Colorectal Liver Metastases: an Update on Palliative Treatment Options

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Abstract

Only approximately 30% of patients with colorectal cancer liver metastasis qualify for curative therapy, which is in most cases liver lesion resection. Due primarily to the extent of the tumors and patient comorbidities, palliative therapy remains the only option in non-resection cases. Palliation enables local, symptomatic control and prolonged survival in some cases. As established methods are continuously improved, new palliative therapy methods are tested in clinical trials and subsequently introduced into clinical practice. The present review provides an overview of current colorectal liver metastasis treatment when resection is not an option. This review gives the basis for an interdisciplinary decision making process for the treatment of liver metastasis.

Key words

Liver metastasis – colorectal cancer – palliative treatment.

Abbreviations

5-FU - 5-fluorouracil; ARDS - acute respiratory distress syndrome; CRLM - colorectal liver metastases; DEB - Drug-eluting beads; DIC - disseminated intravascular coagulation disorder; DSM - degradable starch microspheres; EGFR - epidermal growth factor receptor; FOLFIRI - 5-fluorouracil + leukovorin + irinotecan; FOLFOX - 5-fluorouracil + leukovorin + oxaliplatin; HAI - hepatic arterial infusion; HDR - high-dose-rate; HIFU - High-intensity focused ultrasound; LITT - laser-induced thermotherapy; MRI - magnetic resonance imaging; MTD - maximum tolerated dose; MWA - microwave ablation; PVA - polyvinyl alcohol; RAIC - repeated arterial infusion chemotherapy; Re-188 - Rhenium-188; RFA - radiofrequency ablation; RILD - radiation-induced liver disease; RT - radiotherapy; SAIC - single bolus arterial infusion chemotherapy; SBRT - Stereotactic body radiotherapy; TACE - transarterial chemoembolization; TAE - transcatheter arterial embolization; TNF-alpha - tumor necrosis factor alpha; VEGF - vascular endothelial growth factor; WLRT - whole-liver radiation therapy

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Introduction

Colorectal cancer is the second most commonly diagnosed cancer in Europe, with an annual incidence of 400,000 cases and an annual mortality of more than 200,000 patients [1]. Almost 70 % of colorectal cancer patients develop liver metastasis during the course of disease [2].

Although surgical resection is the gold standard for colorectal liver metastasis treatment, many patients are not surgical candidates because of insufficient residual liver tissue, extrahepatic disease, anatomic constraints of the tumor, or medical comorbidities.

Without treatment, the median survival of patients with colorectal liver metastases is 6 to 12 months, and the 5-year survival is less than 10% [3].

Palliative treatment regimens can achieve local tumor control and a much better survival rate.

The present review summarizes developments in the treatment of colorectal liver metastases and emphasizes new approaches.

Systemic chemotherapy

Palliative chemotherapy is the standard strategy for improving patient survival, decreasing tumor-related symptoms, and improving quality of life for patients with colorectal liver metastases (CRLM). For the past 40 years, 5-fluorouracil (5-FU) has formed the cornerstone of systemic therapy in cases with unresectable liver metastases. As a monotherapy, 5-FU has increased the median overall survival time from 8 to 11 months [4].

Recently, it has been shown that combination therapy regimens with irinotecan (e.g., FOLFIRI) or oxaliplatin (e.g., FOLFOX) produce superior response rates (30 to 56%) with a longer median survival time (18 to 21 months); these medications form the backbone of current treatments [5-7]. Even when used as second-line agents, combination therapy regimens improve median survival time up to 12 months [8]. Neurologic toxicities (oxaliplatin) and diarrhea (irinotecan) commonly limit treatment doses or force the interruption of treatment [7, 9].

