Yttrium-90 Microsphere Radioembolization for Hepatocellular Carcinoma

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Abstract
Yttrium-90 (Y90) radioembolization is an emerging strategy to treat liver malignancies, and clinical data supporting its use have accumulated in recent years. Y90-radioembolization has shown clinical effectiveness in intermediate and advanced hepatocellular carcinoma, with a favorable safety profile. Retrospective data show similar levels of effectiveness to transarterial chemoembolization in intermediate hepatocellular carcinoma, with some evidence of better tolerance. While phase 3 studies comparing Y90-radioembolization to chemoembolization in intermediate hepatocellular carcinoma would be difficult to conduct, studies comparing or combining Y90-radioembolization with sorafenib are under way. Questions also remain about the most suitable modalities for defining the dose to administer. Phase 3 studies are under way to clarify the place of Y90-radioembolization in the algorithm of HCC treatment.

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Introduction
Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer worldwide [1]. As recognized by the Barcelona Clinic for Liver Cancer (BCLC) classification, curative options (surgery or transplantation) can be offered to a minority of patients with early
or very early HCC only [1]. According to the current treatment algorithm, intermediate HCC should be treated with transarterial chemoembolization (TACE) [2], and advanced HCC should be treated with sorafenib [3, 4]. However, the results of both treatments leave room for improvement, the boundaries between stages are not so strict, and other modalities of treatment are currently being studied [5]. Among them, yttrium-90 (Y90) radioembolization has received growing interest as data supporting its use have accumulated over the past 10 years [6].

**Description of the procedure**

Y90-radioembolization is a procedure involving collaboration between clinicians, interventional radiologists, and nuclear medicine specialists [7]. It consists in the administration of microspheres by catheterization of the hepatic artery. Two types of microspheres are currently available, with different physical properties. Glass-microspheres are commercialized under the brand name TheraSphere® by BTG. They are 25 (± 10) µm in diameter and each sphere is loaded with 2500 Bq of activity. Resin-microspheres are commercialized under the brand name SIR-Spheres® by Sirtex. They are 35 (± 10) µm in diameter and each sphere is loaded with 50 Bq of activity. The most notable difference is the relative activity loaded in a single sphere, requiring larger injected volumes for resin microspheres than for glass microspheres. Because of the physical differences between the two types of spheres, specific training and learning curves are required for each. However, to date, no differences in clinical application are recognized between the two types of microspheres.

The radioembolization procedure requires two angiographies. During the first procedure, after embolization of arterial branches coming from the hepatic artery but vascularizing other organs (such as the stomach, duodenum, and diaphragm), technetium-99-labeled macroaggregated albumin (MAA) is administered with the objective of simulating the deposition of the microspheres. Planar and single-photon emission computed tomography (SPECT) gamma-camera imaging is used to detect any uptake of MAA outside the liver. In particular, two different sites of extra-hepatic uptake must be considered: the gastrointestinal tract and the lungs. Gastrointestinal uptake is usually ruled out during the angiography and can generally be efficiently avoided by coiling of the involved artery. Hepatopulmonary shunting should be measured: a shunt higher than 20% or resulting in more than 30 Gy of irradiation of the lung is a contraindication for Y90-radioembolization. Establishing the distribution parameters of MAA allows determination of the dose of Y90 to inject, with the aim of delivering more than 120 Gy to the target area and less than 20 Gy to the lungs [7]. After this first procedure, angiography is repeated after 1- or 2-weeks’ delay to facilitate administration of the calculated amount of Y90-loaded microspheres. It should be noted that the short range (less than 10 mm) of irradiation delivered by Y90, a pure beta-emitter, implies the absence of the need for radioprotective measures. Moreover, the absence of post-embolization syndrome allows for an outpatient procedure. Y90-radioembolization is being studied in different tumor types, but its use in HCC is the best documented and is the object of the current review.

**Rationale for the use of Y90-radioembolization in HCC**

The evolution of HCC is characterized by the majority of the tumor bulk usually remaining localized in the liver for a considerable time: extrahepatic metastases appear quite late in
the natural history of the disease. Even when extrahepatic disease is present, the main cause of death appears to be related to liver failure resulting from the spread of underlying hepatic disease and its frequent association with cirrhosis [1, 5]. This peculiar evolution led to the development of liver-directed therapies, and particularly to trans-arterial procedures [5].

