Radioembolization

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Introduction

Surgical resection is the most effective method for improving survival in patients with colorectal liver metastasis (CLM). However, many patients are deemed unsuitable for liver resection, both at initial manifestation and/or at recurrence [1]. For these patients, the standard of care is systemic treatment with chemotherapy and/or molecular target agents. Eventually, the majority of patients will progress in the liver unless surgically resected, and there remains a high demand for effective treatments in chemo-refractory patients [2]. For these reasons, loco-regional liver therapies are increasingly being employed for the purposes of downstaging for subsequent resection, as an adjunct to improve resectability, and for improving palliative results [1, 2].

Over the last few decades, a number of intra-arterial liver-directed therapies for targeted treatment of CLM have been developed. These therapies are based on the principle that the majority of the blood supply to the liver tumors is originated from the hepatic artery, as opposed to the portal venous system that supplies the non-tumor liver parenchyma. The most widely used intra-arterial therapies for CLM are hepatic arterial infusion chemotherapy, transarterial chemoembolization, and radioembolization with yttrium-90 microspheres [2].

Radioembolization represents a valuable treatment option that is increasingly being considered as part of a multimodal treatment approach for the management of liver tumors. Yttrium-90 can deliver high cumulative doses of radiation preferentially to liver tumors, and has shown encouraging response rates with an excellent tolerance profile [3]. Indeed, accumulating evidence supports the safety and efficacy of this intra-arterial liver-directed treatment for the management of hepatic tumors in patients in whom the liver is the sole or dominant site of disease [3–6].

In this chapter we shall discuss the rationale, benefits, and limitations of radioembolization with yttrium-90 microspheres in the treatment of CLM.

Principles and Technique of Radioembolization

Radioembolization (RE) is defined as the intra-arterial delivery of micron-sized radioisotope-tagged particles that preferentially and permanently embed in tumor as opposed to normal tissue [3]. In the literature, this treatment is also named as selective internal radiation therapy or intra-arterial microsphere brachytherapy.

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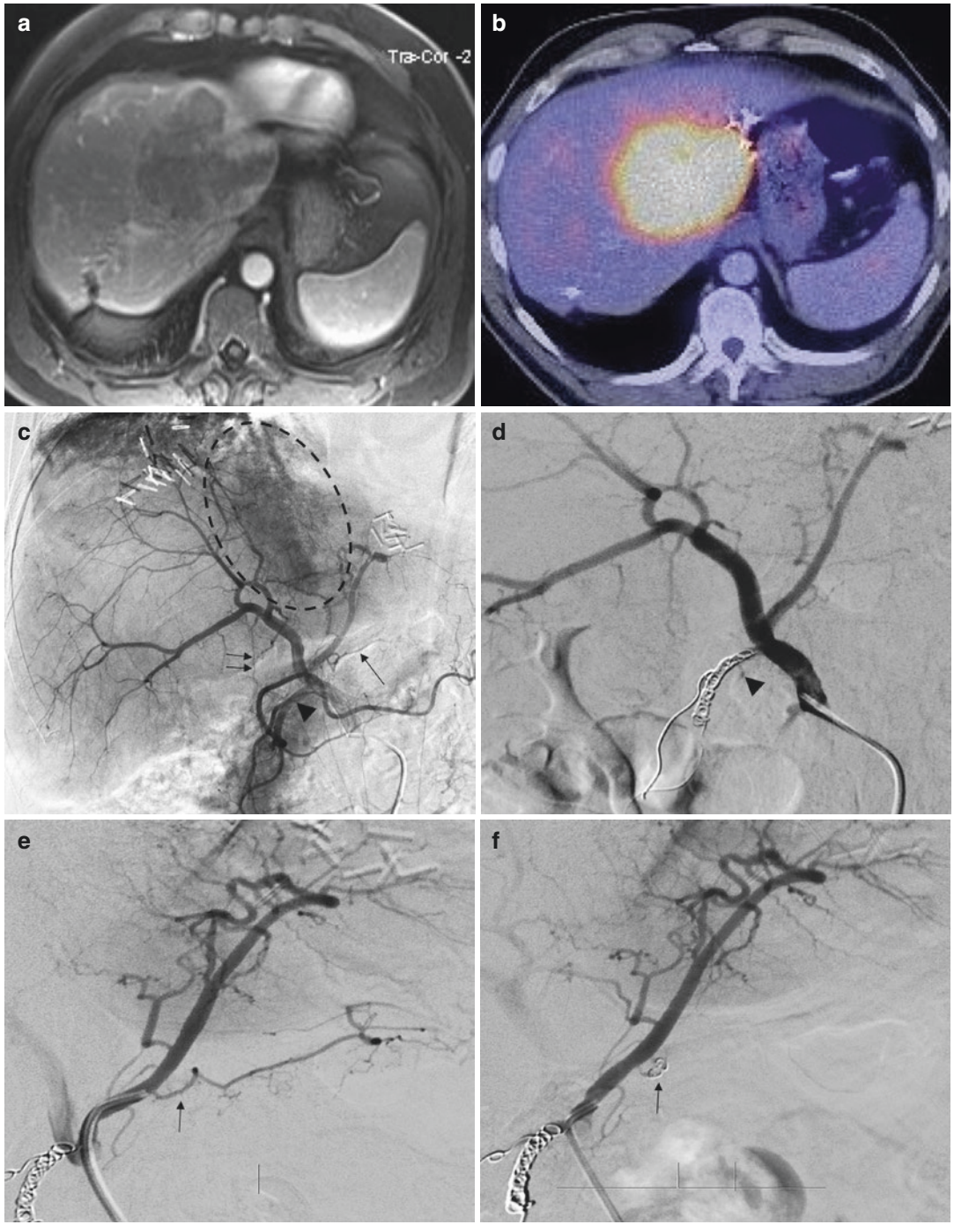
The aim of RE is to selectively target a high radiation dose to all metastasis within the liver regardless of their location, while limiting radiation to non-tumour liver parenchyma within tolerable levels. The preferential intra-arterial deposition of microspheres carrying a high-energy radiation source into the tumor capillary bed provides a tumoricidal dose of radiation (>120 Gy) that is absorbed over a limited time [3, 4]. The most commonly used radiopharmaceutical (high-energy radiation source) in the setting of RE is Yttrium-90 (Y90), a pure *B*-emitter with mean liver tissue penetration of 2.5 mm (maximum 11 mm). Given the short half-life of Y90 of 64 h, approximately 95% of the radiation dose is delivered within 11 days from treatment administration [3–5].

