Radiation segmentectomy for hepatic malignancies: Indications, devices, dosimetry, procedure, clinical outcomes, and toxicity of yttrium-90 microspheres

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ABSTRACT

Radiation segmentectomy (RS) is a new approach to 90Y radioembolization that has been designed to increase the safety and efficacy of radioembolization in patients with unresectable hepatic malignancies. With this technique, high doses (>190 Gy) of radiation are delivered to the tumor through radioembolization performed in a segmental fashion, potentially increasing the radiation dose to the tumor while minimizing injury to the liver parenchyma. The aim of this review is to provide a summary of the indications, device choice, dosimetry, procedure, clinical outcomes, and toxicity of RS based on the clinical series currently available.

1. Introduction

Radiation segmentectomy (RS) with yttrium-90 (90Y) radioembolization for unresectable hepatic malignancies was developed to increase the radiation dose to the target tumor while minimizing injury to the liver parenchyma.1–3 By limiting the perfusion area of 90Y microspheres to liver parenchyma in no more than 2 hepatic segments,3 this technique can achieve a high radiation dose (>190 Gy) to the tumor-containing hepatic segments.4 Preliminary reports have shown that this technique is safe and effective in the management of hepatic malignancies.3,5,6 The purpose of this review is to provide an overview of the indications, device choice, dosimetry, procedure, clinical outcomes, and toxicity of RS based on the clinical series available to date.

2. Indications

Patients eligible for RS therapy are those with 1) a solitary tumor ≤5 cm (primary or secondary liver tumor); 2) liver-only disease (primary liver tumor without extrahepatic metastasis or secondary liver tumor without other organ metastasis); and 3) a tumor that can be isolated angiographically such that no more than 2 hepatic segments are perfused during treatment.4

3. Embolic devices

Two microsphere devices are commercially available: TheraSphere (glass, British Technology Group, UK) and SIR-Spheres (resin, Sirtex Medical, Australia).7 TheraSphere is the only microsphere device that has been used for RS because its activity per microsphere is higher than that of SIR-Spheres (2500 Bq vs 50 Bq).4,6,8 The small particulate volume of these glass microsphere doses allows for superselective small-volume, high-radiation administration while reducing the risk of vascular occlusion/stasis and incomplete administration.

4. Dosimetry

Calculating the correct dose for RS is critical; however, no consensus has been reached regarding how to best calculate doses for this procedure. Salem et al.,3 who were the first researchers to propose the concept of RS, calculated dose based on the mass of the lobe receiving radiation. Biederman et al.10 also reported dosimetry based on lobar volumes, even though all of the radiation particles were delivered to a segmental artery.

In general, radiation dosimetry in radioembolization is calculated primarily based on the assumption that microspheres will be distributed uniformly between the tumor and the normal parenchyma (Table 1; Fig. 1).11 However, this approach has obvious limitations, as the blood
supply to the tumor is predominantly from the hepatic artery, whereas the liver parenchyma is primarily perfused by the portal vein. Therefore, relative hepatic arterial hyperperfusion should be considered as an important factor in dosimetry calculations for radioembolization. With this technique, the tumor is assigned a hypervascularity ratio relative to the surrounding perfused parenchyma according to the subjective assessment of an interventional radiologist who has reviewed the results of an angiogram, a contrast-enhanced cross-sectional imaging study (computed tomography or magnetic resonance imaging), and a technetium-99 m macroaggregated albumin (99mTc-MAA) scan. This ratio ranges from 1 to 10, with a value of 1 representing a tumor with the same vascularity as the surrounding parenchyma and a value of 10 representing a tumor receiving 100% of the blood flowing to the tumor. Doses delivered to the tumor and normal parenchyma are then calculated as follows: 1) dose to tumor: $D_{ST} = 50 \times (1 - LSF) \times (1 - R) \times (P_F/M_T)$ and 2) dose to normal parenchyma: $D_{SN} = 50 \times (1 - LSF) \times (1 - R) \times (P_D)/(M_S - M_T)$, where $D_{ST}$ and $D_{SN}$ are the doses delivered to the mass of infused normal parenchyma ($M_S - M_T$) and tumor ($M_T$) upon segmental infusion, A is the administered activity in GBq, LSF is the lung shunt fraction, R is the fraction of activity remaining in the vial, and $P_D$ is the percentage of the microspheres delivered to the tumor (calculated from the hypervascularity ratio). Recent research has demonstrated that with the use of cone-beam computed tomography, the perfused volume (and hence mass) can now be measured during mapping angiography, resulting in more accurate dosimetry planning for RS. With this method, the total radiation dose used during RS is reduced when compared with the dose used during whole or lobar $^{90}\text{Y}$ radioembolization, but the radiation dose delivered to the tumor is high.

