Selective Internal Radiation Therapy on Hepatocellular Carcinoma

Subjects: Oncology

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Selective internal radiation therapy (SIRT) is part of the treatment strategy for hepatocellular carcinoma (HCC). Strong clinical data demonstrated the effectiveness of this therapy in HCC with a significant improvement in patient outcomes. Recent studies demonstrated a strong correlation between the tumor response and the patient outcome when the tumor-absorbed dose was assessed by nuclear medicine imaging. Dosimetry plays a key role in predicting the clinical response and can be optimized using a personalized method of activity planning (multi-compartmental dosimetry). Moreover, some patient and tumor characteristics predict a worse outcome, and toxicity related to SIRT treatment of advanced HCC patient selection based on the performance status, liver function, tumor characteristics, and tumor targeting using technetium-99m macro-aggregated albumin scintigraphy can significantly improve the clinical performance of SIRT.

Keywords: hepatocellular carcinoma ; liver radioembolization ; selective internal radiation therapy

1. Introduction

Liver radioembolization (RE) or selective internal radiation therapy (SIRT) is part of the treatment strategy for hepatocellular carcinoma (HCC) [1]. This treatment involves the injection of radioactive microspheres via the liver arterial blood supply of the tumor(s). These microspheres are trapped in the arterioles of the tumor(s) and the targeted liver parenchyma. The liver parenchyma is primarily supplied by the portal vein, while HCC perfusion is primarily supplied by the hepatic arteries. This preferential vascularization allows a high irradiation of tumors while limiting radiation of the healthy liver [2]. The tumor-absorbed dose can range from 100 to 1000 Gy [3]. In comparison, the dose that can be delivered to tumors is limited to a maximum of 70 Gy, with external beam radiotherapy to avoid irreversible liver damage [4]. Yttrium-90 (^{90}Y)-resin microspheres (Sir-Spheres®; Sirtex Medical Ltd., Sydney, Australia), ^{90}Y-glass microspheres (Therasphere®; Boston Scientific, Boston, MA, USA), and holmium-166-poly-L-lactic acid microspheres (QuiremSpheres®; Quirem Medical B.V., Deventer, The Netherlands) are the three commercially available radioactive microspheres, differing by their physical and irradiation properties [5].

SIRT is planned in two phases. First, a simulation is always performed to evaluate the feasibility of the treatment. An interventional radiologist catheterizes the liver artery(ies) and evaluates the arterial feeding of the tumor(s). A non-therapeutic nuclear medicine agent, technetium-99m macro-aggregated albumin (MAA), is injected into the liver artery(ies) supplying the tumor(s) for simulating the distribution of the radioactive microspheres. Thereafter, the MAA distribution is assessed by nuclear imaging using single-photon emission computed tomography combined with computed tomography (MAA SPECT/CT). This imaging confirms the accurate targeting of the tumor(s) and the absence of risk of toxicity (digestive or lung irradiation). Then, the phase of treatment is scheduled with injection of the radioactive microspheres in the same technical conditions. The recommended methods for calculating the amount of radioactive microspheres needed for the treatment (activity) differ between the different available microspheres [6][7][8]. These methods are semi-empirical, based on the body surface area for resin microspheres, and using a mono-compartmental model (based on the liver volume) for glass and holmium-166-poly-L-lactic acid microspheres [9]. During the workup, the MAA distribution in the tumor, the healthy liver, and the lung compartments can also be evaluated to perform a more personalized method of activity planning (multi-compartmental or partition model) [1].

2. Clinical Results of SIRT in HCC

The treatment options for HCC depend on the Barcelona Clinic Liver Cancer (BCLC) staging system [10]. This classification takes into account the tumor characteristics (i.e., size, number of tumors, portal vein invasion, or extra hepatic spread), underlying liver function (via Child–Pugh score) and patient performance status (via Eastern Cooperative

Oncology Group (ECOG) scale) [11]. The BCLC stage is a well-established accurate predictor of patient survival and in routine clinical use worldwide to help determine the best treatment options.

Recent recommendations of the European Society for Medical Oncology consider SIRT as an alternative treatment for patients with BCLC stages A, B, and C [12][13]. For BCLC stage A patients, a recent large, retrospective study demonstrated that SIRT was very efficient to address unresectable solitary HCC alone or for use as a neoadjuvant bridge in a curative surgical approach [14]. For intermediate HCC (i.e., BCLC B), transarterial chemoembolization is recommended for first-line therapy. However, a meta-analysis of previous prospective randomized studies comparing SIRT to transarterial chemoembolization demonstrated similar survival outcomes [15]. Moreover, a randomized study comparing SIRT to transarterial chemoembolization in a population of BCLC A and B patients demonstrated similar survival times but showed that the former was associated with a longer time to progression [16].