The availability of monoclonal antibodies has increased the treatment options for systemic therapy. Bevacizumab, a human monoclonal antibody that targets vascular endothelial growth factor (VEGF), has been shown to prolong progression-free survival as a first- or second-line therapy combined with chemotherapy. In combination with a 5-FU bolus and irinotecan (as a first-line therapy) or combined with FOLFOX (as a second-line therapy), the antibody has been shown to prolong overall survival when compared to treatment with chemotherapy alone [10]. Cetuximab and panitumumab are agents that depend on the absence of an activating mutation in the epidermal growth factor receptor (EGFR) downstream effector molecule K-ras [11]. Cetuximab has been shown to improve overall survival as a monotherapy in pretreated patients compared to the current best supportive care in combination with FOLFIRI as first-line therapy when compared to treatment with FOLFIRI alone [11, 12]. Most active arms of first-line studies have demonstrated a median overall survival time of nearly 2 years following treatment of patients with metastatic colorectal cancer [13]. Median survival following second-line treatment approaches 13 months [14].

The use of panitumumab is limited as third-line agent. A common side effect of EGFR antibodies is skin toxicity. The common side effects of bevacizumab are hypertension, arteriothrombotic events, proteinuria and wound healing disturbances [10].

Regional techniques

Currently used regional techniques can be divided into four groups. The first group comprises ablative techniques that cause local, thermically induced tumor destruction, such as radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), microwave therapy, high intensity focused ultrasound and cryotherapy.

Direct chemotherapeutic infusion of the liver is possible in the second group because liver neoplasms are primarily fed by the hepatic artery. Transarterial administration of single anticancer drugs, either as hepatic chemoperfusion or as hepatic arterial infusion (HAI), can be combined with vascular occlusive agents (transarterial chemoembolization [TACE]) or bland vascular embolization (transcatheter arterial embolization, TAE).

The third group consists of either external beam radiotherapy (conformal radiotherapy, intensity modulated radiation therapy, stereotactic body radiation therapy, proton radiation therapy, heavy ion radiation therapy) or high-dose-rate interstitial brachytherapy (afterloading).

The fourth group comprises nuclear medicine methods that are dependent upon radioisotopes for selective internal radiotherapy.

Thermoablative methods

Thermal ablation produces waves that pass through the liver tissue. The waves cause an elevation in the temperature of the tissue that can lead to tissue necrosis.

When cellular temperatures are increased to 42°C - 45°C for 30 to 60 minutes, irreversible cellular damage occurs. Between 60° and 100°C, the time required to achieve irreversible changes decreases exponentially. In addition to temperature distribution in the tumor, thermal ablation is dependent on the perfusion pattern of the tissue and the optical properties of the laser-treated tissue. In situ ablation techniques require a thermal safety margin of approximately 0.5 to 1 cm around the metastasis to decrease the likelihood of recurrence [15]. The partial removal of metastatic lesions should be avoided. In cases of partial removal, tumor recurrence is often detected away from the ablated area.

Radiofrequency ablation (RFA)

RFA is widely used, and the clinical benefit of this treatment is generally acknowledged. During the treatment, a needle is placed into the center of the metastasis and functions as an electrode. Alternating current with a frequency of 350 to 480 KHz and a power of 15 to 50 watts is applied. The electricity induces oscillations of tissue ions in the tumor cells. The resulting frictional heat, which can locally reach up to 100°C, causes coagulative necrosis and irreversible tissue injury.

Currently, different systems, including mono-, bi- or multipolar applicators are used for RFA techniques. The use of new needles and saline injection at the metastatic site can lead to better electrical conduction.

The ablation zone varies in shape and size. Vessels situated next to the ablated tissue interfere with the ablative techniques by the “heat sink effect”. One possible solution to this problem is the Pringle maneuver performed during a laparoscopy or laparotomy. The maneuver leads to a vascular occlusion and an accompanying reduction of the “heat sink effect” [16].

Minor complications occur in 2.4 to 12% of patients, whereas major complications have been described in up to 5.6% of patients. The mortality rate is approximately 0.5% [17, 18].