HCC cell lines appear to be sensitive to radiation in vitro [8]. However, the use of external radiotherapy has been historically limited due to the radiosensitivity of normal liver tissue. Treatment with conventional fractionation is limited to doses lower than 40 Gy to a large portion of normal liver, thus precluding effective treatment of liver malignancies [7]. Such irradiation of a large portion of normal liver is responsible for radiation-induced liver disease (RILD), which consists of liver failure with ascites, with a risk of lethal evolution. New external radiotherapy modalities are currently being investigated, but are still limited to series of small numbers of patients treated [8]. The obvious limitations of external radiotherapy encouraged the development of alternative modalities to deliver radiation to liver tumors.

One initial procedure of metabolic radiotherapy directed at the liver used the administration of intra-arterial iodine-131-labeled lipiodol [6]. Lipiodol is a contrast agent with specific affinity to HCC when injected intra-arterially. Iodine-131 requires radioprotective measures, with patient isolation for about 1 week. This procedure showed, in a randomized trial, comparable efficacy to TACE with lower toxicity, as well as promising results demonstrated in randomized trials in two contexts that exceeded the recognized indications of TACE: portal vein thrombosis (PVT) and in the adjuvant setting [9–11]. However, the pharmaceutical company decided not to proceed to large phase 3 studies, and commercialization of the treatment was abandoned. However, it provided the first evidence of effectiveness for the administration of a radio-isotope for the treatment of HCC.

Current Evidence of the Effectiveness of Y90-Radioembolization in HCC

Riaz et al presented a pathologic analysis of explanted livers after Y90-radioembolization. In their series analyzing 38 tumors in 35 patients, microscopic examination confirmed complete histologic response in 23 tumors [12]. This rate was as high as 89% when tumors were <3 cm in largest diameter, and more than 66% when transplantation occurred more than 3 months after treatment. These data obviously offer a strong rationale for the effectiveness of the procedure, with a high rate of complete response when administered to small tumors and after allowing time for the maximal response to be realized.

Non-comparative studies of Y90-radioembolization in HCC

Several series of Y90-radioembolization have been published [13–23]. These studies were mostly retrospective in their design. Three studies included more than 100 patients. The study by Hilgard et al was a prospective monocentric study including 108 patients [13]. While the response rate was 16% by Response Evaluation Criteria in Solid Tumors (RECIST) and 40% by European Association for the Study of Liver (EASL) criteria, the disease control rate was as high as 90% with both criteria. Median time-to-progression (TTP) was 10.0 months (95% confidence interval (CI): 6.1–16.4), and median overall survival (OS) was 16.4 months overall (95% CI: 12.1–infinite). The study by Sangro et al was a retrospective multicentric study including 325 patients [14]. The median OS was 12.8 months (95% CI: 10.9–15.7) overall, 24.4 months (95% CI: 18.6–36.1) for BCLC A, 16.9 months (95% CI: 12.8–22.8) for BCLC B, and 10.0 months (95% CI: 7.7–10.9) for BCLC C patients. The study by Salem et al was a prospective monocentric study including 291 patients [15]. Response rates were 42% by World Health Organization criteria and 57% by EASL criteria. Median TTP was
7.9 months (95% CI: 6.0–10.3). Median OS was 26.9 months (95% CI: 17.0–30.2) for BCLC A patients, 17.2 months (95% CI: 13.5–29.6) for BCLC B patients, and 7.3 months (95% CI: 6.5–10.1) for BCLC C patients. Overall, these publications and some smaller series demonstrated the feasibility of the treatment for HCC and reported similar results to those of TACE for intermediate HCC, with around 1000 patients overall included in these studies. Moreover, Y90-radioembolization showed a clinical effect in advanced HCC, with median reported OS comparable to that of sorafenib [14, 15]. However, those data could be criticized by the absence of a comparative arm.