Considering advanced stage patients (i.e., BCLC C), systemic therapies are often preferred; these include immunotherapy (e.g., atezolizumab plus bevacizumab) or targeted therapy (e.g., sorafenib, regorafenib). Patients treated with atezolizumab plus bevacizumab demonstrated superior survival and progression-free survival compared to patients treated with sorafenib [17]. However, randomized controlled trials comparing SIRT to sorafenib have failed to demonstrate a superior outcome with SIRT [18][19][20]. Consequently, the place of SIRT in advanced HCC is an alternative and possibilities for therapy optimization should be investigated.

Controlled trials currently investigate the combination of SIRT plus immunotherapy in patients with intermediate and advanced stages of HCC. Preliminary results of the combination of nivolumab three weeks after SIRT demonstrated a favorable tolerability and encouraging response rates [21][22]. A randomized trial (NCT04541173) is also investigating the safety and effectiveness of SIRT followed by the combination of atezolizumab plus bevacizumab. In theory, the combination of immunotherapy after SIRT may give a synergistic clinical effect and improve tumor control and patient survival. Ionizing radiation may induce the release of tumor-associated antigens targeted by antigen presenting cells and result in a stimulation of the immune response, boosting the effects of immunotherapy [23]. SIRT must be performed before the initiation of immunotherapy, when the biological effects of ionizing radiations are effective.

3. Clinical Dosimetry in SIRT

Tumor dosimetry is a predictive factor of SIRT efficiency. Previous data have demonstrated a correlation between tumor-absorbed dose and radiological response [24][25][26]; indeed, a high tumor-absorbed dose is associated with a high probability of tumor control. In addition, a multitude of clinical data demonstrating strong correlation between tumor-absorbed dose, radiological response, and survival of HCC patients are currently available.

4. Personalized Dosimetry in SIRT

To improve the clinical results of RE, the activity prescription can be more personalized and optimized to reach higher tumor-absorbed doses. As previously described, the recommended activity prescription is calculated using semi-empirical methods. While these methods are safe, they can induce suboptimal absorbed doses to tumors [27]. A recent prospective study confirmed the clinical benefits of performing multi-compartmental dosimetry (known as “the partition model”) [28]. In the partition model, activity planning is based upon the MAA distribution in the different compartments, simulating an absorbed dose under the threshold of toxicity for the healthy liver and above the efficacy threshold for the tumor(s).

The dose to the healthy liver can be accurately predicted with MAA SPECT/CT, controlling the risk of liver toxicity [29]. Indeed, an excess of liver radiation can induce liver damage (i.e., RE-induced liver disease). The toxicity threshold doses have been well-demonstrated through non-tumoral, whole-liver dose (reaching 90 Gy for glass microspheres and 40–50 Gy for resin microspheres) [30][31]. As such, with MAA SPECT/CT dosimetry simulating an absorbed dose to the healthy liver under these thresholds, the activity can be planned safely. Moreover, the external beam radiotherapy models have shown that no liver damage can occur if the treated liver volume does not exceed 40% [32]. When a small part of the liver volume is targeted by the treatment, the planned activity can be increased for performing a safe radiation segmentectomy. For treatments applied to a majority of the liver (>60%), the planned activity can be adjusted to reach the maximal tolerable liver absorbed dose. With this method, the planned activity would be the highest possible and would therefore increase the activity in the tumor compartment to maximize the tumor-control probability.

Moreover, a large HCC tumor size (≥5 cm) was a factor of poor prognosis in some studies [33][34][35]. These studies included patients treated by glass microspheres, using the recommended method of activity planning (80–150 Gy to the targeted liver). Given this, Garin et al. [36] demonstrated a significant lower response rate in large HCC tumors (size ≥ 5

cm) using this same method of activity planning, probably because of tumor underdosing. More interestingly, using an optimized method of activity planning increasing the tumor-absorbed dose, Garin et al. [37] demonstrated a high response rate in large HCC tumors and no correlation between the tumor size (≥5 cm) and the patient survival.

