treatment results and to increase the proportion of patients exposed to all active agents, a combined administration of 5FU/LV, irinotecan and oxaliplatin (FOLFIRINOX) has been developed. FOLFIRINOX was evaluated in the first line in comparison with the standard FOLFIRI (folinic acid, fluorouracil, irinotecan). FOLFIRINOX proved to be more effective [in ORR, progression free survival (PFS) and OS] than FOLFIRI and was associated with a higher secondary resection rate of liver metastases (36% *vs* 12%, $P = 0.017$). This regimen had high ratio of side effects (grade 3/4 neutropenia = 50% *vs* 28%) and requires close follow up[62,63].

Additional agents aimed at improving outcomes in combination with CTX are the use of biological agents, such as Bevacizumab and Cetuximab. These two molecules are currently included in the first line treatment of metastatic CRC. Bevacizumab is a humanized monoclonal antibody targeting the most important factor implicated in tumor angiogenesis called vascular endothelial growth factor (VEGF), and was the first molecule developed in the treatment of CRLM in which studies have confirmed its benefits[64-69]. Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR). Two randomized trials in metastatic setting showed that adding cetuximab to FOLFIRI or FOLFOX, improved outcomes in patients with K-RAS wild-type tumors. With the use of bevacizumab and cetuximab in combination with CT, survival of patients has improved to more than 24 mo[68,69].

PREOPERATIVE CTX

Neoadjuvant CT, which is the administration of CTX pre-operatively in patients with resectable diseases, has a number of potential benefits, such as increasing resectability, limiting the hepatectomy, treating micro-metastases and enabling the evaluation of chemosensitivity of the disease, which will in turn provides direction as to whether CTX should be given after the resection of metastases. The most important problem associated with neoadjuvant CT is the progression of metastases during neoadjuvant CT[12].

The duration of CT administration has shown to be an important factor affecting morbidity rates. One study with more than 12 courses of CT, was associated with higher risk of postoperative complications, whereas another showed that postoperative morbidity was higher in patients receiving more than six cycles of CT before surgery[70,71]. The administration of preoperative CTX has been shown to improve postoperative disease-free survival[72]. Preoperative CTX may result in certain side effects, such as liver damage, which increases hepatectomy-associated complications. CTX-associated steatohepatitis (CASH), a syndrome characterized by liver steatosis, splenomegaly and thrombocytopenia, has been

described[73]. Another possibility is that tumors may become unresectable during CTX. It is for this reason that the choice of regimen and duration of administration are important factors in preoperative CTX for resectable cases[16].

RECURRENCE AND REPEAT RESECTION

Up to 55%-60% of patients will develop recurrent liver metastasis, the majority within the first 2 years[74]. Even when liver resection is performed with curative intent, 60%-70% of patients will develop local, regional, or distant recurrence[74]. Multiple studies have shown that the results of repeated curative resection are comparable to the first resection in terms of overall survival[75], and compared to the first resection, the only difference of the second and the third hepatectomy is that the surgical technique becomes more difficult[11].

Additional to liver recurrences, lung, abdominopelvic, bone and brain recurrences may also occur. Control of liver disease can enhance long-term survival; however, the eventual sites of cancer recurrence justify systemic adjuvant therapy[6]. The same criteria as those for initial liver resection can be applied to intraliver recurrence after hepatectomy, in principle, and resection is actively repeated[38,76].

MANAGEMENT OF COLORECTAL LIVER METASTASIS WITH SYNCHRONOUS PERITONEAL CARCINOMATOSIS

Development of distant metastases from CRC to the peritoneum, *i.e.,* peritoneal metastases (PMs) are seen in 10%-25% of CRC patients. The sole site of metastasis is the peritoneum in up to 25% of patients[5,77]. PMs are generally considered a local form of CRC dissemination[78].

Although untreated PM is associated with poor survival rates of about 6-12 mo, even modern systemic CTX does not seem to gain any clinically significant gain in survival for patients presenting with PM[79,80].

The presence of liver metastasis is considered a contraindication for colorectal surgery and hyperthermic intraperitoneal CTX[81]. Additionally, the presence of PM is also considered a contraindication for curative resection of CRLMs[82]. Both separate sites of metastasis have been curatively treated by surgery, and cases have been reported of patients with PM of CRC that have been treated with a combination of resection, including that of liver metastases and HIPEC. This has proven to be feasible[80].

Despite the fact that the presence of CRLM is officially a contraindication for cytoreductive surgery and HIPEC, there is a selected group of patients presenting with a combination of CRLM and PM that may be curatively treated by an aggressive surgical approach[82-84].

In 2008, a consensus was agreed upon, stating that concomitant liver metastases are only to be resected when confined to three or less well-resectable lesions[85,86]. In addition, eligible patients should have a good performance status and low co-morbidity[87]. The literature also reports that disease that responds adequately to neoadjuvant systemic CTX, *i.e.*, a reduction of overall tumor burden or no progressive disease during treatment, as having less aggressive tumor biology. This is cited as a favorable factor in selecting patients for this aggressive approach[88].

ABLATIVE TREATMENT

Alternate treatment strategies for patients with unresectable liver tumors or as adjuncts in total cancer therapy have been developed. These liver treatment procedures can be divided into two groups: regional transarterial therapies and local (chemical and thermal) ablative therapies. Transarterial therapies deliver the chemotherapeutic agents to the tumors *via* their blood supply to induce cytotoxic ischemia. Chemical and thermal ablative therapies, by contrast, cause tumor necrosis by injection of cytotoxic or ischemia-inducing chemicals or transmission of thermal energy into the tumor tissue itself[89,90].

For liver malignancies that are unresectable, various ablative modalities are available- the most frequent one being radiofrequency ablation (RFA). Several large case series studies have demonstrated long-term survival rates for patients treated with RFA, which are comparable to those of resected patients[91,92]. However, the lack of complete coagulative necrosis and the persistence of residual tumor cells after RFA result in high local recurrence rates[93,94].

The role of RFA in CRLM is limited to patients with unresectable liver metastasis because of lesion size, location or other comorbidities precluding surgical procedure. The results for RFA are undoubtedly inferior to surgical resection, with 3-year survival rates of 46%, and 5-year survival rates less than 20%. As in HCC, RFA of CRLM is also associated with a high recurrence rate (12% at 1 year and 50%-70% at 5 years) and the size of ablated lesion is an important predictive factor for local recurrence and overall survival; such that a 5-year overall survival rate of 56% is observed after RFA of solitary lesions < 2.5 cm, compared with only 13% for lesions > 2.5 cm[90]. Tumor ablation has also increasingly been used in combination with resection. This procedure should only be used in those patients who are not completely resectable[6].

Another type of ablative treatment is microwave radiation, which refers to heat matter by agitating water molecules in the surrounding tissue, producing friction and heat, thus producing cellular death *via* coagulative necrosis[95]. A study by Shibata *et al*[96] compared microwave coagulation therapy to surgical resection and showed no statistically significant difference in survival rates; the only difference was the amount of intraoperative blood loss.

CONCLUSION

Despite broader criteria and recent advances of CTX,

surgery is not possible in most CRLM patients. The role of other local therapeutic techniques, alone or combined with surgery or CTX, is not yet established in a multidisciplinary therapeutic approach. It is critical to understand molecular mechanisms of tumorigenesis underlying new therapeutic strategies that specifically target tumors. This will lead to the evolution of personalized therapies for patients with CRLM.

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