The preferential delivery of Y90 microspheres to liver tumors is based on several anatomic and pathologic factors that are unique to the liver and hepatic solid tumors, and follows the rationale of all modalities of intra-arterial liver therapies. It has long been established that normal liver parenchyma derives approximately 80% of its blood from the portal vein, whereas macroscopic liver tumors derive almost 100% of their blood supply from the hepatic artery [1, 2]. In addition, there is an increased microvascular density up to 20:1 ratio in liver tumors compared with normal liver parenchyma [1–4].

The size of the microspheres is critical to optimal implantation in the tumor vascular bed. To be effective, Y90 microspheres must be deposited within the network of tumor vessels (tumor capillary bed). As the median penetration of Y90 is 2.5 mm, any microsphere situated within the afferent tumor vessels, more than that distance from the tumor would probably not have a direct antitumor effect [3]. For this reason, the microspheres currently used for RE are small enough (average 32 μm) to allow optimal access and deposition within the tumor plexus, but large enough to prevent systemic passage through the capillary bed into the venous circulation [1].

The RE-Y90 procedure is performed in an angiographic suite provided with cone beam computed tomography (CBCT) under local anaesthesia, percutaneous femoral puncture, and on outpatient basis. It is a two-step procedure performed in 2–4 weeks interval: the preparation/simulation phase and the treatment phase [2, 7]. In the former, a liver arterial angiogram is performed to identify the arterial anatomy of the liver, potential arterial variants, tumor feeders, and extrahepatic branches coming off the hepatic arteries, which might require proximal coil embolization in this session in order to avoid Y90 microsphere delivery in these territories during the treatment phase [7]. The right gastric artery, and sometimes the falciform artery, should be coiled when left or medial lobe treatment is foreseen during the treatment phase. The gastroduodenal artery and cystic artery embolization is controversial when a right lobe treatment is foreseen, but it is highly recommended to deposit the injection catheter beyond its origins. The main concept is to avoid or otherwise embolize any arterial branch supplying an extrahepatic territory downstream of the final catheter position for microsphere injection [5, 7] (Fig. 9.1). In the same angiographic session, once the position of the catheter that will be used for the treatment phase is decided, a standard dose of technetium-99m-labeled macro

Fig. 9.1 Fifty-two-year-old male with recurrent CLM in the left lobe (liver resection was performed 4 years earlier) with liver progression despite three lines of chemotherapy. (**a**) Gadolinium-enhanced MRI. (**b**) PET-CT. (**c**) Hepatic angiogram at preparation phase shows tumor enhancement (*dotted circle*). Notice the right gastric (*arrow*), gastroduodenal (*arrowhead*) and falciform (*double arrow*) arteries. (**d**) Hepatic angiogram after gastroduodenal coil embolization (*arrowhead*). (**e**) Left hepatic angiogram clearly depicts the right gastric artery (*arrow*) supplying the lesser stomach curvature. (**f**) Left hepatic angiogram after right gastric artery coil embolization (*arrow*). Notice that the stomach is no longer supplied. (**g**) Selective angiogram of left hepatic artery (LHA) before Y90 infusion*. (**h**) Selective angiogram of middle hepatic artery (MHA) before Y90 infusion. (**i**) Follow-up PET-CT at 6 months after RE-Y90 showing complete response (no hyper metabolic activity) and calcification at the treatment site. *An ice pack was placed on the umbilical skin to induce flow arrest of distal falciform vessels (not shown)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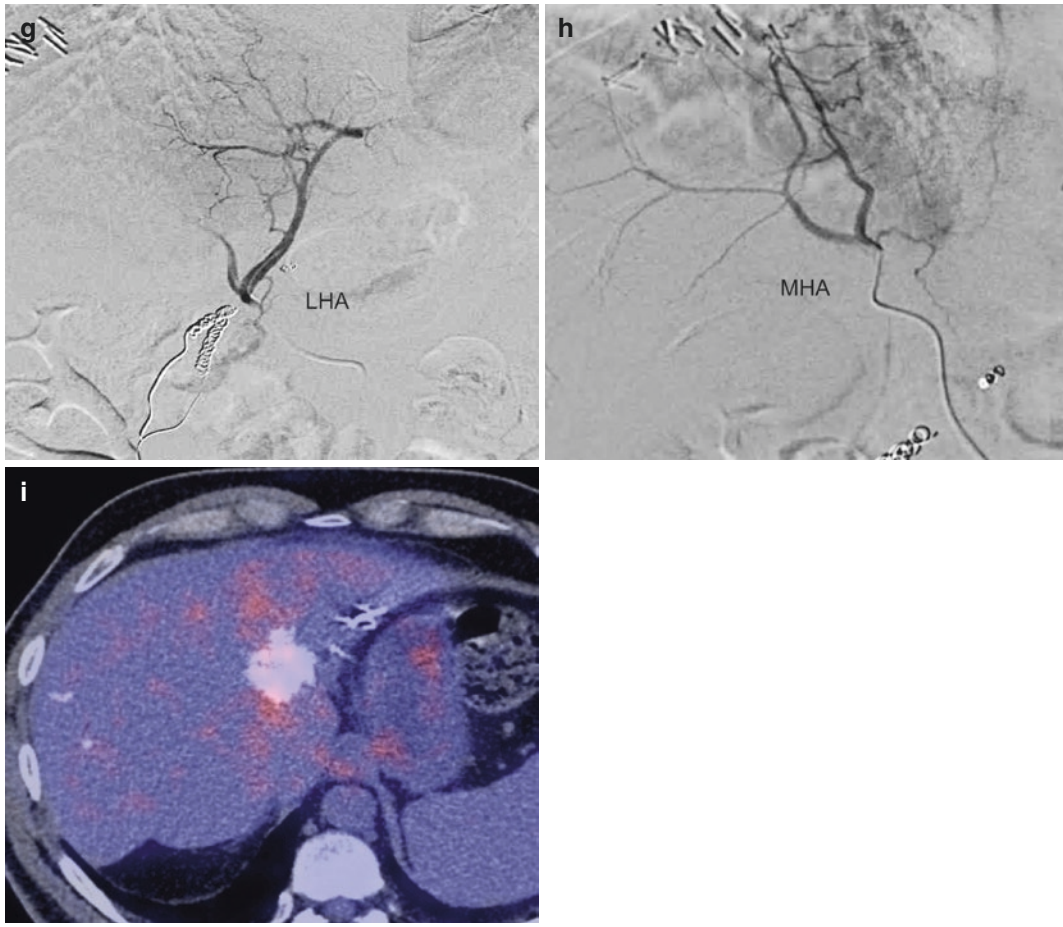


