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REVIEW

Radioembolization with Yttrium-90 microspheres in hepatocellular carcinoma: Role and perspectives

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Abstract

Transarterial radioembolization (TARE) is a form of brachytherapy in which intra-arterially injected yttrium-90-loaded microspheres serve as a source for internal radiation purposes. On the average, it produces disease control rates exceeding 80% and it is a consolidated therapy for hepatocellular carcinoma (HCC); however, current data are all based on retrospective series or non-controlled prospective studies since randomized controlled trials comparing it with the other liver-directed therapies for intermediate and locally advanced stage HCC are still underway. The data available show that TARE provides similar or even better survival rates when compared to transarterial chemoembolization (TACE). First-line TARE is best indicated for both intermediate-stage patients (staged according to the barcelona clinic liver cancer staging classification) who have lesions which respond poorly to TACE due to multiple tumors or a large tumor burden, and for locally advanced-stage patients with solitary tumors, and segmental or lobar portal vein tumor thrombosis. In addition, emerging data have suggested the use of TARE in patients who are classified slightly beyond the Milan criteria regarding radical treatment for downstaging purposes. As a second-line treatment, TARE can also be applied in patients progressing to TACE or sorafenib; a large number of phase Ⅱ/Ⅲ trials are ongoing with the purpose of evaluating the best association with systemic therapies. Transarterial radioembolization is very well tolerated and has a low rate of complications which are mainly related to unintended non-target tissue irradiation, including the surrounding liver parenchyma. The complications can be additionally reduced by accurate patient selection and a strict pre-treatment evaluation including dosimetry and assessment of the vascular anatomy. Since a correct treatment algorithm for potential TARE candidates is not clear and standardized, this comprehensive review analyzes the best selection criteria for patients who really benefit from TARE and also the new advances of this therapy, which can be a very important weapon against HCC.

Key words: Yttrium-90; Hepatocellular carcinoma; Radioembolization

Core tip: Transarterial radioembolization (TARE) is a consolidated therapy for hepatocellular carcinoma. TARE is best indicated for both intermediate-stage patients (according to the Barcelona clinic liver cancer staging classification) who have lesions which respond poorly to chemoembolization due to multiple tumors or large tumor burden, and for locally advanced-stage patients with solitary tumors, and segmental or lobar portal vein tumor thrombosis. Moreover, emerging data have suggested the use of TARE in patients who are classified slightly beyond the Milan criteria regarding radical treatment for downstaging purposes. This review analyzes the best selection criteria for patients who really benefit from TARE.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide, with more than 700000 cases diagnosed yearly[1] and is the third most common cause of cancer-related mortality[2,3].

The current staging system, the barcelona clinic liver cancer (BCLC) staging classification recommends transarterial chemoembolization (TACE) as the standard of care for intermediate HCC (BCLC-B stage) and systemic therapies for advanced HCC (BCLC-C stage)[4,5].

Albeit a systematic review by Llovet *et al*[6] has reported an increased survival rate in patients treated with TACE; its low efficacy has however been demonstrated in large (> 5 cm) and in multinodular tumors[7-10]. A multicentric Japanese[11] study showed a significant decrease in 3-year survival after superselective TACE for lesions > 5 cm and multiple lesions (four or more) and an inverse correlation between survival and tumor size and number; in fact they obtained, in group of Child-Pugh A, the highest 3-year survival (80%) in patients with single lesion $\leqslant$ 2 cm and the lowest 3-year survival (30%) in patients with more than 4 lesions $\geqslant$ 5.1 cm and, in the group of Child-Pugh B, highest 3-year survival (65%) in patients with 2 lesions $\leqslant$ 2 cm, and the lowest (0%) in patients with three lesions $\geqslant$ 5.1 cm.

Regarding Sorafenib, a receptor tyrosine kinase inhibitor, two large randomized trials[12,13], together with other studies[14-16], have reported a benefit in terms of survival rate in advanced HCC with distant metastasis and/or vascular invasion. However, in a subsequent subanalysis of these trials, the tolerability of Sorafenib was revealed to be suboptimal; it was down-dosed in more than half of the patients and interrupted in 45% of patients due to severe adverse events (AEs) or liver function deterioration[17].