Common complications of this procedure include fever, pain, pulmonary complications (such as pleural effusion and pneumothorax), liver insufficiency, liver abscess, and mechanical complications with injuries to the vessels or bile duct, including hemorrhage, biliary leakage, and even perforations of the gastrointestinal wall [19].

Published data indicate that RFA treatment can achieve a 1-year survival rate of 78%, a 2-year survival rate of 64% and 3-year survival rate of 25% [20-22]. The combination of RFA and systemic chemotherapy has been shown to achieve a 5-year survival rate of 30% [23, 24].

Laser-induced thermotherapy (LITT)

Laser-induced thermotherapy (LITT) is also a local ablative technique. Fibers consisting of a quartz crystal with a diameter between 400 and 600 µm are placed into the colorectal metastases. Next, a special laser light with a wavelength between 800 and 1064 nm is applied.

The application of the light leads to a local heating/warming effect that destroys the metastatic tumor cell tissue.

Relatively low power (5 to 40 W) is used during LITT to avoid rapid tumor heating close to the fiber tip, which would otherwise lead to carbonization and impede light penetration into the surrounding tumor. Modern diffusing fibers allow more homogeneous laser light emission. Cooled systems allow for an enlargement of the ablation area. The ablation of intrahepatic tumors is mainly guaranteed by a temporary blood flow occlusion of the liver. The embolization of the hepatic artery is performed by intra-arterial degradable starch microspheres (DSM) (percutaneous access) [25].

The overall morbidity of this procedure is approximately 7.5% and includes pleural effusion, pneumothorax, liver abscess, hemobilia, cholangitis and liver hematoma. Cardiac involvement, such as bradycardia, and pulmonary embolism have also been reported following the procedure. Minor complications include post-interventional fever and pain. The 30-day mortality for the procedure is approximately 0.1% [26, 27]. Local tumor control is achieved in approximately 97% of the patients who receive LITT (6 months post-intervention) [28-30].

Microwave ablation (MWA)

For microwave ablation, microwaves with a frequency of at least 900 MHz are used to agitate water molecules in the tissue and produce frictional heat. This frictional heat leads to large volumes of coagulative necrosis.

When high power (between 70 and 90 W) is used, a coagulation with a 2-cm ablation zone can be achieved in one minute [31].

Microwave ablation has some theoretical advantages over RFA. In MWA, transmission is not limited by tissue desiccation and charring (as in RFA, which relies on the conduction of electricity). The lack of transmission limitation allows intratumoral temperatures to be higher, leading to a larger ablation zone, shorter treatment time, and more complete tumor killing [32].

The complications of microwave techniques include asymptomatic pleural effusions, liver abscess, intraperitoneal bleeding, tumor seeding along the needle and bile duct stenosis with icterus [33, 34].

In a selected database of patients with unresectable colorectal liver metastases, the use of microwave techniques led to 3- and 5-year survival rates of 51% and 32%, respectively [35-37].

The addition of MWA to HAI or systemic chemotherapy for patients with unresectable CRLM results in a significantly improved survival rate when compared to patients receiving only chemotherapy [38, 39].

High-intensity focused ultrasound (HIFU)

High-intensity focused ultrasound is an innovative technique for the extracorporeal treatment of different tumor masses, e.g., prostate or kidney cancer. The treatment is administered with a lens-focused transducer that creates a focused beam of 30 to 40 W/cm^2 at peak intensity. The beam elevates the tissue temperature to 60°C. The elevated temperature induces coagulation necrosis with destruction of the tumor cells. In addition to the destruction that accompanies the elevated temperature, the mechanical effects of the high-intensity ultrasound assist the destruction of the tumor cells [40]. Initial results from using this procedure have already been published and include reports of mild adverse effects such as skin flushing and transient pain [41].