**Comparative studies of Y90-radioembolization vs standard treatments**

Different studies have retrospectively compared the results of TACE with those of Y90-radioembolization [16, 17, 19, 20, 22–25]. Most of these studies are limited by the small number of patients, but one important study by Salem et al retrospectively compared 123 patients treated by Y90-radioembolization with 122 patients treated by TACE [24]. Despite comparable baseline characteristics and therapeutic indications, patients treated with Y90-radioembolization experienced longer TTP (median 13.3 months for Y90-radioembolization vs. 8.4 months for TACE, p=0.046). OS was not statistically different (median 20.5 months for Y90-radioembolization vs. 17.4 months for TACE, p=0.243), but favorable trends were observed for United Network for Organ Sharing (UNOS) stage T3 tumors (median 35.7 months for Y90-radioembolization vs. 19.2 months for TACE, p=0.098) and BCLC C tumors (median 22.1 months vs. 9.3 months, p=0.08). Results of the other comparative studies, limited by their lack of power, either show better results for Y90-radioembolization or similar results to those of TACE. The studies also consistently reported less toxicity with Y90-radioembolization, mainly due to the absence of post-embolization syndrome, which translates to lower incidences of abdominal pain, nausea, and fever. A small study also reported a better quality of life after Y90-radioembolization than after TACE [26].

To date, only one study has compared patients treated with Y90-radioembolization and patients treated with sorafenib for intermediate or advanced HCC [27]. This study was limited by its retrospective nature, the small number of patients included (64 patients for Y90-radioembolization and 74 for sorafenib), and an imbalance in baseline characteristics between the two groups of patients. However, results appeared to be similar between the two groups in terms of OS.

**Specific clinical settings: Portal vein thrombosis and neoadjuvant**

Some clinical situations have been the focus of particular interest in Y90-radioembolization for HCC. Among them, the presence of PVT has been the subject of different studies or sub-analyses of previously discussed work [28–30]. Y90-radioembolization for HCC patients with PVT appears particularly interesting because TACE is viewed by most authors as contraindicated in patients with thrombosis involving the trunk or a major branch of the portal vein (and for some even in cases of segmental thrombosis). The Chicago team demonstrated that Y90-radioembolization is not associated with a strong embolic effect and thus could be applied safely in patients with thrombosis [29, 31]. Results of sorafenib in the pivotal phase 3 SHARP trial showed a dismal median OS of 8.3 months for patients with PVT [32]. Y90-radioembolization appears to be feasible in patients with PVT, with no additional toxicity. While being inferior to those seen in patients without PVT, reported median OS of patients with PVT treated with Y90-radioembolization ranged from 10 to 18 months, seemingly better than that for sorafenib. However, direct comparisons have still not been carried out.

Y90-radioembolization was retrospectively compared to TACE in the setting of downstaging to surgery or transplantation, and seemed to provide better results [33]. For UNOS T3 lesions, downstaging to T2 was more frequent with Y90-radioembolization than with
TACE (58% vs. 31%, respectively). Different publications have shown the feasibility of the technique before either resection or transplantation [12, 34, 35]. However, a prospective study of the combination of sorafenib with Y90-radioembolization before transplantation raised concerns about a potential increase in complications [35].

**Safety**

Y90-radioembolization appears to be a safe procedure [13, 36]. Adverse events seem less frequent than with TACE due to the absence of significant post-embolization syndrome, because microspheres do not completely interrupt the blood flow [31]. However, some specific adverse effects should be discussed. The first angiography of the procedure has the objective of ruling out any significant extra-hepatic uptake of the microspheres [7]. If gastroduodenal uptake does occur, ulceration could develop; such complications can be avoided by careful work-up during the first angiography, i.e., by coiling the arteries responsible for such uptake. In the case of gallbladder uptake, aseptic cholecystitis could occur; if gallbladder uptake is seen on post-treatment scintigraphy, antibiotics and steroid prophylaxis are usually recommended. Major hepatopulmonary shunt must also be ruled out after the first angiography because of the risk of pulmonary fibrosis if the radiation dose to the lung is excessive [37]. However, with current recommendations, pulmonary toxicity appears almost nonexistent, and some authors have even questioned the need for assessing hepatopulmonary shunt, at least with glass microspheres [37].