A recent prospective trial performed with patients with HCC, mostly with advanced stage disease, demonstrated better outcome achieved with personalized dosimetry and MAA imaging (using glass microspheres) [28]. When an approach reaching a maximum dose of 120 Gy to the targeted healthy liver, and at least 205 Gy to tumors (>250 Gy if possible) was used, the clinical outcome was highly improved as compared to patients treated with the standard (120 Gy to the targeted liver) dosimetric approach. The main results of this trial are summarized in **Table 1**. The median activity was increased by 38%, as shown upon comparison of the standard method to this personalized method of activity planning. Similarly, in a retrospective study using personalized dosimetry with a whole, normal liver dose reaching 40 to 70 Gy (glass microspheres), the median survival was 14.1 mo in HCC patients with portal vein invasion (95% confidence interval (CI): 10.7–17.5 mo) [38]. These results were higher than expected, considering other published data from a similar population treated with a standard dosimetric approach (median: 10.4 mo, 95%CI: 7.2–16.6) [35].

Table 1. Main results of the DOSISPHERE-01 randomized controlled trial [28].

	Personalized Dosimetry	Standard Dosimetry
Number of patients	**28**	**28**
Activity planned in GBq, median	**3.6 ***	**2.6**
Response rate at 3 mo, EASL criteria	**71% ***	**36%**
Curative surgery intent after SIRT	**36% ***	**4%**
REILD	**9%**	**10%**
Overall survival in mo, median	**26.6 +**	**10.7**

However, using this optimized method of activity planning, patients with risk factors for RE-induced liver disease must be carefully evaluated before treatment to limit the liver toxicity probability. For this purpose, ^{99m}Tc–mebrofenin scintigraphy with SPECT/CT can evaluate and quantify the global and regional liver functions and predict the risk of post-radiation liver damage. In patients who undergo major liver resection, the remnant liver uptake of mebrofenin correlated well with the risk of postoperative liver failure (cut-off value: 2.69%/min/m^2) [39]. This technique could also be applied to SIRT for evaluating liver function in patients with risk factors (e.g., advanced cirrhosis, large tumor involvement, etc.). Indeed, the mebrofenin liver uptake of the non-treated liver was also predictive of RE-induced liver disease in some case series [40] [41].

5. Good HCC Candidates for SIRT

The collective research efforts have provided a good understanding of the factors responsible for treatment ineffectiveness in HCC, helping clinicians to select the best candidates for SIRT. Currently, using tumor dosimetry, MAA imaging can generally select patients who will respond well to SIRT (high tumor uptake and high absorbed dose) or those who will not respond (low tumor uptake, low absorbed dose) [42]. The interest of this dosimetry applied to MAA SPECT/CT was confirmed in the recent DOSISPHERE randomized controlled trial [28] and was also well-illustrated in a retrospective study of 41 patients treated for advanced HCC with portal vein thrombosis. The overall survival was only 4.3 mo when the tumor-absorbed dose was less than 205 Gy and 18.2 mo when at least 205 Gy (glass microspheres) [37]. Moreover, patients with portal vein thrombosis and poor targeting via MAA imaging had a very poor prognosis.

HCC is a heterogeneous group of tumors with different behaviors; some can be very aggressive, with a tumor doubling time ranging from 3 mo to 1 year [43]. [^{18}F]-Fluorodeoxyglucose (FDG) PET/CT has low sensibility, with a significant uptake in less than 50–65% of the cases [44]. However, data have indicated that HCC tumors with high [^{18}F]FDG uptake are more aggressive, with patients at higher risk of recurrence and poorer survival [45]. SIRT is less effective in this population, with a significant reduction of the local control, progression-free survival (PFS) and overall survival (OS) [46][47]. In advanced HCC, randomized trials have failed to demonstrate a superior PFS and OS in patients treated by RE compared to sorafenib despite a significant increase of the tumor response rate in the RE arm. Loco-regional therapies such as SIRT may be less effective for patients with aggressive HCC tumors, and [^{18}F]FDG PET/CT could be useful to identify these patients. Decompensated liver function is also a strong predictor of poor survival. The baseline bilirubin level, the Child–Pugh score, and the albumin–bilirubin grade were independent predictors of poor survival in patients

treated with SIRT [38][48][49]. The median overall survival rates reported for advanced HCC patients treated with sorafenib range from 6.5 mo to 14.7 mo [50][51][52][53]. To compare, some markers of poor prognosis have been identified in large retrospective studies of advanced HCC patients treated with SIRT. Patients with poor performance status (ECOG 2 or more), extrahepatic metastases, portal vein thrombosis extending to the main left/right branch, tumor burden > 50% of the liver volume, and a baseline alteration of the liver function (albumin–bilirubin score of 3 or bilirubin level of 2–3 mg/dL) have reported median survival rates that fall between 4.3 and 8.2 mo.

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