The use of this procedure is limited in patients with gas-bubbles in the gut or liver tissue changes, such as fatty liver or fibrotic liver tissue. In these cases, high-intensity focused ultrasound can cause excessive cell damage [42]. Tumor cell dissemination following the procedure has yet to be reported [43]. Further studies are necessary to confirm these findings.

Cryotherapy

Cryotherapy uses liquid nitrogen or argon to cool tumor tissue down to -180°C. The formation of intracellular ice crystals leads to a mechanical destruction of the interstitium. Cells on the borderline of the ablation zone are destroyed by dehydration and occlusion of small vessels. Repeating cycles of freezing and thawing are used to ensure irreversible cell damage.

Complications are reported in approximately 30% of all cases and include bleeding, bile duct infection, liver abscess, pneumonia, a temporary elevation of liver enzymes, thrombocytopenia and renal failure due to myoglobinuria. The published mortality rates of this treatment range between 1.5% and 4% [44, 45].

An “ice-cracking” of the liver tissue is seen in 5 to 28% of the patients receiving the treatment [46]. Transient hypothermia can be avoided by using warmed infusions.

The risk of systemic cryoshock increases if more than 35% of the liver tissue is treated [44, 47]. Cytokine-induced factors (IL-1, IL-6, and TNF-alpha) cause systemic disorders, such as fever, tachycardia and tachypnea that can result in acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation disorder (DIC). Renal disorders result in necrosis of the tubuli. The cryoshock incidence of 1% following large-volume ablations has been decreased by limiting the volume of frozen tissue [48].

Hepatic cryosurgery can achieve survival rates of 44% (3-year survival) and 26% (5-year survival) [49-51]. Although the use of cryosurgery is effective in inducing tumor cell death, lingering concerns over increased local recurrence rates and higher complication rates have led to a diminishing use of this technique.

Local chemotherapy (hepatic arterial infusion; HAI)

Transarterial chemotherapy takes advantage of the fact

that tumor cells in CRLM larger than 3 mm derive up to 95% of their blood supply from the hepatic artery, whereas normal hepatocytes receive up to 75% of their blood supply from portal veins.

Intra-arterial chemotherapy is performed via a temporary catheter placed in the hepatic artery (single bolus arterial infusion chemotherapy, SAIC) and via permanent port catheter systems that are percutaneously implantable for long-term repetitive infusion therapy (repeated arterial infusion chemotherapy, RAIC) without arterial puncture.

In contrast to systemic chemotherapy, a higher (up to 16-fold) concentration of drugs can be obtained in the neoplasm with less systemic toxicity by the direct administration of chemotherapeutic agents through the hepatic artery.

Complications occur in up to 57% of cases. Local complications due to the arterial puncture include mild hematoma, hemorrhage, mild pain and discomfort. Technical or mechanical complications include extrahepatic or incomplete perfusion of the metastatic tissue, mesenteric ischemia, infections, and accidental embolization of the hepatic artery during catheter fixation [52, 53]. Pharmacological complications due to prolonged chemotherapeutic drug infusion include gastroduodenitis, gastroduodenal ulcer, cholecystitis, hepatobiliary toxicity with biliary sclerosis and other consequences, such as arterio-biliary fistula [54]. No deaths have been linked to local chemotherapy or hepatic arterial infusion of chemotherapy for the treatment of liver colorectal cancer metastases [55].

Regional intra-arterial chemotherapy has demonstrated a local control effect and a long-term advantage in median survival. Randomized studies have indicated a response rate of up to 41% and a median survival time of 15 months, with a 5-year overall survival rate of 45% [56, 57]. A significant overall survival benefit difference between local and systemic chemotherapy regimens has not been detected [58, 59].

The combination of local and systemic chemotherapy does not have a major impact on the outcome of the disease [60-62].

With the application of more effective systemic chemotherapy drugs, a decrease in the use of local chemotherapy is expected.

Bland vascular embolization (TAE)

The goal of vascular embolization is the occlusion of the metastatic blood supply.

