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Transarterial radioembolization for hepatocellular carcinoma: An update and perspectives

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Abstract

In the last decade trans-arterial radioembolization has given promising results in the treatment of patients with intermediate or advanced stage hepatocellular carcinoma (HCC), both in terms of disease control and tolerability profile. This technique consists of the selective intra-arterial administration of microspheres loaded with a radioactive compound (usually Yttrium^{90}), and exerts its therapeutic effect through the radiation carried by these microspheres. A careful and meticulous selection of patients is crucial before performing the radioembolization to correctly perform the procedure and reduce the incidence of complications. Radioembolization is a technically complex and expensive technique, which has only recently entered clinical practice and is supported by scant results from phase Ⅲ clinical trials. Nevertheless, it may represent a valid alternative to transarterial chemoembolization (TACE) in the treatment of intermediate-stage HCC patients, as shown by a comparative retrospective assessment that reported a longer time to progression, but not of overall survival, and a more favorable safety profile for radioembolization. In addition, this treatment has reported a higher percentage of tumor shrinkage, if compared to TACE, for pre-transplant downsizing and it represents a promising therapeutic option in patients with large extent of disease and insufficient residual liver volume who are not immediately eligible for surgery. Radioembolization might also be a suitable companion to sorafenib in advanced HCC or it can be used as a potential alternative to this treatment in patients who are not responding or do not tolerate sorafenib.

Key words: Hepatocellular carcinoma; Radioembolization; Transarterial chemoembolization; Sorafenib; Staging; RECIST, Modified RECIST; Downsizing; Clinical trial

Core tip: This review provides an overview of trans-arterial radioembolization, a new therapeutic option for patients with hepatocellular carcinoma. In particular, the practical aspects of the technique and available data on disease control will be presented, with reference to patients in either early or advanced stages of disease, treated with trans-arterial embolization alone or within combination regimens.

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks fifth among the most common cancers worldwide and represents the third most frequent cause of cancer-related mortality[1,2]. In the majority of cases, HCC is diagnosed in the intermediate-advanced stage [stage B and C according to the Barcelona Clinic Liver Cancer (BCLC) staging categories], when radical therapy is no longer possible. A number of curative and/or palliative therapies are available in this setting, but they are not always characterized by a favorable safety/efficacy ratio. Therefore, new therapeutic options are eagerly awaited.

Preliminary data on the use of trans-arterial radioembolization have demonstrated a good tolerability profile and promising results of this technique in terms of disease control. Although radioembolization has been studied more extensively in BCLC-B and BCLC-C HCC patients, its use has been evaluated also in the early stages (BCLC-A).

This review provides an overview of trans-arterial radioembolization. In particular, the practical aspects of the technique and available data on disease control will be presented, with reference to patients in either early or advanced stages of disease, treated with trans-arterial embolization alone or within combination regimens.

TRANS-ARTERIAL RADIOEMBOLIZATION: GENERAL CONCEPTS

Trans-arterial radioembolization, also known simply as radioembolization or as selective internal radiation therapy, consists of the selective intra-arterial administration of microspheres loaded with a radioactive compound - usually Yttrium^{90} or Lipiodol labelled with iodine^{131} or rhenium^{188} - through a percutaneous access.

Table 1 Main characteristics and differences between TheraSphere® and Sir-Spheres

	Sir-Spheres®	TheraSphere®
Diameters (μm)	32 ± 10	22 ± 10
Specific weight (g/dL)	1.6	3.6
Activity per microsphere to date calibration (Bq)	50	2500
Number of microsphere (vial, million)	40-80	1.2-8
Material	Resin	Glass
Activity in the vial (GBq)	3% ± 10%	3, 5, 7, 10, 15 or 20

Yttrium^{90} is a pure β emitter characterized by short half-life (64.2 h) and limited tissue penetration (average 2.5 mm, maximum 11 mm). Two types of microspheres are available, namely TheraSphere®, made of glass, and Sir-Spheres®, made of resin. They differ in size, activity for individual bead, and number of microspheres injected (as shown in Table 1), but available data suggest the equivalence of the two methods[3]. Differing from other embolizing treatments such as trans-arterial chemoembolization (TACE), radioembolization does not exert a macroembolic effect: therefore, both the benefits and the toxic effects of the treatment are dependent upon the radiation carried by the microspheres and not by any ischemic effect.

The different features of the two types of microspheres can explain the hypothetical different use for each patient and the difference in the mode of administration and in the activity calculation.