One matter of concern is the occurrence of radioembolization-induced liver disease (REILD), which is similar to RILD observed after external radiotherapy. REILD was first described by Sangro et al as the development of ascites and an increase in bilirubin levels, usually with a benign evolution, but in rare case with evolution to liver failure and even death [38]. The same group proposed an adaptation to the standard dose calculation protocol to diminish the risk of REILD in patients with risks factors (cirrhosis, small liver volume, prior chemotherapy, and very small tumoral involvement) when whole-liver treatment was offered [39]. They also introduced prophylaxis with ursodeoxycholic acid and steroids. With this protocol, they obtained a rate of REILD of 5.4% and of severe REILD of 2.2%. In HCC specifically, the incidence of REILD could be difficult to ascertain because liver failure could be due to cirrhosis or progression of disease, without direct contribution of the treatment. In a cohort of 515 patients treated by resin-microsphere Y90-radioembolization, REILD was observed after 4% of the treatments, with most cases occurring at one center that used the empiric method to determine the level of activity to be administered [40].

**Areas of Controversy and Future Development**

Y90-radioembolization is an emerging treatment strategy, and many points will need to be clarified in the coming years.

*Response evaluation*

As with other HCC treatments, response evaluation is not optimally performed by relying on the maximal diameter of the lesion, as is done in RECIST. The maximum response in terms of size reduction could take 4–6 months to be achieved [7]. Alternative criteria have been proposed, such as EASL, modified RECIST, and the Choi criteria [1, 41, 42]. Conflicting results have been published concerning the comparison of these new criteria, but overall, authors agree
that focusing on the viable part of the lesion allows more accurate evaluation than RECIST does. Riaz et al. showed better correlation of these new criteria with pathological necrosis, compared with RECIST or World Health Organization criteria [12]; however, a second study failed to reproduce these results [42]. Other functional modalities, such as diffusion-MRI or perfusion-CT have also been proposed, as well as use of the alpha-fetoprotein response, but their usefulness still needs to be clarified.

**Evolution of liver volumes after Y90-radioembolization**

Another matter of debate is the evolution of liver volumes after unilateral Y90-radioembolization. Several groups reported significant and delayed increase of contralateral liver volume after treatment, thereby strengthening the potential role for Y90-radioembolization as a preoperative treatment, as opposed to sequential TACE-portal vein embolization [43–45]. Conversely, one study showed that the tendency to increases in liver volume could be less than those seen after portal vein embolization [46]. The results also depend on the presence or absence of any underlying cirrhosis [44]. However, Y90-radioembolization could present different advantages when compared with the previous sequence (TACE + portal vein embolization) in a preoperative setting, because the treatment, given in a single session, is associated with high response rates, better tolerance, and a slow increase of contralateral liver volume and is likely not associated with the hypersecretion of proangiogenic factors.

**Boosted-radioembolization**

The first angiographic procedure allows the level of activity to be delivered to the tumor and the surrounding liver to be determined. The administered dose is usually calculated depending on the dose predicted to be received by the liver, thus the dose actually received by the tumor could depend on the tumor size and the ratio between tumoral and liver volumes and uptakes [7]. Different groups have demonstrated that there is a relationship between the dose received by the tumor and results in terms of response and OS [47, 48]. Different thresholds for optimal dose received by the tumor have been proposed. Continuing in this direction, our group developed the concept of “boosted-radioembolization,” meaning that if the dose to be delivered to the tumor, calculated with usual method, is predicted to be under the predefined threshold of 205 Gy, we increase the dose to reach this threshold, while limiting the dose to the non-tumoral liver to below 120 Gy. Our preliminary results suggest that this approach is highly promising [49].