Vascular occlusive agents can be either temporary agents, such as degradable starch microspheres (DSM), collagen and gelatin sponge (Gelfoam) or permanent agents, such as polyvinyl alcohol (PVA, Ivalon) [63]. The PVA particles produce an intense inflammatory reaction and a mechanical occlusion of the vessel due to contact with the intima of the vessel. The inflammation and occlusion cause permanent vessel damage and increase distal ischemia. Larger vessels usually recover from this process and further embolization procedures may be required. TAE problems can occur when smaller arteries are closed, preventing a deeper penetration of the target tissue.

Under the current treatment standard, a whole liver segment or a whole liver lobe undergoes transarterial chemoembolization in cases with multiple metastases. Because the healthy liver tissue gets its main blood supply via the portal vein, it does not interfere with the transarterial chemoembolization.

A complete necrosis of the metastases is not expected following TAE. Therefore, survival rates are usually lower compared to regional ablative methods [64]. Future TAE strategies are being planned to involve a combination of transarterial chemoembolization and chemo- or radiotherapeutic treatments.

Transarterial chemoembolization (TACE)

The addition of a chemotherapeutic agent to the embolization procedures creates an arterial devascularization and a targeted cytotoxic effect against the CRLM. The cytotoxic effect is extremely effective in the embolized areas of the metastases due to hypoxia.

Traditionally, a mixture of a cytotoxic drug and lipiodol are injected. As an oil-based contrast agent, Lipiodol has a slight embolic effect and can improve the passage of the chemotherapeutic drug through the tumor. Thus, lipiodol significantly enhances the effect of chemotherapy [65]. Because lipiodol can remain in lesions for many months and even years, it also aids in targeting treatment at subsequent sessions. In addition to lipiodol, starch microspheres have been evaluated in clinical studies and demonstrate similar safety and effectiveness compared with Lipiodol [66].

The most common TACE-associated complication is “post-embolization syndrome” or “tumor lysis syndrome”. In this complication, the patient suffers right-upper quadrant pain, nausea, vomiting, elevated liver enzymes, and fever. This complication occurs in 3.8% to 100% of patients who undergo this treatment. It is typically transient and is resolved within 7 to 10 days [67, 68]. The risk of irreversible liver damage is reduced by the application of transarterial and systemic chemotherapy with an attenuated drug dose [69].

Serious complications, such as tumor rupture, acute liver failure, liver abscess, and pulmonary lipiodol embolism are extremely rare [16, 68, 70]. Mechanical complications include catheter displacement, thrombosis, occlusion, and mesenteric ischemia [15].

Beneficial effects of this procedure are reported in 80% of all patients [63, 71].

The median survival rates associated with the different therapy regimens vary between 9 and 62 months [63]. Recent studies have reported a 2-year survival of 28% when TACE was used as a second-line treatment [72].

Drug-eluting beads (DEB)

Drug-eluting beads are small particles loaded with chemotherapeutic agents. The uniform particles, or beads, do not aggregate; rather, they carry the cytotoxic drugs to the capillary bed, where they are released in a sustained and controlled way.

The systemic dose of the drug when administered via a DEB is significantly lower than with conventional

chemoembolization, whereas the concentration of the drug in the liver lesion is massively increased. Additionally, the volume of tissue necrosis is significantly greater when using drug-eluting beads compared to conventional TACE [73].

Initial studies with drug-eluting beads have indicated a decrease in CEA levels. In addition, there is a decrease of metastatic tissue enhancement, as measured by CT [74].

Following treatment with drug-eluting beads, the median survival rates without tumor progression have been reported to be 8 to 11 months [75].

Radiotherapy

External beam radiotherapy (RT) is a noninvasive treatment option that can be offered to patients who are not suitable for surgery or other ablative therapies. Radiotherapy has historically played a minor role in the treatment of patients with unresectable liver metastases from colorectal cancer. This can be mainly attributed to the low tolerance of the whole liver and many sensitive adjacent normal tissues to radiation.