TheraSphere has a minimal embolic power (average number of glass microspheres injected: 4 million) with a higher activity for each sphere (2500 Bq *vs* 50 Bq for Sir-Spheres). These characteristics prevent vascular stasis and reflux during the administration, but in the case of a large lesion an inadequate coverage of the treated volume can occur, because the higher specific weight can limit the distribution of the microspheres.

On the other hand, Sir-Spheres, with a higher number of microspheres injected (average 40 million), have an important embolic power. Thanks to the number of microspheres injected it is possible to achieve an adequate and more homogeneous coverage of the lesion when compared with TheraSphere; however, the higher embolic power requires slow injections and accurate angiographic control during the administration.

The different coverage of the lesion is also reflected by the different median lethal dose: for Therasphere it oscillates between 205[4] and 257 Gy[5], instead for Sir-Spheres we can find a lower value, 120 Gy[6]. Of note, these values were calculated with the dosimetric

approach, which differs from the empiric activity calculation method (described below).

The first studies on Yttrium^{90} for the treatment of oncological diseases date back to the 1960s[7,8]. However, radioembolization has entered clinical practice only in the last decade. Available evidence supports the potential effectiveness of Yttrium^{90} microspheres in the treatment of primary (HCC and cholangiocarcinoma) and metastatic liver cancer[9-12].

Methods

Radioembolization can be divided into consecutive stages: (1) patient pre-selection: a multidisciplinary assessment identifies patients possibly eligible for this therapy[13]; (2) patient selection: a diagnostic angiography is performed with the aim of evaluating vascular anatomy and to identify and embolize any extrahepatic branch which could disperse the microspheres to non-target organs[14]. Moreover, angiography allows the establishment of the most appropriate point of injection of the catheter. During this visit, macroaggregates of albumin (MAA) labeled with Tc^{99} are injected. They present a diffusion similar to that of radioembolization microspheres, and can help predict the distribution of the microspheres. The diffusion of these macroaggregates is studied by a single photon emission computed tomography (SPECT/CT), performed within 1 h from the injection[15]; After the selection phase, other contraindications might exclude patients from treatment. Among these, a hepato-pulmonary shunt > 20% of the injected dose[16] or vascular abnormalities not correctable by embolization; (3) dose calculation: the amount of Yttrium^{90} administered is determined specifically for each patient (as discussed below); and (4) injection of microspheres: microspheres are injected by a catheter no later than 4 wk from the selection of patients.

Dose calculation

All the calculation activity methods used today are generally based on empiric data.

In order to perform the calculation of the activity (A) of TheraSphere to be injected, the following formula is generally used:

A = 120 (Gy) × M/[(1 - S) × 50]. Where M is the mass of the whole liver and S is the lung-liver shunt. 120 Gy is the dose (lethal dose) that we want to disburse to the lesion, assuming that there is a uniform distribution of the glass spheres in the target volume[17].

For Sir-Sphere, 3 methods are available for calculation activity[18]: (1) Empirical Method[18]. The amount of activity to be injected is chosen in relation to tumor over whole liver percentage (T): T < 25% → Gbq; 25% < T ⩽ 50% → 2.5 GBq; T > 50% → 3 Gbq. With this method however, the dose to healthy liver is not considered and patients could be exposed to non-necessary radiation toxicity; (2) BSA-Method[18]. In the calculation of activity to be injected, the ratio between tumor lobe (where the lesion is localized) and whole liver volumes and the body surface area (BSA) of the patient are considered. This method accounts for the relation between the size of the patient and their liver and enables the treatment of different lesions in separate lobes, preserving healthy tissues; and (3) Partition model[16]. Following the Medical Internal Radiation Dose (MIRD) method, the partition model takes into account the different distribution of the microspheres in the lesions and in the healthy tissue. The evaluation of these distributions is based on the results of the SPECT/TC with 99mTc-MAA. A (GBq) = Dliver × [(T/N × Mtumor) + Mliver]49670 × (1 - S). Where Dliver is the dose to healthy liver (chosen by nuclear medicine physician in order to preserve it), Mliver is the whole organ mass, Mtumor is lesion mass, S is the lung-liver shunt and T/N is the ratio between activity over mass for tumor and liver: T/N = (Alesion/Mlesion) (Aliver/Mliver). This method is indicated in patients who have compromised hepatic functionality.

Another possible approach is voxel dosimetry, in which the calculation of the activity takes into account the biological damage required for tumor and healthy cells[5]. The final aim of this method, which is based on the evaluation of the real distribution, voxel by voxel, of the microspheres, simulated by 99mTc-MAA, is to treat the lesions with high doses, without overcoming the dose constraint to healthy liver, chosen for the single patient. Following this approach, it is possible to maximize the treatment of the lesion while limiting liver toxicity and thus giving the chance of a more specific and individualized cure to each patient[5].

