Review Article

Narrative review of the role of yttrium-90 selective internal radiation therapy in the surgical management of colorectal liver metastases

Maitham A. Moslim, D. Rohan Jeyarajah

Methodist Richardson Medical Center, Richardson, TX, USA

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Correspondence to: D. Rohan Jeyarajah, MD, FACS, DABS, Chair of Surgery. Department of Surgery Methodist Richardson Medical Center, TCU/UNTHSC School of Medicine, 2805 E. President George Bush Highway, Richardson, TX, USA. Email: rohanjeyarajah@gmail.com.

Abstract: The management of colorectal liver metastasis (CRLM) is complicated and benefits from a multidisciplinary team approach. Liver-directed therapy has been emerging as a modality for better progression-free control. In its early years, selective internal radiation therapy (SIRT) with yttrium-90 (Y-90) was confined as an end-of-line therapy. However, literature has supported other roles including: a first-line treatment for CRLM alone or in combination with systemic chemotherapy; an adjunct to second or third-line chemotherapy; and a salvage treatment for chemo-refractory disease. Although future liver remnant (FLR) hypertrophy may take 3–12 months, the SIRT effect on loco-regional disease control has rendered it to be a useful tool in some pathologies with certain strategic goals. This paper reviews the use of SIRT with Y-90 in a surgical treatment pathway. This includes: (I) an element of multidisciplinary treatment of low-volume CRLMs, (II) convert an R1 to R0 resection by sterilizing the margins of tumor near critical structures, and (III) radiation lobectomy to induce contralateral hypertrophy in order to aid in a safer resection. There are many opportunities to validate the role of SIRT as a first-line therapy along with surgical resection including an umbrella clinical trial design.

Keywords: Colorectal liver metastasis (CRLM); liver-directed therapy; selective internal radiation therapy (SIRT); yttrium-90 (Y-90); liver resection

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Introduction

In the United States, it is estimated that 147,000 new cases of colorectal cancer (CRC) were diagnosed in 2020 and 53,000 deaths were reported in 2017 (1). The liver is the most common metastatic site with 20% presenting synchronously and 25–50% metachronously (2). Colorectal liver metastases (CRLMs) are responsible for two-thirds of CRC mortality (3). The prognosis of untreated CRLM is grim with 5-year survival of less than 5% (4). Although it has never been compared against supportive medical treatment in a randomized clinical trial, resection of CRLM has evolved as the mainstay in intent-to-cure multimodality therapy (1). Unfortunately, only 15–20% of CRLMs are initially amenable to curative resection (5). Although 80% are not surgical candidates at the time of diagnosis, the 5-year survival has doubled in the three decades following the introduction of more effective chemotherapy regimens, targeting biological agents, and advanced surgical, ablative, radiotherapeutic and chemotherapeutic liver-directed modalities (4,6). The main goal of such innovative interventions is to downsize tumors, improve R0 resection rate, and enhance potential resectability of CRLM with the

preservation of a functional future liver remnant (FLR) (6).

The median survivals of patients who undergo resection with and without perioperative chemotherapy are 61 and 54 months, respectively (5). Such prolongation in survival resulted in increased rate of recurrence as more than half of patients do experience relapse within 2 years after liver resection (4), and two thirds of these recurrences are in the residual liver (4). Creasy *et al.* followed more than 1,200 patients who underwent liver resection for CRLM between 1992–2004. Recurrence-free survival at 10 years was observed in 20.6%. Extrahepatic metastasis, R1 resection, carcinoembryonic antigen >200 ng/mL and >10 tumor foci were strong predictors of poor cure rates (<10%) (7). Metachronous disease, node-negative primary CRC, numbers of metastases <5, largest tumor less ≤5 cm, and absence of extrahepatic disease were associated with cure rates >20% (7). Somatic mutations in certain genes such as *KRAS*, *BRAF* and *TP53* are independent predictors of early recurrence and worse survival (8,9). These data would suggest that, even in those where cure is not possible, surgical therapy can prolong life and convert mCRC to "chronic disease". This can result in prolonged survival with good quality of life.

Liver-directed therapy has been emerging as a modality for better progression-free control. The goal of this narrative review is to discuss the current role of selective internal radiation therapy (SIRT) with yttrium-90 (Y-90) in the management of liver-dominant mCRC. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jgo-21-96).