Fig. 9.1 (continued)

aggregated albumin (Tc99-MAA) is injected to check the distribution of the radio isotopic agent, simulating exactly what would be done in the second procedure. Planar and single-photon emission computed tomography are immediately obtained to identify potential extrahepatic deposits of Tc99-MAA, measure the lung shunt fraction (LSF), and to determine the intake ratio of the tumor relative to adjacent liver parenchyma. Once extrahepatic deposits of Tc99-MAA and a high LSF are ruled out, the dose of Y 90 to be delivered at the treatment phase is then calculated using a specific formula. Once the preparation/simulation phase is completed, the patient is rescheduled for the treatment phase (on average 2–4 weeks later) again as an outpatient (Fig. 9.2).

In the treatment phase, a new hepatic angiogram performed from the catheter is positioned in the exact position established during the simulation phase, and the liver vasculature is again verified in order to check the stability of the previous embolization of extrahepatic arteries and to rule out any new extrahepatic supply, preferentially using CBCT. Although uncommon, supplementary embolization may be performed if needed. In this session the Y90 microspheres are then slowly injected, mimicking the injection of Tc99-MAA at the simulation phase. The same day, before leaving hospital, a positron emission tomography (PET) or bremsstrahlung nuclear imaging is performed to check the intra arterial injected Y90 distribution.