The simulation by 99mTC-MAA is important not only to determine the dose delivered to the injected healthy liver, but also as a predictive factor. Garin *et al*[4] reported that quantitative 99mTC-MAA SPECT/CT is predictive of response to treatment, progression free survival (PFS) and overall survivial (OS), and has therefore a fundamental role in the selection of patients and the adaptation of treatment planning. The personalization of the activity planning could be further improved by using dual-tracer 99m Tc-MAA-99m Tc-SC fusion SPECT, an imaging tool that merges data on radioactivity distribution with physiologic liver mapping that has been recently presented by Lam and colleagues[19].

Management of complications

Complications of radioembolization are either caused by delivering a toxic dose to non-tumoral tissues, or by procedural complications during the catheter's placement and manipulation. The main complications include: (1) liver failure or radio-induced liver disease (RILD)[20,21], with an incidence up to 4%; (2) biliary complications[22] (incidence < 10%); (3) post-radioembolization syndrome (PRS), characterized by fatigue, nausea, vomiting, anorexia, fever, abdominal pain[23,24] (incidence 20%-55%); (4) gastrointestinal complications, with an incidence < 5% when an

accurate angiographic phase is performed[25,26]; and (5) radio-induced pneumonia, whose incidence is < 1% if the hepato-pulmonary shunt is adequately calculated[27,28].

A careful and meticulous selection phase is crucial to reduce the incidence of complications. In addition, there is some consensus on the use of pre-medications to help prevent complications, such as proton pump inhibitors (starting one week before treatment and continuing for one month after the procedure), corticosteroids (for approximately 5 d from the interventions to reduce the incidence of PRS)[29], antiemetics and analgesics before the interventions and as needed.

RADIOEMBOLIZATION IN HCC TREATMENT: CURRENT EVIDENCE

Since radioembolization has only recently entered clinical practice, results from phase Ⅲ clinical trials are still scant. As a consequence, radioembolization is not currently listed among possible treatment options for HCC in some guidelines such as those issued by the American Society of Clinical Oncology. However, other scientific societies such as the European Society of Medical Oncology consider radioembolization as a promising therapeutic option either as a "bridging" treatment or as the main therapy for patients with diffuse intrahepatic tumor spread[30]. In addition, the National Comprehensive Cancer Network guidelines consider radioembolization suitable for patients with unresectable disease due to inadequate hepatic reserve, poor performance status, comorbidities, or specific location and extension of the tumor[31]. Lastly, according to the National Cancer Institute (NCI) recommendations, radioembolization may be considered in selected patients with liver-confined HCC, who are not eligible for transplant or resection[32].

Thanks to its versatility, radioembolization has been evaluated in different clinical situations, as summarized in the following paragraphs.

Radioembolization for early stage HCC

Patients with early-stage (BCLC-A) HCC are candidates for curative treatments such as liver transplant. However, the low number of donors and the long waiting list expose patients to the risk of disease progression, with subsequent withdrawal from the waiting list.

Therefore, patients on the waiting list are frequently treated with locoregional approaches, such as percutaneous ablation or TACE, in order to limit the risk of local progression.

Recently, radioembolization has been proposed as a valuable therapeutic option for patients on the transplant waiting list[33], although this approach is not widely performed due to its procedural costs.

Radioembolization for intermediate-stage HCC

Patients with intermediate-stage (BCLC-B) HCC represent a very heterogeneous population[34,35]. TACE is usually considered the treatment of choice in this setting, although alternative loco-regional and medical (sorafenib) treatment do retain efficacy. In addition, the use of TACE is limited by a number of absolute and relative contraindications[36]. In this population of patients, radioembolization may be a viable therapeutic option, given the low incidence of associated adverse effects.

To date, no randomized trials have directly compared radioembolization and TACE in patients with intermediate-stage HCC, available data are therefore based mainly on retrospective assessments.

Salem *et al*[37] compared 123 patients treated with radioembolization with 122 subjects who had received TACE: overall, median time to progression - but not overall survival - was longer after radioembolization (13.3 mo *vs* 8.4 mo, $P = 0.046$), and this latter intervention was also associated with a more favorable safety profile. Similar results have been reported by other authors[38-41]. For instance, a very recent study by El Fouly *et al*[41] has shown that radioembolization presents a similar efficacy, but a lower incidence of adverse events and need for hospitalization when compared with TACE. From a healthcare-utilization perspective, radioembolization is definitely more complex and expensive than TACE; however, TACE requires more frequent, repeated treatments than radioembolization and may be associated with a less favorable safety profile, thus increasing indirect costs.