Methods

Based on a recent evidence-based expert consensus algorithm developed by the senior author (10), an extensive literature review on the role of SIRT with Y-90 in patients with mCRC was performed. The reviewed studies include systematic reviews and meta-analyses, randomized controlled trials, phase I and II clinical trials, cohort studies, case series, and consensus guidelines. Non-systematic reviews, single-case reports, and publications prior to 2009 were excluded. Liver-dominant mCRC was stratified according to intend-to-cure resectability into: operable and eligible to curative surgical/ablative/locoregional interventions in the setting of adequate FLR with no extrahepatic disease dissemination (resectable), potentially resectable but presents technical and oncologic challenges to achieve R0 resection due to involvement of critical vascular and biliary structures or inadequate FLR (borderline resectable), and advanced disease that is not amenable to curative resection (unresectable).

Discussion

In the era of precision medicine, the role of a multidisciplinary team approach to achieve a personalized approach for CRLM is mandated and critical. Once CRLM is diagnosed, radiologic evaluation of the hepatic inflow, outflow, biliary drainage, adequate FLR, R0 resectability, extrahepatic disease and performance status are the most essential steps taken towards curable liver resection. Parenchymal sparing approach is a safe and efficient modality to achieve adequate oncological outcomes especially in the settings of threatened FLR and numerous liver lesions (11). An extended right or left hepatectomy that results in inadequate liver remnant can be mitigated by using several approaches to allow for safer surgery. One can be performed staged hepatectomy to achieve optimal oncological results and avoid post-hepatectomy liver failure (12). Portal vein embolization/ligation (PVE/PVL) with or without hepatic vein embolization has been widely performed by liver surgeons to maximize FLR preoperatively (13). In the light of complete preoperative staging, adequate FLR and the ability of achieving R0 resection, upfront surgical resection with adequate disease clearance remains one of the first line treatment options. Despite the lacking evidence of benefits with chemotherapy use in resectable CRLM, most would agree that surgery and chemotherapy are critical to maximizing survival in the mCRC patient. However, the sequencing of chemotherapy is an area of controversy. Although many would utilize the common practice of neoadjuvant chemotherapy with surgical approach, it is still acceptable for patients to undergo surgery-first approach. In some landmark trials, resectable CRLMs have not demonstrated a significant improvement in overall survival (OS) from adjuvant or perioperative medical therapies despite improvement trends in progression-free survival (PFS) (5,14-16). The administration of neoadjuvant cetuximab plus chemotherapy in patients with operable CRLMs rendered worse survival in the multicenter, open-label, randomized, phase III New EPOC trial (17). However, not all technically resectable CRLMs do benefit from upfront oncologic resection and neoadjuvant chemotherapy may provide a better strategy in the setting of unfavorable high-risk CRLMs (18).

Large tumors with involvement or close margins to

major venous or arterial vascular structures can render CRLM unresectable. Chemotherapy has evolved with the addition of new effective drugs (i.e., oxaliplatin and irinotecan) and targeting biological agents, which has been utilized as conversion therapy to down-size such tumors and allow margin-negative resection. Post-chemotherapy conversion rate can reach 30–40% and improve 5-year survival to 35–50% (19-21). One of the most aggressive and effective regimens is fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab, which was reported in the TRIBE trial to be associated with a response rate of 65% (22). However, oxaliplatin and irinotecan-induced hepatotoxicity resulting in steatohepatitis and sinusoidal obstruction, respectively, is a considerable disadvantage of chemotherapy and may affect FLR and increase perioperative morbidity and mortality (23,24). Tumor response to chemotherapy diminishes after four months of treatment; thus, long term planning of conversion therapy should be applied carefully in the appropriate context. Cross-sectional radiographic restaging should be utilized in short interval following the initiation of therapy to assess for loco-regional progression and extrahepatic metastases (25).