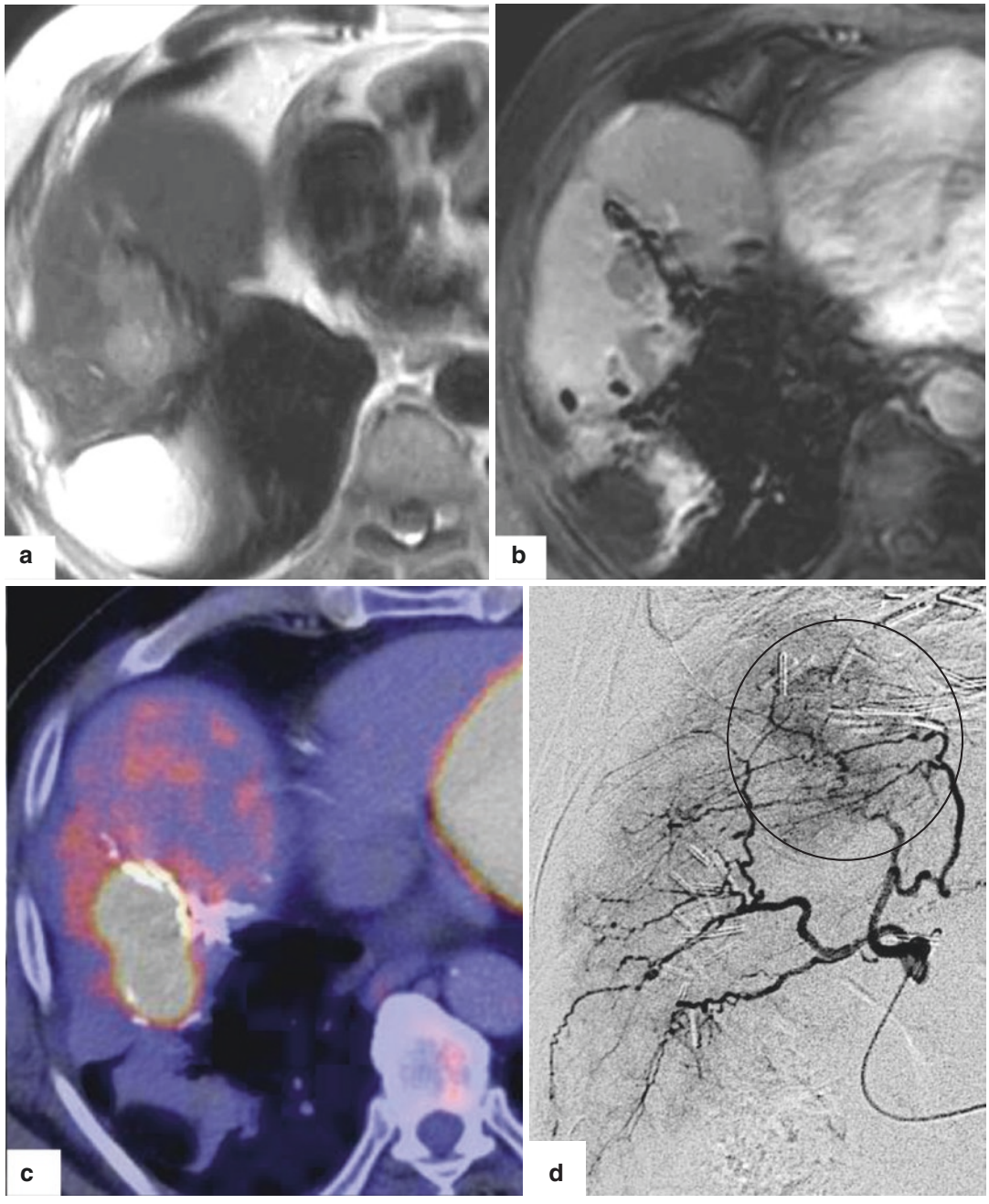
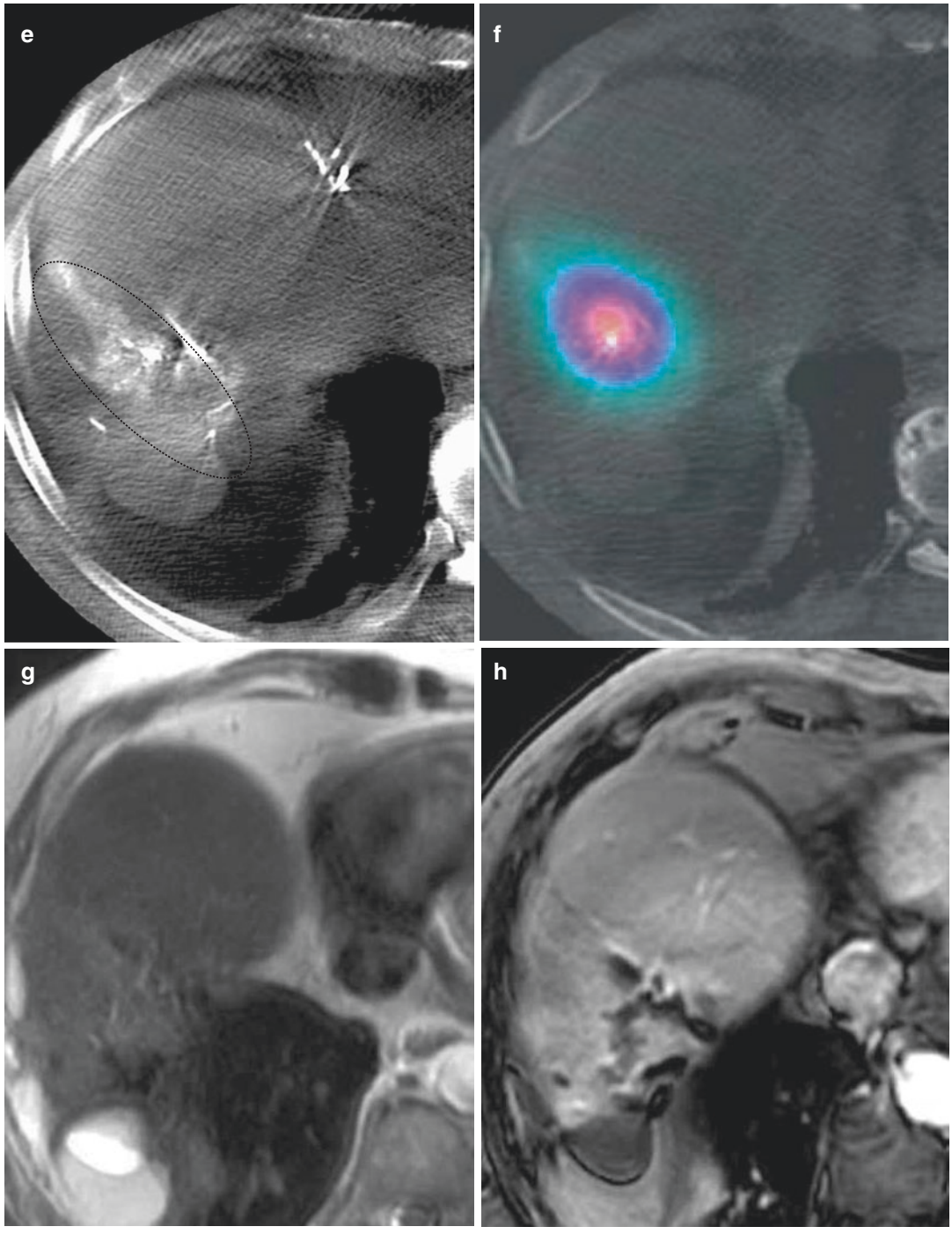


Fig. 9.2 Seventy-eight-year-old male with recurrent isolated CLM in segment VIII despite previous surgery and two lines of chemotherapy. (**a**) T2-weighted MRI. (**b**) Gadolinium-enhanced MRI. (**c**) PET-CT. (**d**) Selective angiography of segment V and VIII shows tumor enhancement (*circle*). (**e**) Intra-arterial CBCT confirms tumor enhancement in segment VIII (*dotted circle*). (**f**) MAA tumor uptake at SPECT-CT confirming correct catheter position for treatment. (**g**) T2-weighted MRI. (**h**) Gadolinium enhanced MRI at 3-month follow-up after RE-Y90 shows treatment response by tumor lack of enhancement and shrinkage (*arrows*). (**i**, **j**) Follow-up contrast-enhanced CT at 15 months confirms complete tumor response