5. Procedure

The RS procedure follows the procedure established by general consensus for $^{90}\text{Y}$ radioembolization therapy. All patients undergone mapping angiogram so that the operator can 1) determine the vascular anatomy of the region, 2) identify the vascular supply of the tumor, 3) prophylactically embolize vessels that may lead to nontarget deposition of microspheres, and 4) perform 99mTc-MAA scans to determine LSF and splanchnic shunting. The feeding vessel of the segment(s) targeted for treatment is then identified and catheterized. The key to successful RS is to catheterize the target arterial territory as selectively as possible, including the entire tumor and excluding as much normal liver as possible, as this will increase efficacy while decreasing risk.

6. Clinical outcomes and toxicity

To assess the clinical outcomes and toxicity of RS in the management of hepatic malignancies, we conducted a systematic search of the literature. The PubMed database was searched for studies describing RS published between January 1, 1991 (introduction of first commercially available $^{90}\text{Y}$ product) and June 2018, using the keywords “radiation segmentectomy,” or “radiation lobectomy,” and “English language.” Review articles, animal studies, laboratory investigations, case reports, and duplicated clinical studies were excluded. A total of 4 prospective clinical studies were identified through this search. From these studies, a total of 155 cases, including 145 cases of hepatocellular carcinoma (HCC) and 10 cases of hepatic metastases (colorectal cancer, n = 7; breast cancer, n = 5; leiomyosarcoma, n = 1; carcinoid tumor, n = 1), were included in the final analysis (Table 2). Glass microspheres were used in all patients. Of note, 12 cases with segmental portal vein tumor thrombus were included in 1 study.

Table 3 summarizes the clinical outcomes of RS with respect to tumor response, time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The tumor response at 3 or 6 months was reported for all patients, with a complete response (CR) rate ranging from 20% to 81.8%, a partial response (PR) rate ranging from 10% to 70%, a stable disease (SD) rate ranging from 1.8% to 40%, and a progressive disease (PD) rate ranging from 0% to 8%. The disease control rates ranged from 92% to 100%. Two out of 4 studies reported the median TTP (10.6 and 28.8 months). and a median PFS of 7.1 months was reported in 1 study. The OS was reported in 2 studies (37.6 and 80.4 months). One-year survival rates of 86.5% and 98% were reported in 2 studies, and 1 study reported 3- and 5-year survival rates of 66% and 57%, respectively.

Among the patients enrolled in the 4 studies, only 1 patient developed rapidly progressive disease, exhibiting grade 3 bilirubin and albumin toxicity 3 months after RS and dying 4 months after RS. Grade 3 toxicity was reported in 9 patients, and Grade 1 and 2 toxicity was reported in 11 patients (Table 4).

7. Discussion

Although HCC is a radiosensitive tumor, the use of radiation in patients with HCC has been limited by the risks of nontargeted tissue exposure and radiation injury, as radiation affects both tumor cells and uninvolved normal cells. A typical safe dose (ie, one that does not cause substantial organ damage) of external beam radiotherapy is approximately 30 Gy for the whole liver. However, this dose is likely not high enough to lead to a tumor response. Catheter-based administration of $^{90}\text{Y}$ microspheres into the hepatic artery is thought to preferentially deliver therapy to the tumor, sparing the normal liver parenchyma. This technique allows for locoregional delivery of radiation doses of 80–150 Gy (or even higher).