Locoregional liver-directed therapy

The concept of liver-directed therapy relies on the seminal work performed by two pathologists at the University of Pennsylvania, who demonstrated the main hepatic arterial supply of liver metastases, compared to the dual parenchymal blood supply from the hepatic artery and portal vein (26). The role of liver-directed therapies has bloomed over the last two decades, especially in the setting of chemo-resistant CRLMs. The importance of treatment sequence cannot be overstated as each line of therapy dictate the next treatment, predict outcomes and interact with other therapeutic modalities. Due to variability in treatment methods, bias in institutional practices, and lack of comparative randomized studies, there are no set criteria to prefer one modality over the other (10). In order to maintain the goal of promoting resection, when possible, primary evaluation of CRLM by experienced hepatobiliary surgeons in the setting of multidisciplinary team approach is advised prior to any treatment initiation (27).

Whole liver radiation is restricted to a low dosage of 30 Gy and short-term palliation (28). Higher doses have been associated with veno-occlusive radiation-induced liver disease (29,30). Radiofrequency ablation (RFA), microwave ablation (MWA), cryotherapy, high-intensity focal ultrasound and ablative radiotherapy are viable options for highly-selected unresectable oligometastatic CRLMs, but limited by tumor size, imaging guidance, respiratory motion variation, fractionation requirements and injury risk to adjacent major vascular, biliary structures and gastrointestinal organs (31-33). RFA and MWA achieve similar survival benefits to surgical resection for lesions that meets the size criteria (≤3 cm) (34). The application of safe stereotactic ablative radiotherapy (SABR) as a bridge to oncologic resection is challenged by large tumors, low FLR and nearby radiosensitive anatomic structures (35). Intra-arterial therapies have been proposed as another modality to treat patients with advanced chemo-resistant CRLM. It allows the delivery of a more precise concentrated dosage of a tumoricidal agent to the tumor foci and minimizes the systemic and hepatotoxic effect of treatment. Such approach can be achieved by conventional transarterial chemoembolization (cTACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), hepatic arterial infusion pump (HAIP) therapy, or SIRT with Y-90 (10). The purpose of this paper is to review the use of SIRT in a surgical algorithm for patients with CRLM.

SIRT with Y-90

The concept of SIRT revolves around the delivery of intra-arterial brachytherapy to the targeted tumor via the hepatic artery branches (36,37). Due to the tumor micro-angiogenesis derived from the hepatic artery, the beta-emitting radioisotope Y-90-labeled microspheres demonstrates a preferential affinity to the tumor tissue rather than the normal liver parenchyma. The average penetration range of the emitted radiation is 2.5 mm with half-life of 64 hours (37). SIRT results in tumor hemorrhage, necrosis, fibrosis, dystrophic calcifications and atrophy of the targeted liver lobe with contralateral hypertrophy ranging between 25–120%, to some extent similar or greater than PVE (36,38,39). The two commercially available Y-90 radio-microsphere products are glass microspheres (Thera-Sphere; MDS Nordion, Ottawa, Ontario, Canada) and resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). Both of which have comparative size between 20–40 μm and stay in the liver permanently (37).

When studying primary liver malignancies, adding SIRT to sorafenib treatment in patients with advanced hepatocellular carcinoma (HCC) did not improve OS in the randomized SORAMIC trial (40). However, it demonstrated a survival

benefit in intrahepatic cholangiocarcinoma (CCA) according to the phase II Y-90 Microspheres in Cholangiocarcinoma (MISPHEC) trial (41). In this single-arm study, 41 treatment-naïve patients with unresectable intrahepatic CCA were treated with combined SIRT and a chemotherapy regimen of gemcitabine and cisplatin. Median OS was reported to be 22 months, with 45% survived at 24 months (41). Nine patients (22%) were downsized to become eligible to conversion surgery and 8 patients (20%) underwent R0 resection. Relapse-free survival in patients who underwent hepatectomy was not reached (41). This was a significant improvement compared to the historical median survival control of 11.7 months in the Advanced Biliary Cancer-02 (ABC-02) trial (42).