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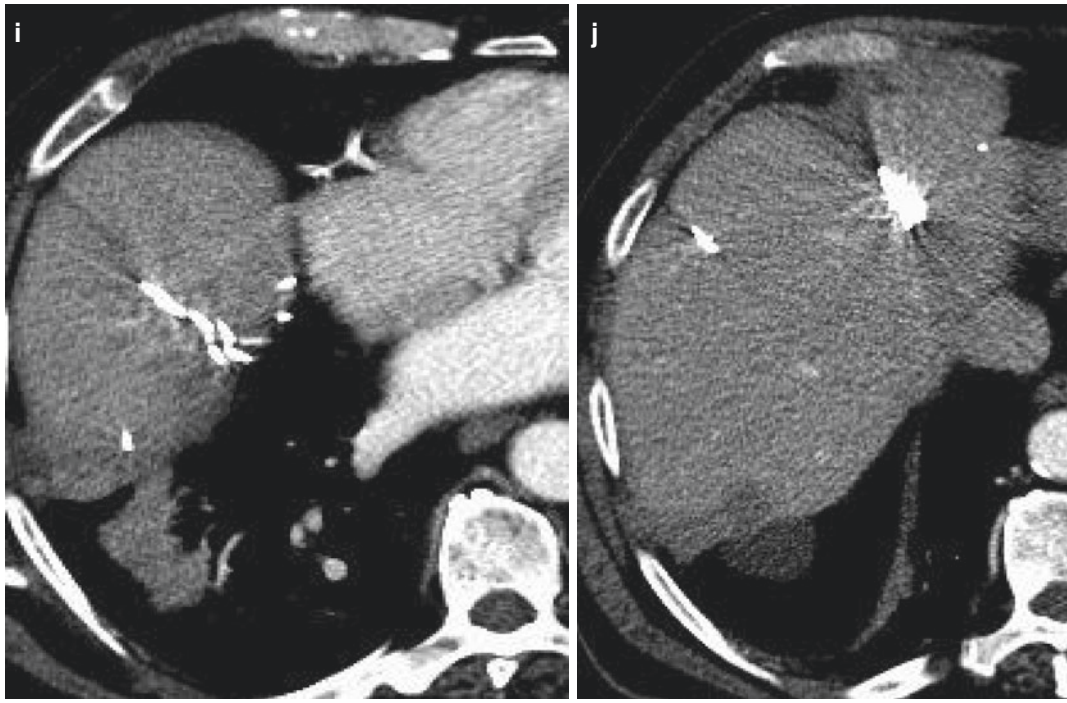

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Indications, Contraindications, and Patient Selection

RE-Y90 in CLM is reserved for patients that are not candidates for surgical resection. A Consensus Panel Report by the Radioembolization Brachytherapy Oncology Consortium provides detailed guidelines for RE-Y90 eligibility and patient selection [3]. Main indications of RE-Y90 are suited in different clinical settings such as failed first- or second-line systemic chemotherapeutic regimens, salvage or palliative treatment and neoadjuvant therapy prior to surgical resection [2, 3, 6, 8]. Recent publications showed promising results of RE-Y90 in earlier metastatic disease associated with induction and maintenance chemotherapy, including level 1 evidence of better liver progression-free survival (PFS) when FOLFOX was associated to RE as first-line treatment [9, 10].

The best candidates for RE are patients with unresectable liver-only or liver-dominant tumor burden, preserved liver function, and good general clinical status [6]. Therefore, pre-treatment evaluation includes not only a clinical and laboratory check-up but also imaging studies, including a chest CT together with a three-phase MDCT and/or gadolinium-enhanced MRI of the liver, not only for assessment of liver tumor burden but to rule out or measure extrahepatic disease. A whole-body FDG-PET/CT may contribute to decision-making due to its high sensitivity for intrahepatic and extrahepatic tumor. Furthermore, therapy–response assessment is more accurate if a metabolic imaging has been performed before the RE-Y90, as well as MDCT or MRI.

In patients with excessive tumor burden and/or limited hepatic reserve, demonstrated by elevated levels of bilirubin (>3 mg/dl), elevated liver enzymes (AST/ALT 5 × upper normal limit), altered INR (>1.6), or reduced serum albumin (<3 g/dl), RE is contraindicated because of the risk of developing radiation-induced liver failure [3–8]. Patients with poor clinical condition

(Eastern Cooperative Oncology Group: ECOG >2) are also at a higher risk of developing severe side–effects, and treatment outcome is usually worse; therefore, the indication of RE is questionable in this clinical situation [3–8].

As in any other intra-arterial liver-directed therapy, the renal function and the biliary integrity should be monitored before treatment. Renal function impairment is a relative contraindication because of the use of iodine contrast media necessary to perform the diagnostic and therapeutic angiogram previous to RE-Y90. Patients with impaired biliary sphincter at the duodenum junction (biloenteric anastomoses, papillotomy, biliary stenting) may be at a higher risk of cholangitis and liver abscess formation in the follow-up weeks after RE, but this does not constitute an absolute contraindication [5, 7]. In a specific patient, these potential hazards have to be weighed against the potential benefit of the RE treatment.

In a small number of patients, RE could be contraindicated due to vascular abnormalities or the extent of lung shunting (lung exposure >30 Gy). These criteria are established at the work-up procedure performed by the interventional radiologist (preparation/simulation phase) before the RE-Y90 is confirmed, thereby preventing inappropriate treatment of the patient. The interventional radiologist may correct some cases of excessive shunting to the lung or gastrointestinal tract by proper vessel embolization, as described in previous paragraphs [6, 7]. Thus, an appropriate previous preparation/simulation test (low LSF, no extrahepatic deposits of Tc 99-MAA, acceptable dosimetry) is mandatory to perform the RE treatment safely.