The response of HCC to radiation therapy is dose dependent. In a group of 158 patients with HCC who were treated with 3D conformal radiotherapy, Park et al. observed response rates of 29.2%, 68.6%, and 77.1% in patients treated with doses <40 Gy, 40–50 Gy, and >50 Gy,
respectively. Similar results have been obtained with the use of 90Y microspheres. For instance, Vouche M et al. reported 102 patients with HCC who underwent RS because they were not candidates for surgical resection or radiofrequency ablation. Of these 102 patients, 33 (32.4%) patients were treated with RS. Padia et al. and Riaz et al. reported median doses to the tumor of 536 Gy (66.7% vs 25%; respectively), which is higher than in those exposed to lower radiation doses that exceeded 190 Gy than in those exposed to lower doses (66.7% vs 25%; respectively). Similar results have been obtained with the use of 90Y microspheres. For instance, Vouche M et al. reported 102 patients with HCC who underwent RS because they were not candidates for surgical resection or radiofrequency ablation. Of these 102 patients, 33 (32.4%) patients were treated with RS. Padia et al. and Riaz et al. reported median doses to the tumor of 536 Gy (66.7% vs 25%; respectively), which is higher than in those exposed to lower radiation doses that exceeded 190 Gy than in those exposed to lower doses (66.7% vs 25%; respectively). In the studies included in our analysis, Padia et al. and Riaz et al. reported median doses to the tumor of 536 and 1214 Gy (Table 5), approximately 10 times higher than the tumor-icidal dose of 60 Gy.

The purpose of RS, therefore, is to deliver an “ablative” dose to a target area in order to completely destroy the tumor along with the tumor-bearing parenchyma. This is achieved by prospectively determining lobar volumes, prescribing an intended lobar dose, and administering the dose into the feeding vessel(s) to increase safety and minimize radiation to normal parenchyma.

7.1. Imaging response and survival

Limited comparison data exist regarding hepatic imaging response and OS with RS therapy versus other local treatment methods. Only 2 such studies in patients with HCC who underwent RS because they were not candidates for surgical resection or radiofrequency ablation. Of these 102 patients, 33 (32.4%) cases underwent liver transplantation, and the pathology analysis demonstrated that complete necrosis was more common in patients treated with radiation doses that exceeded 190 Gy than in those exposed to lower doses (66.7% vs 25%; P = .03). In the studies included in our analysis, Padia et al. and Riaz et al. reported median doses to the tumor of 536 and 1214 Gy (Table 5), approximately 10 times higher than the tumor-icidal dose of 60 Gy.

The purpose of RS, therefore, is to deliver an “ablative” dose to a target area in order to completely destroy the tumor along with the tumor-bearing parenchyma. This is achieved by prospectively determining lobar volumes, prescribing an intended lobar dose (>120–150 Gy), and administering the dose into the feeding vessel(s) to increase safety and minimize radiation to normal parenchyma.

Table 2

| Study                  | Publication date | No. of cases | Type of malignancy | BCLC stage, no. of cases (A, B, C, D) | Child-Pugh classification, no. of cases (A, B, C) | Median dosage |
|------------------------|------------------|--------------|--------------------|--------------------------------------|------------------------------------------------|--------------|
| Lewandowski et al.5    | 2018             | 70           | HCC (solitary tumor ≤5 cm) | 70, 0, 0, 0                          | 70, 0, 0                                          | N/A          |
| Biederman et al.16     | 2018             | 55           | HCC (solitary tumor ≤3 cm) | N/A                                  | N/A                                              | Ds: 1.4 Gbq (1.1–2.1) |
| Meiers et al.5         | 2017             | 10           | Hepatic metastases | N/A                                  | N/A                                              | Ds: 261 Gy   |
| Padia et al.14         | 2014             | 20           | HCC (median, 3.9 cm); 12 cases with segmental portal vein tumor thrombus | 2, 2, 15, 1                                      | 11, 8, 1                                          | Ds: 255 Gy   |

BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; N/A = not available; Ds and Df = doses delivered to masses of the segment and tumor, respectively.