Role of SIRT with Y90 in CRLM

The precise indications for this treatment have been debatable until the publication of a recent evidence-based expert consensus algorithm (10). Many oncologists use SIRT as a salvage line of therapy for chemotherapy-refractory high-volume liver-dominant disease, patients with poor performance status, or those who fail, do not tolerate or cannot access other standard therapies. The utilization of SIRT with Y-90 as a tool for downsizing of unresectable CRLMs has yielded higher rates of resections ranging between 10–21% (10,43-45). SIRT is well tolerated by patients who are undergoing concurrent chemotherapy or have portal vein thrombosis with some studies have demonstrated a pathological complete response in 33% of cases (36,38). SIRT with Y-90 is still a valid option for patients with unresectable liver-dominant disease who failed chemotherapy or require a chemotherapeutic holiday while maintaining a progression-free grace period (46,47). Many surgeons would prefer to delay operating on patients who progress on first-line chemotherapy, even in the setting of resectable CRLMs, thus SIRT can be introduced as a concurrent therapy with second-line chemotherapy in this group until an acceptable radiographic response is achieved (18,48). Moreover, this allows for liver tumor control while ensuring lack of progression systemically, thereby allowing for selection of appropriate candidates for an aggressive surgical approach.

Adam *et al.* (48,49) reported that none of the 29 patients who demonstrated complete pathologic response in their 767-patient cohort had complete clinical response on preoperative imaging. Even when complete radiographical response is ascertained, chemotherapy only achieves complete pathological response in less than 20% of cases (50). Therefore, SIRT role as consolidation therapy after first-line chemotherapy or as adjunct therapy to second-line or further treatments was reported by many experts as a valid consideration to improve loco-regional response (10,46). Patients with high volume diffuse bilateral and liver-dominant CRLMs who fail multiple lines of systemic therapy may benefit for SIRT with Y-90 as a salvage treatment (51). In a multicenter, randomized phase III trial conducted by Hendlisz *et al.* (52), patients with unresectable, chemo-resistant liver-limited CRLMs were randomized to receive infusional fluorouracil (5-FU) alone versus SIRT with 5-FU. The addition of SIRT demonstrated a better time to liver progression (5.5 versus 2.1 months, P=0.003) and time to tumor progression (4.5 versus 2.1 months, P=0.03) with acceptable toxicity profile. The earliest the introduction of radioembolization in non-operable situations, the better probability that less damaged livers can tolerate toxicity with the potential of superior loco-regional disease control (10).

As in any treatment modality, the selection of the right therapy for the right patient in the setting of a dedicated multidisciplinary team approach is a key for treatment success (53). The role of SIRT with Y-90 in resectable disease can be summarized into three main domains.

Element in the multidisciplinary treatment of low-volume liver metastases

Patients who are more likely to benefit from SIRT with Y-90 may include those with fewer than 6 intrahepatic foci, no extrahepatic disease, and a tumor-to-liver ratio of less than 25%. SIRT with Y-90 showed promising roles in operable disease as a supportive modality for multidisciplinary treatment of low-volume disease with subsequent definitive resection or ablation (10). Although more studies are required, poor response is predicted in patients with extensive disease volume, failure of multiple lines of chemotherapy, significant disease progression on therapy, cirrhosis, higher levels of tumor markers, and certain somatic mutations (*KRAS*, *BRAF* and *TP53*) (10). Lewandowski *et al.* (54) reported in their prospective non-randomized study 214 patients with metastatic CRC who were treated with SIRT over 12 years. Each patient received 1–3 treatments with an average of 1.8. The authors concluded the safety of the intervention with no reported treatment-related mortalities. Interestingly, patients with good performance status, albumin >3 g/dL, exposure to ≤2 cytotoxic drugs, no biologic usage, and no extrahepatic disease had longer survival (54). A

small phase II randomized trial has compared systemic fluorouracil/leucovorin chemotherapy with and without single administration of SIRT in 21-patient with metastatic CRC (55). There was a significant improvement in time to progressive disease (18.6 versus 3.6 months, P<0.0005) and median survival (29.4 versus 12.8 months, P=0.02) in the combination therapy group (55).