A retrospective analysis has also suggested that both radioembolization and sorafenib are effective in patients with intermediate-stage HCC, and are associated with a similar survival[42].

Radioembolization for downsizing

In the large population of intermediate-stage HCC patients, tumor shrinkage, or "downsizing" may convert the disease to surgical resectability or may offer the opportunity for transplant[43]. Several options, either percutaneous or trans-arterial, are now available to achieve tumor downsizing, and radioembolization has become part of this armamentarium.

A retrospective study has compared radio-embolization and TACE for pre-transplant downsizing, and has shown that the percentage of tumor shrinkage was higher after radioembolization (58% *vs* 31%, $P = 0.023$)[44].

Radioembolization also represents a promising therapeutic option in patients with large extent of disease and insufficient residual liver volume, who are therefore not immediately eligible for surgery. In these patients, portal vein embolization (PVE) has been proposed to induce hypertrophy of the contralateral lobe and make surgical resection possible.

However, PVE is associated with some risks of tumor progression within the liver lobe during hypertrophy. Radioembolization can induce a marked hypotrophy of the treated hepatic lobe, associated with an evident hypertrophy of the contralateral lobe (the so-called "radiation lobectomy")[45]. Therefore, radioembolization has been proposed as an alternative to PVE in HCC patients. In addition, radioembolization offers the advantage of treating the cancer itself, thus reducing the risk of pre-interventional tumor progression, and represents a therapeutic option also in patients with neoplastic venous thrombosis[46]. Of note, 6-12 wk are necessary to achieve radiation lobectomy; during this time span, patients with more favorable biological tumor behavior and who may therefore gain most benefit from surgical resection can be identified[46].

Radioembolization for advanced stage HCC

Sorafenib represents the treatment of choice in patients with advanced stage (BCLC-C) HCC, and is associated with an overall survival of about 11 mo[47-50]. The overall survival associated with radioembolization in this setting ranges from 6 to 10 mo[9,10]; given its good safety profile, radioembolization might represent a potential alternative to sorafenib in selected patients who are not responding or do not tolerate this treatment. Of note, the preliminary results of the SORAMIC randomized trial, which compares radioembolization plus sorafenib with sorafenib alone in BCLC-C HCC patients, have shown that radioembolization followed by sorafenib appears to be as well tolerated as sorafenib alone[51].

Among patients with advanced HCC, radioembolization may provide the best outcome in subjects with PVT involving segmental or lobar branches, where the median overall survival has reached 17 mo with glass microspheres[37,52] and 23.2 mo using MAA SPECT/CT based dosimetry[53]. This compares with a median survival of 3-6 mo for patients with PVT of the common portal trunk. Less satisfactory results are documented for patients with distant metastases[12,54].

DIFFERENT CRITERIA TO EVALUATE THE OUTCOMES OF RADIOEMBOLIZATION

The therapeutic effects of radioembolization are evaluated mainly by the changes in the level of tumor markers and by radiological findings[55,56].

Tumor markers, in particular α-fetoprotein, are usually non-specific[57]. A decrease of α-fetoprotein may suggest a good response to treatment, but its increase does not provide any well-grounded clinical indication, as it can be determined not only by tumor progression, but also by lithic phenomena, infectious diseases or changes in liver function.

Imaging therefore becomes paramount to evaluate the response to treatment and therefore guide therapeutic choices. To this end, the American Association for the Study of Liver Diseases has proposed the "mRECIST criteria"[58]: according to mRECIST, the response to a given treatment is evaluated according to the reduction of the diameter of vital residual portion. These criteria have been shown to be accurate in identifying the complete necrosis of tumor mass after radioembolization[59]. However, post-radioembolization diagnostics still remain an open issue, especially in patients with partial response or stable disease - which represent the majority of cases. In fact, tumor necrosis is often irregular in distribution and contrast enhancement, making it difficult to measure vital portions. Therefore, the routine use of volumetric measurements of tumor necrosis have been proposed as a more accurate, reproducible and sensitive method for the early identification of responding patients[60,61].

The optimal time for the evaluation of treatment response is also debated. Although the first dimensional changes may already be observed after 1 mo, it is widely accepted that at least 3 to 4 mo are necessary to reliably estimate the actual response and therefore evaluate whether re-treatment may be considered.

CONCLUSION

Radioembolization represents a feasible and promising therapy for the treatment of all stages of HCC. Although it is technically complex and expensive, radioembolization may represent a valid alternative to TACE in intermediate-stage HCC and may be a suitable companion to sorafenib in advanced HCC.

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