Technological advances in RT planning and delivery have made it possible to safely deliver high radiation doses to focal liver metastases, while sparing most of the normal liver [157]. Methods to facilitate safe delivery of high-dose RT include conformal RT planning, image-guided RT, stereotactic body RT and respiratory motion management. The maximum tolerated dose (MTD) of proton beam irradiation is currently being investigated in clinical phase I trials.

Whole-liver radiation therapy

Whole-liver radiation therapy (WLRT) is predominately used as a palliative treatment for patients with liver metastases who present with local pain.

One of the most serious complications of liver irradiation is radiation-induced liver disease (RILD), a clinical syndrome of anicteric hepatomegaly, ascites, elevated liver enzymes and impaired liver function occurring within 3 months after the completion of therapy [76]. RILD has been observed after fractionated whole-liver irradiation with 30 to 35 Gy [77].

The duration of response and patient survival after WLRT tend to be short [78, 79]. Therefore, whole liver irradiation is combined with systemic or regional chemotherapy. In most studies, the patient outcomes appear to be modestly better than the outcomes obtained from radiotherapy alone [80, 81].

Stereotactic body radiotherapy (SBRT)

A limited number of highly focused, ablative radiation treatments are used for stereotactic body radiotherapy. The term “stereotactic” describes the relationship of the tumor target position with known fiducials that define a coordinate system and can be used to target the tumor, orient the treatment planning process, and guide the therapy toward the intended location in the body. Therefore, SBRT combines potent dose fractionation, careful target definition, motion management (4D therapy), image guidance, conformal dose distributions, and high levels of quality assurance.

Clinical results of studies using SBRT for the treatment of liver metastases are emerging. Phase I and II studies have demonstrated excellent local control and occasional long-term survivors [82-84]. Patients should be considered for participation in randomized clinical trials when possible because the efficacy of liver metastasis SBRT has not yet been fully established. SBRT can treat liver metastases safely; radiation doses >47 Gy (3 to 6 fx) can improve local control. The optimal fractionation has yet to be clearly defined [82, 85].

With appropriate patient selection (e.g., no active extrahepatic disease and liver function with a Child-Pugh A score more than 2 weeks after the most recent chemotherapy), sparing of the uninvolved areas of the liver (focal tumor distribution: ≤ 5 liver metastases < 10 cm each [ideally < 8 cm], >700 cc uninvolved liver, > 250 to 500 cc uninvolved liver, < 10 Gy in 6 fractions, and effective liver volume < 60%), technological advances, tumor imaging, respiratory motion management, RT planning and RT image guidance, serious toxicity can be avoided. Out-of-field recurrences are common, providing a rationale for combining systemic or regional therapies with RT for these patients. RILD is rare after SBRT for liver metastases, but it has been recommended to keep the dose to 700 cc of uninvolved liver to less than 15 Gy delivered in 3 fractions or ensuring that no more than 50% of the liver receives 15 Gy in 3 fractions (or 7 Gy in 1 fraction) and no more than 30% of the liver receives 21 Gy in 3 fractions (or 12 Gy in 1 fraction) [86]. Fibrosis of the portions of the liver included in the high-dose volume is common, as is compensatory hypertrophy of the portions of the liver spared from radiation. Biliary sclerosis and hepatic subcapsular injury are other potential problems. Gastrointestinal bleeding, small bowel obstruction, gastric outlet obstruction, and fistula formation are other possible late sequelae if the esophagus, stomach, duodenum, or large bowel is irradiated at high doses. Hemorrhagic gastritis has been reported to develop after a dose of 14 Gy was delivered in 2 fractions to the gastric wall of a patient with liver metastases. Ulcers and perforations were observed when greater than 30 Gy in 3 fractions was delivered to the intestine [86, 87].