Efficacy and Clinical Results

Multiple studies suggest that RE-Y90 is effective in slowing disease progression and improving survival. Localized high-dose tumor-directed radiation is an effective treatment for reducing the burden of CLM [4, 6, 8, 11–14]. A single treatment with RE induces profound cytoreduction of CLM in the liver, and significantly prolongs time to progression (TTP), PFS, and overall survival (OS), even among patients with highly chemo-refractory disease [3, 4]. The recruitment of a large proportion of these patients for RE has been among those with advanced, chemo-refractory disease [3–6, 15–17]. However, RE-Y90 has recently been shown to downsize tumors for potentially curative surgical resection in patients with earlier unresectable CLM that have received chemotherapy before or are chemo-refractory[18]. In clinical practice, RE-Y90 is integrated in the paradigm of management of CLM in three different settings: as first-line treatment, second-line treatment or as salvage therapy [4, 6, 9].

Radioembolization as First-Line Treatment

The current clinical data support the potential of RE-Y90 in downstaging and delaying liver disease progression in patients with CLM. Such findings provide opportunities to develop RE-Y90 treatment in patients with predominant liver disease to prolong first-line DFS and OS, and to impact positively on tumor downstaging for the potential of conversion to allow hepatic metastases resection [6, 9].

Two pioneering randomized clinical trials performed in the last decade showed the utility of RE-Y90 in the first-line treatment of patients with CLM, with encouraging results in terms of overall response rates (ORR), PFS, and OS [11, 12]. These studies compared the use of intra-arterial FUDR with and without RE and intravenous FU/LV with and without RE respectively, and clearly showed the benefits of RE-Y90. These studies have some limitations, such as the small size and the use of cytotoxic drugs that are not currently used as first-line treatments. To study the utility of RE-Y90 in the current paradigm of CLM chemotherapy regimens, three international randomized Phase III trials (the SIRFLOX, FOXFIRE and Global FOXFIRE) were conducted to report on the PFS and OS [10, 19, 20]. The SIRFLOX study showed improvement in liver PFS, with 31% reduction in risk of liver progression when combining RE-Y90 with FOLFOX, while not increasing toxicity [10].

The FOXFIRE and Global FOXFIRE are still ongoing, and will be powered to test the impact of RE-Y90 on OS [20].

Some authors suggest the incorporation of RE-Y90 in the first-line treatment, for the purpose of extending clinical benefits from maintenance therapy [9]. Indeed, the most common approach toward unresectable CLM involves the use of induction chemotherapy combined with bevacizumab. However, chemotherapy-induced toxicities encountered with combination regimens may lead in some patients to a milder maintenance form of treatment after few weeks of induction therapy. Maintenance therapy, usually fluoropyrimidine with bevacizumab, has limited efficacy and progression occurs in few months in the majority of patients. The combination of RE-Y90 during induction therapy or during maintenance therapy has the potential to prolong liver PFS, therefore improving patient outcome and delaying the need for more toxic second-line combination treatments [9]. Interestingly enough, the European Society of Medical Oncology (ESMO) consensus guidelines suggest that RE-Y90 of CLM in earlier treatment lines may be interesting as consolidation treatment [20].

Another beneficial possibility to combine RE-Y90 in the first-line setting is in those patients who cannot tolerate intensive chemotherapy. Aged patients with CLM and vascular comorbidities may be frail enough to be considered for combination chemotherapy or antiangiogenic agents. For such patients, first-line treatment is often limited to single agent 5-FU/LV or capecitabine monotherapy, a strategy associated with a median PFS of 4–5 months [9]. The integration of RE-Y90 with fluoropyrimidine in the first-line treatment of liver-predominant CLM has the potential of delaying progression without significantly impacting patients' performance status [9]. An advantage of RE-Y90 which should always be considered is its favorable toxicity profile when combined with fluoropyrimidine or FOLFOX, and yet it results in major clinical responses in the majority of the treated population [13].

The high efficacy of conversion therapy with aggressive chemotherapy such as FOLFOXFIRI discourages the initial use of RE-Y90 in CLM in the neoadjuvant setting, except for specific situations such as intolerance or inadequate initial response to induction chemotherapy [9]. However some authors suggest that RE-Y90 may be a good alternative in potential candidates for resection, but with small future liver remnant volume [8, 21, 22]. A matched-pair analysis comparing RE-Y90 with portal vein embolisation showed a lesser, but still pronounced benefit of RE-Y90 with regard to contralateral liver hypertrophy, following simultaneous treatment of the ipsilateral tumor load with Y90 [22].

Radioembolization as Second-Line Treatment

Limited prospective data exist on the second-line integration of RE-Y90 in combination with chemotherapy in the second-line treatment of metastatic colorectal cancer [9]. A Phase I clinical trial has evaluated the combination of irinotecan plus RE-Y90 in patients with CLM who failed at least one line of 5-FU- based treatment [14]. In this study, ORR was found in 48% of patients, with median PFS and OS considered favorable in comparison to second-line irinotecan therapy, where responses are historically <10% [14]. Median survival following RE-Y90 in the second-line setting after chemotherapy compares well with similar patients receiving second-line chemotherapy combined with aflibercept and bevacizumab beyond progression [18, 23]. These results are in line with the first-line clinical trials, and substantiate the potential of RE-Y90 in enhancing chemotherapy response and delaying tumor progression. Some authors suggest using this strategy in patients with KRAS or BRAF mutations with no further options of salvage therapy, to delay progression of liver disease [9].