Despite the analytic limitations in the randomized phase III SIRFLOX trial, the addition of SIRT to the standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen as a first-line treatment in patients with liver-dominant or liver-only CRLMs was associated with improved objective response in the liver and acceptable rates of adverse events (56). This study demonstrated no improvement in PFS, although it included many subjects with significant extrahepatic metastatic disease (56). Subsequent combined meta-analysis of the FOXFIRE, SIRFLOX, and FOXFIRE-Global randomized studies was published in 2017 (57). This aggregate analysis addressed the clinical value of adding SIRT to chemotherapy in 1,103 chemotherapy-naïve patients with unresectable or ablatable liver-dominant CRLMs. Of the enrolled patients, 65% had liver-limited disease. Patients were randomized to FOLFOX therapy with or without single administration of SIRT. The authors concluded that the addition of SIRT to first-line FOLFOX regimen did not improve OS (hazard ratio: 1.04; 95% CI, 0.90–1.19; P=0.61), and thus such combination is not recommended for universal use. There was no significant difference in conversion resection which might have been explained by extrahepatic disease progression, despite the better liver control and improved radiological response in the combination therapy group (57). Two of the weakness of these trials the large number of patients with extrahepatic disease and the under-utilization of the new biological, immuno- and actionable mutation targeting therapies during the 8-year recruitment period. These advanced therapies could have improved extrahepatic control and therefore improved conversion hepatectomy rate.

Margin accentuation

SIRT provides the ability of testing tumor biology and response in the setting of borderline resectable CRLMs. The proximity of the tumor to portal venous bifurcation, bile duct confluence, or hepatic venous junction with inferior vena cava may place a challenge on resectability. The anticipation of R1 resection on radiographic studies should avert the surgeon from proceeding to resection in patients with CRLM. Debulking has not proven to provide survival benefits in CRLM as it did in neuroendocrine liver metastases (58). In these situations, concurrent use of SIRT with chemotherapy may prepare patients with such borderline disease to get ultimate R0 resection or ablation (59,60).

Radiation lobectomy and contralateral hypertrophy

While PVE/PVL can induce immediate FLR hypertrophy, SIRT has the advantage of controlling the liver disease and allowing FLR hypertrophy over an extended period of time (3–12 months) (38,61). The innovation of hybrid interventional radiology/operating suites helps fast-track patients with bilobar liver disease. This integrated approach, we propose, was reported earlier and revolves around resection the left lobar disease and performing right-sided SIRT during the same session, then after inducing left-sided hypertrophy in 4–12 weeks, the surgeon proceeds to perform a right or right extended hepatectomy (62). This setup prevents the interruption of systemic therapy for prolonged time, allows to assess for hidden contralateral disease, or even boost loco-regional control during the resumption of systemic therapy while anticipating a safer second-stage hepatectomy (10). Inadequate FLR after SIRT with Y-90 can be salvaged with PVE as it was proven to be safe and effective (61).

Future aspects of transarterial radioembolization

There have been many strides in the field of therapeutic nuclear medicine. Ethiodized oil is a radio-opaque agent that serves as an appropriate vehicle for therapeutic radionuclides (63). It has a direct uptake affinity to cancer cells in the liver. Beta-emitting Iodine-131 (^{131}I) conjugated with this agent has showed higher tumor radiation dose compared to Y-90 microspheres. The concern about the low energy transfer and resistance development of beta-emitting radioisotope has led many investigators to look for alternatives (63). Targeted alpha-particle therapy (TAT) has been emerging as a potential treatment for metastatic disease using alpha-emitting particles such as Actinium-225 (^{225}Ac), astatine-211 (^{211}At), and Lead-212 (^{212}Pb) (64,65). They provide a short range of high linear energy transfer to cancer cells with minimal toxicity to surrounding tissues. Utilizing radioimmunotherapy approaches, these particles are attached to monoclonal antibodies or peptides that attracts to tumor antigens or receptors (66). These promising targeting therapies with better energy delivery are the future of precision medicine, as we hope they find their way to patients with CRLM.

Summary

Despite the fact that SIRT with Y-90 is commonly used as an end-of-line therapy, it may have more opportunities. Although FLR hypertrophy may take 3–12 months, the concurrent SIRT role of influencing a loco-regional disease control has rendered it to be a useful tool in some pathologies with certain strategic goals. We believe that the main roles of this therapy in operable disease are to treat minimal low-volume disease as an element of definitive treatment with subsequent resection or ablation, induce contralateral hypertrophy in ipsilateral large-volume disease and increase margin accentuation while maintaining clearance of critical structures in the liver.

There are more opportunities to validate the role of SIRT with Y-90 as a first-line therapy adjunct to surgical resection. One opportunity is to initiate a study designed as an umbrella clinical trial, where CRLMs are classified by central radiographic review into resectable with wide margins, resectable with narrow margins, borderline resectable with vicinity to major vascular/biliary structures, and unresectable groups.

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Footnote

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