Brachytherapy

A promising alternative to locally ablative treatment is CT-guided catheter implantation and high-dose-rate (HDR) interstitial brachytherapy using an afterloading technique. Iridium-192, as a radiation source, is moved stepwise along these catheters inside or next to the tumor. This minimally invasive procedure offers circumscriptive high-dose-rate irradiation of the lesion for treatment; it achieves rapid dose fall-off, resulting in less radiation dose to the surrounding normal tissues and accounts for the movement associated with physiologic processes such as respiratory motion. 3D treatment planning of the numbers and tracks of catheters, target contouring, preliminary dose sketching, and sparing

of surrounding tissues at risk is performed using MRI scans of the liver correlated with a helical CT scan. This liver radiation method is highly specialized and is only available in a few centers worldwide.

Studies with small numbers of patients have indicated a local tumor control rate of 72% after 14 months. The control rate was equal or superior to that of laser-induced thermotherapy-treated lesions [88]. A strong dose dependency of local tumor control after CT-guided brachytherapy for colorectal liver metastases was demonstrated [89].

Mild adverse effects, such as nausea, vomiting or transient liver enzyme elevation were reported in 28% of treated patients. Relevant adverse effects occurred in less than 10% [90]. A combination of brachytherapy with systemic or local chemotherapy will be examined in further studies.

Nuclear medicine methods: Selective internal radiotherapy (SIRT)

Selective internal radiotherapy is a combination of embolization and radiation. Millions of microscopic radioactive spheres (approximately 35 microns in size) are administered through a catheter in the hepatic artery. The microscopic radioactive spheres occlude the small branches of the hepatic artery, which reduces the blood supply to the metastatic tissue.

In the current version of this treatment, the microspheres are labeled either with pure beta emitters (e.g., yttrium-90: Y-90) or with combined beta/gamma emitters (e.g., rhenium-188: Re-188) [141]. The advantage of the latter is a significantly higher imaging quality for dosimetric calculation. Furthermore, various radionuclides with different energies and physical half-lives are available, allowing an adaption to the individual patient's needs regarding the number, size and distribution of the CRLM. The decay of the radionuclide results in prolonged radiation of the tumor tissue, with a dosage of approximately 150 to 200 Gy. Because the radionuclides used are beta emitters, the energy is deposited only in a few millimeters around the microsphere; e.g. 90% of the energy is deposited within 5.3 mm in the case of Y-90. The normal liver tissue is preserved in this method [91].

The most common clinical symptom associated with this treatment is a mild post-embolic syndrome that includes fatigue, vague abdominal discomfort, pain, and fever. As a side effect of non-target radiation, symptoms like cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, radiation pneumonitis, and RILD occur rarely [92].

Currently, SIRT is commonly used as a third- or fourth-line therapy for non-resectable multiple liver metastases.

Initial study results have indicated a possible benefit of SIRT for life quality and survival. Tumor-free survival up to 9 months has been reported, along with a median survival of 17.5 months [93-95]. Tumor-free survival time has been improved by the combination of local intra-arterial chemotherapy and 5-FU; however, no significant difference could be found for overall survival [96].

The addition of systemic chemotherapy stabilized the tumor lesions in approximately 80% of the patients in one study [97]. Phase II studies have indicated a significantly longer overall survival when SIRT is combined with chemotherapy when compared to systemic chemotherapy alone [98].

Conclusion

There has been enormous progress in the management of CRLM in recent years. Moreover, new therapeutic options and approaches to improving patient outcome are expected to be established in the foreseeable future. The limited possibilities available for the treatment of unresectable colorectal metastases belong in the past. Therefore, to provide optimal outcomes for patients with CRLM, it is imperative to consider all treatment options available based on each patient's comorbidities and tumor extent. All treatment approaches should be undertaken in a tertiary care center, where a multidisciplinary approach can be offered and pursued with the collaboration of surgeons, medical oncologists, radiooncologists, and interventional radiologists.

Conflicts of interest

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