Radioembolization as Salvage Treatment

Patients with CLM who are refractory to first- or second-line chemotherapy have a dismal prognosis, even with the newly developed antibiologic

agents. In this setting, several prospective studies have shown that RE-Y90 is safe and efficient alone or combined with a radio-sensitizing chemotherapy regimen as salvage therapy [3, 8, 12, 13, 16].

The results of clinical trials combining RE with second- or third-line chemotherapy indicate that an objective response may be seen in 30–48% of patients [8, 14]. Furthermore, studies in chemo-refractory patients have reported that disease progression is delayed following RE-Y90, and that survival is prolonged compared to either randomized, matched-pair, or historical controls [3, 15, 16]. The median survival following RE-Y90 in patients with two or three prior lines of chemotherapy respectively compares favorably with patients in a similar setting using regorafenib or placebo [23]. The evidence in the literature shows that, even among heavily pretreated patients, RE-Y90 appears to have a favorable risk/benefit profile and offer a more target approach for the management of dominant CLM [24]. This approach is confirmed by the ESMO consensus guidelines in CLM, which recommend the use of RE-Y90 for patients with liver-limited disease failing available chemotherapeutic options [21].

Side-Effects and Complications

For better tolerance of RE-Y90, some medications are regularly indicated before and after treatment, although side-effects and toxicity are low if the procedure is carefully performed. The most common side-effect of RE-Y90 is a mild post-embolization syndrome that occasionally may last some days after treatment [4, 5]. The most common side-effects include fatigue, nausea, and abdominal pain, the former being the most prominent symptom. Fever is uncommon but may be present as a consequence of the inflammatory effect of liver radiation or tumor necrosis, and should not be confused with bacterial infection. Symptomatic treatment of post-embolization includes corticoids, anti-emetics and analgesics starting the same day of treatment [4, 5, 7]. In some patients, nausea may last several days, occasionally being severe enough to require long-standing anti-emetic medication that should be continued until the symptoms subside. As organs adjacent to the liver may also receive radiation doses if microspheres are lodged on the periphery of the liver, some radiation gastritis is expected after treatment in such a case [4, 5]. Therefore, prophylactic pump proton inhibitors are commonly indicated before RE-Y90, and continued for at least 1 month after treatment [5, 7].

Severe complications are uncommon given correct patient selection, adequate pretreatment assessment (preparation/simulation phase), and a meticulous Y90 microsphere delivery during treatment. Anyway, serious complications of RE-Y90 have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than the liver [5, 25]. Non-target infusion of Y90 may lead to ulceration or bleeding in the gastro-intestinal tract and pancreatitis. The gastro-intestinal ulcers are resistant to medical therapy, and may need surgery [25]. These complications may be spared with careful analysis of pre-treatment angiography and SPECT-CT, together with the use of CBCT to rule out extrahepatic deposits of Tc-99 MAA or contrast medium. In addition, Y90 should be carefully delivered on the treatment day ,avoiding at all means arterial reflux or over-injection of the radioactive material [7].

Radiation-induced pneumonitis is another uncommon complication that may occur because of lung sensibility to radiation. It should be noticed that after any intra-arterial injection into the liver, a small fraction of the delivered substance is shunted into the lung through tumor arteriovenous shunts [4, 5]. The risk of radiation-induced pneumonitis can be somewhat predicted in the simulation phase by measuring the LSF by planar scintigraphy [3, 7, 26]. Pulmonary toxicity is avoided if the LSF is <20% or the accumulated lung dose <30 Gy [4, 5]. The symptoms indicating radiation pneumonitis include dry cough, progressive dyspnea, and restrictive ventilation deficits resulting in deteriorated lung function, and usually respond to corticoid therapy [5, 25].

Radiation-induced liver disease (REILD) is a rare complication, with an incidence ranging between 0–4% [5]. It results in various degrees of hepatic decompensation, and is indistinguishable from hepatic veno-occlusive disease [5, 25]. It is usually manifested clinically by the development of anicteric ascites and increased abdominal girth, as well as rapid weight gain with hypo albuminemia [5]. Although jaundice may be present, it is uncommon at presentation. Blood tests show normal or mild increase in the bilirubin levels, with a substantial increase of alkaline phosphatase. Several reports have indicated that REILD is more likely with liver tumor burden <70% and delivery dose to the liver <150 Gy [4, 5, 25]. Since radiation dose is related to liver toxicity, performing RE-Y90 in a repeated fractioned fashion is recommended to reduce the risk of liver toxicity, especially in patients with previous heavy chemotherapy treatment if a whole-liver treatment is needed [8, 26]. In such a case, Y90 is infused in the right hepatic artery separated by 4 weeks from infusion via the left hepatic artery. Prophylaxis with corticoids may be of benefit, and is regularly administered, as mentioned above. If REILD occurs despite cautious measures, treatment is instituted with diuretics, sodium restriction, and continuous corticoid therapy. Hepatotoxic drugs should be avoided, and in extreme cases a TIPS procedure may be of benefit.

Other complications such as radiation-induced cholecystitis and biliary tract injury are uncommon, and may be prevented with proper patient selection and by sparing the cystic artery before Y90 infusion [5, 7].

Follow-Up and Response Assessment

Follow-up is mandatory for results assessment and to detect eventual complications, as well to integrate this treatment among multimodality options. It is usually performed in a multidisciplinary fashion, and depends on the treatment plan of each patient.

Clinical evaluation and liver blood tests after RE-Y90 are recommended to determine the outcome of treatment. Contrast-enhanced CT or MRI and tumor biomarkers are performed for response assessment and to rule out intra- or extrahepatic new disease at 6 and 12 weeks. Oncologic responses at cross-sectional imaging are usually depicted after 3 months of treatment, with the best results shown after 6 months. Metabolic imaging under PET-CT may contribute to better response assessment if it has also has been performed at baseline.