Table 3

| Study                  | Assessment criteria | Tumor response, % (CR, PR, SD, PD) | Disease control rate, % | Time to progression, mo | Progression-free survival, mo | Overall survival, mo | 1-, 3-, 5-year survival, % |
|------------------------|---------------------|-----------------------------------|------------------------|-------------------------|-----------------------------|----------------------|---------------------------|
| Lewandowski et al.5    | EASL                | 44, 42, 6, 8 at 6 mo              | 92 at 6 mo             | 28.8 (median)           | N/A                         | 80.4                 | 98, 66, 57                |
| Biederman et al.10     | mRECIST             | 81.8, 10.9, 1.8, 5.5 at 3 mo      | 94.5 at 3 mo           | N/A                     | N/A                         | 37.6                 | N/A                       |
| Meiers et al.5         | PERCIST             | 50, 10, 40, 0 at 3 mo             | 100 at 3 mo            | N/A                     | 7.1                         | N/A                  | N/A                       |
| Padia et al.14         | WHO                 | 20, 70, 10, 0 at 1 mo             | 100 at 3 mo            | 10.6 (median)           | N/A                         | N/A                  | 86.5, N/A, N/A            |

Table 4

| Study                  | Complications and side effects |
|------------------------|--------------------------------|
| Lewandowski et al.5    | Grade 3: RILD (n = 3; 4.2%), including 1 patient (1.4%) who developed rapidly progressive disease, exhibited grade 3 RILD at month 3, and died 4 months after RS |
| Biederman et al.10     | Grade 3: RILD (n = 6; 11%) |
| Meiers et al.5         | Grade 1: Pheoniric irritation (n = 1; 10%) |
| Padia et al.14         | Grade 1 and 2: Fatigue (n = 6; 30%), abdominal pain (n = 2; 10%), postembolization syndrome (n = 2; 10%) |

RILD = radiation-induced liver disease.

7.2. Bridge-to-resection/transplant

RS has demonstrated efficacy in downstaging HCC by achieving local tumor control and is therefore considered a bridging therapy for tumor resection or transplant. Biederman et al. reported that 14.5% (8/55) of patients who underwent RS in their study eventually underwent liver transplant. Similarly, Vouche et al. reported that 32% (33/102) of patients who underwent RS in their study eventually underwent liver transplant. Therefore, there is no definitive evidence that RS treatment is superior to other locoregional therapies.
patients they assessed underwent liver transplant after RS.

RS can lead to volumetric changes of the liver depending on the volume exposed to radiation; the most common outcome is atrophy of the treated volume and compensatory hypertrophy of the rest. This effect can help to identify patients who would benefit most from surgery, thereby improving postoperative outcomes and minimizing recurrence rates. In one study, Vouche et al.15 reported that right lobe atrophy and left lobe hypertrophy were observed as soon as 1 month after RS, and the median percent of future liver remnant hypertrophy reached 45% after 9 months (P < .001). The clinical significance of this finding is that hypertrophy of the normal liver tissue may potentially be of benefit for surgical lobectomy.

7.3. Safety

Of the patients included in this analysis, only 1 case developed rapidly progressive disease, exhibiting grade 3 radiation-induced liver disease 3 months after RS and dying 4 months after RS. All other patients with grade 1 and 2 (7.1%) or grade 3 (5.8%) toxicities were treated conservatively and recovered uneventfully. These results suggest that RS is a generally well-tolerated procedure, underscoring the increased safety that superselective intra-arterial infusion of the $^{90}$Y microspheres offers by reducing nontarget liver parenchymal exposure.

8. Limitations

Our analysis of clinical outcomes and safety had several limitations. Only a few studies of RS have been published since the technique was first introduced, and we identified only 4 retrospective studies that were eligible for inclusion in our analysis (ie, included data regarding clinical outcomes and safety). There was no consensus among the studies regarding dosimetry for RS. The 4 studies also varied in their inclusion outcomes and safety). There was no consensus among the studies eligible for inclusion in our analysis (ie, included data regarding clinical outcomes and safety). There was no consensus among the studies regarding dosimetry for RS.

9. Conclusions

RS therapy involves superselective administration of Y-90 microspheres to hepatic malignancies. With this technique, a high dose of radiation is delivered to the target tumor and surrounding parenchyma, thus increasing the tumoricidal effect while minimizing side effects. The studies of RS performed to date provide some evidence that RS can achieve these goals. However, the data are limited and further research is needed, particularly prospective studies with large patient populations that include patients with metastatic disease.

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Conflicts of interest

The authors indicate no potential conflicts of interest.

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