**Selective Y90-radioembolization**

Another approach, which probably also relies on an increase in tumoral dose, consists in choosing a selective approach to perform the injection, performing what could be called a “radiation segmentectomy” [50, 51]. With this approach, a recent publication focusing on lesions <5 cm showed impressive mRECIST response rates of 47% complete response, 39% partial response, and 12% stable disease, with only one patient out of 99 progressing [52]. This approach was also associated with 52% complete necrosis in the 33 patients who had surgery following treatment. This study also showed a higher rate of complete necrosis when the dose was higher than 190 Gy. Boosted-radioembolization and radiation segmentectomy both indicate that, despite limitation of the dosimetry based on SPECT, consideration of the dose administered to the tumor clearly has an impact on the results of the treatment, while not interfering with the level of tolerance of the treatment.

One important field of research in the next few years will be the possible combination of Y90-radioembolization with other treatments. Indeed, because Y90-radioembolization would probably share indications with TACE or sorafenib, the question will arise whether these treatments could be used in combination or sequentially [35, 53]. Moreover, the prop-
Timing of treatment combination could raise concerns, as concomitant treatment could be at once more efficient but more toxic.

Absence of randomized studies

However, the main limitation to our knowledge about Y90-radioembolization remains the absence of phase 3 randomized studies comparing this treatment with current standards. In the context of advanced HCC, different studies are currently ongoing, either comparing Y90-radioembolization vs. sorafenib, or a sequence of Y90-radioembolization and sorafenib vs. sorafenib alone (Table 1). Inclusion criteria of these studies show some differences, but they will have sufficient power to clearly demonstrate whether Y90-radioembolization is superior to sorafenib in advanced HCC. The challenge is more difficult for intermediate HCC. Indeed, retrospective data suggest that Y90-radioembolization can achieve comparable results to those of TACE in terms of efficacy, but with improved tolerance [24]. However, when trying to design a phase-3 study powered to prove the non-inferiority of Y90-radioembolization compared to TACE in the intermediate HCC setting, some authors evaluated the number of patients to be included to exceed a thousand, which would not appear feasible in the current context [24]. Because Y90-radioembolization already has regulatory agency approval in the United States and in Europe, the funding and accrual of patients for such a study is not realistic. However, a prospective phase 2 study, the PREMIERE study (clinical trial identifier NCT00956930), is currently randomizing patients with either unresectable HCC or HCC not treatable by radiofrequency ablation between Y90-radioembolization and TACE. The primary endpoint of this study is not OS but TTP, and the inclusion of 124 patients is planned to be completed in 2016.

Conclusion

During the past few years, Y90-radioembolization has proved its feasibility in multicenter studies and has achieved consistent results. Results of retrospective comparative studies suggest that Y90-radioembolization has comparable efficacy and better tolerance than TACE in intermediate HCC, and there is evidence of a therapeutic effect in advanced HCC, especially in patients with PVT. These results have led some organizations to include Y90-radioembolization in their guidelines as a treatment option (e.g., the European Society of Medical Oncology,

Table 1. Ongoing phase 3 trials

| Acronym | Clinical trial identifier | Number of patients | Target population | Experimental arm | Standard arm | Estimated completion date |
|---------|---------------------------|--------------------|-------------------|-----------------|-------------|---------------------------|
| SORAMIC | NCT01126645               | 660                | BCLC B or C       | SIR-Spheres® + Sorafenib | Sorafenib | September 2014 |
| SIRvenib| NCT01135056               | 360                | BCLC B or C       | SIR-Spheres®    | Sorafenib | July 2015       |
| SARAH   | NCT01482442               | 400                | BCLC B or C       | SIR-Spheres®    | Sorafenib | December 2015  |
| STOP-HCC| NCT01556490               | 400                | BCLC B or C       | TheraSpheres® + Sorafenib | Sorafenib | October 2016   |
| YES-P   | NCT01887717               | 328                | Portal vein thrombosis | TheraSpheres®   | Sorafenib | December 2017  |

BCLC = Barcelona Clinic for Liver Cancer.
National Comprehensive Cancer Networks), while others still await results from randomized studies (EASL, American Association for Study of the Liver). However, the results of randomized studies will be presented in the next few years and will hopefully clarify the relative place of Y90-radioembolization in the treatment algorithm of HCC. Moreover, there is still opportunity for improvement in the indications and techniques of this modality of metabolic radiotherapy; approaches focusing on increasing the dose to the tumor are being studied, as are the combination of Y90-radioembolization with other treatments.

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