The RECIST system is not an accurate method to assess oncologic response, as is the case with other imaging-guided liver-directed therapies. Indeed, tumor size after treatment does not reflect the number of viable tumor cells, tumor enhancement being a more reliable alternative. The most common imaging findings at cross-sectional images after RE-Y90 are liver edema congestion, and microinfarction that should not be mistaken for progression disease [4, 5]. These signs are reversible and are probably due to radiation inflammatory liver and tumor reactions. Tumor objective response may be demonstrated by tumor necrosis (absence of enhancing tumor at CT or MRI), but evidence of morphological changes may require 3 or more months after treatment. Tumor size reduction often may be observed at 6 months follow-up in good responders.

Since PET-CT has the ability to give information about tissue metabolic activity, comparison of a follow-up study to baseline PET-CT is highly contributive. In clinical practice, response is usually assessed clinically, by tumor markers and cross-sectional imaging as in any other type of treatment, but limitations of RECIST and the potential role of PET-CT should be considered.

Conclusions

RE-Y90 is a powerful tool in patients with liver metastasis due to the potential of augmenting regional response of systemic chemotherapies, and increases the number of patients who are candidates for resection. Application of this recently introduced liver-directed therapy might contribute to extending the benefits

of curative hepatic resection to a broader group of patients. Caution with regard to patient selection, treatment preparation, and performance is particularly important to prevent serious toxicity being associated with this highly efficacious treatment [4, 7]. Improvements in predicting dosimetry will lead to optimization of treatment outcome, even in borderline treatment candidates [26]. With the sustained accumulation of promising clinical results, RE-Y90 is moving forward from the salvage setting indication to its use in earlier stages of CLM. The optimal modern management of CLM requires a multidisciplinary team with various specialists including liver surgeon, medical oncologist, interventional radiologist, nuclear medicine physician, and others who have a thorough understanding of the latest diagnostic and therapeutic options.

References

1. Mahnken AH, Pereira PL, De Baère T. Interventional oncologic approaches to liver metastases. Radiology. 2013;266:407–30.
2. Xing M, Kooby DA, El-Rayes BF, et al. Loco regional therapies for metastatic colorectal carcinoma to the liver-an evidence-based review. J Surg Oncol. 2014;110:182–96.
3. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68(1):13–23.
4. Kennedy A, Coldwell D, Sangro B, et al. Radioembolization for the treatment of liver tumors: general principles. Am J Clin Oncol. 2012;35(1):91–9.
5. Ahmadzadehfar H, Biersack HJ, Ezziddin S. Radioembolization of liver tumors with yttrium-90 microspheres. Semin Nucl Med. 2010;40:105–21.
6. Coldwell D, Sangro B, Wasan H, et al. General selection criteria of patients for radioembolization of liver tumors: an international working group report. Am J Clin Oncol. 2011;34(3):337–41.
7. Denys A, Pracht M, Duran R, et al. How to prepare a patient for transarterial radioembolization? A practical guide. Cardiovasc Intervent Radiol. 2015;38(4):794–805.
8. Wasan H, Kennedy A, Douglas C, et al. Integrating radioembolization with chemotherapy in the treatment paradigm for unresectable colorectal liver metastases. Am J Clin Oncol. 2012;35:293–301.
9. Fakih M. SIR-spheres radioembolization in the management of metastatic colorectal cancer: a medical oncology perspective. ColorectCancer. 2014;3(4):331–43.
10. Van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol. 2015;33(15):3502.
11. Gray B, Van Hazel G, Hope M, et al. Randomized trial of SIR-spheres plus chemotherapy vs chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol. 2001;12:1711–20.
12. Van Hazel G, Blackwell A, Anderson J, et al. Randomized phase 2 trial of SIR-spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol. 2004;88:78–85.
13. Sharma RA, Van Hazel GA, Morgan B, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol. 2007;25:1099–106.
14. Van Hazel GA, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol. 2009;27:4089–95.
15. Van den Eynde M, Hendlisz A, Peeters M, et al. Prospective randomized study comparing intra-arterial injection of yttrium-90 resin microspheres with protracted IV 5 FU continuous infusion versus IV 5 FU continuous infusion alone for patients with liver limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2009;27(15S):4096.
16. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103:324–31.
17. Seidensticker R, Denecke T, Seidensticker M, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35(5):1066–73.
18. Van den Eynde M, Flamen P, El Nakadi I, et al. Inducing resectability of chemotherapy refractory colorectal liver metastasis by radioembolization with yttrium-90 microspheres. Clin Nucl Med. 2008;33:697–9.
19. Sharma RA, Wasan HS, Love SB, et al. FOXFIRE: a phase III clinical trial of chemo-radio-embolisation as first-line treatment of liver metastases in patients with colorectal cancer. Clin Oncol (R Coll Radiol). 2008;20(3):261–3.
20. Dutton SJ, Kenealy N, Love SB, et al. FOXFIRE Protocol Development Group and the NCRI Colorectal

Clinical Study Group. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. BMC Cancer. 2014;14:497.
21. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27:1386–422.
22. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatology. 2014;59:1864–73.
23. Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for 90Y resin microspheres. Gastrointest Oncol. 2015;6(2):134–42.
24. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J ClinOncol. 2010;28:3687–94.
25. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. J Vasc Interv Radiol. 2009;20(9):1121–30.
26. Liu DM, Westcott M, Garcia-Monaco R, et al. Down and dirty with dosimetry: a practical understanding and approach to radioembolization. Endovasc Today. 2016;15