This scenario has led to new therapies for the best management of intermediate/advanced-stage HCC and, in this setting, available data have shown that transarterial radioembolization (TARE) could be an effective therapeutic option.

In the present review, the recent results of TARE regarding technical aspect, tumor response, survival rates, adverse events and safety have been summarized. The potency of TARE has been focused on, with the aim of providing its optimal use in daily practice in different settings and for conducting effective clinical trials on patients with intermediate/locally advanced-stage HCC. The new dosimetric advances affecting tumor response and safety have also been reviewed and the future direction for TARE has also been discussed.

TECHNICAL ASPECTS

The aim of TARE is to selectively target a high radiation dose to tumors within the liver, regardless of their cell of origin or location, while radiation to the normal liver is kept at tolerable levels. This is achieved by the preferential deposition of microspheres carrying a high energy radiation source [Yttrium-90 (90Y), 0.97 MeV], a beta-emitter, within the tumor capillary bed so that a tumoricidal dose of radiation (100 to 1000+ Gy) is absorbed over a limited range (mean tissue penetration 2.5 mm; maximum 11 mm) for a limited time; 90Y decays to stable zirconium-90 with an average half-life of 2.67 d (64.2 h)[18].

Transarterial radioembolization is defined as the injection of micron-sized embolic particles loaded with a radioisotope by means of percutaneous transarterial techniques in order to deliver high focal doses of radiation to tumors.

Transarterial radioembolization is similar to TACE as regards the technical aspects of the procedure since both require selective or superselective catheterization of the tumor-feeding vessels; however, both the principles and the mode of action of radioembolization are fundamentally different from conventional embolization or TACE. For the latter to be effective, the vessels feeding the tumor are filled with chemotherapeutic agents and are subsequently embolized with particles to ensure a static, ischemic environment in order to maximize exposure to those agents, and to promote ischemic necrosis. In contrast, for intra-arterial radioembolization to be effective, optimal perfusion and blood flow are required to allow the generation of free radicals by ionization of the water molecules near the DNA of the tumor cells. In the presence of normal oxygen tension, permanent DNA damage is caused to one or both DNA strands, and apoptosis is initiated or reproductive death is eventually achieved[18]. Maximal cytoreduction by radiation requires not only normal oxygen tension in the target cells but also sufficient microsphere coverage of the tumor nodule to avoid gaps in cumulative radiation due to crossfire "cold spots" or a low total dose of radiation in the tumor[18]. For this reason, the particles

Table 1 Characteristics of commercially available Yttrium-90-microspheres for transarterial radioembolization (modified from Sangro *et al*[72])

	SIR-Spheres[1]	TheraSphere[2]
Isotope 90Y	Attached to the surface	Incorporated into the glass matrix
Half-life (h)	64.1	64.1
Microsphere material	Resin	Glass
Microsphere diameter (μm)	20-60	20-30
Average size (μm)	32.5	25
Approximate activity per microsphere (Bq)	50	2500
Number of microspheres per 3 GBq	40-80 × 106	1.2 × 106
Specific gravity (g/mL)	1.6	3.6
Activity per commercially available vial (GBq)	3 (can be divided)	3, 5, 7, 10, 15, 20
Activity calculation	Compartmental MIRD macrodosimetry or empirical formula based on liver volume and tumor volume	Non-compartmental MIRD macrodosimetry
Estimated dose to the central vein area (Gy) in the montecarlo simulation[3]	59	58
Embolic effect	Moderate	Mild
Contrast agent injection	During infusion	None
Indication	United States (FDA PMA): colorectal liver metastases	United States (FDA HDE): hepatocellular carcinoma

[1]Sirtex Medical, North Sydney, Australia; [2]BTG International Canada Inc., Ottawa, Ontario, Canada; [3]From Gulec *et al*[40]. 90Y: Yttrium-90; MIRD: Medical Internal Radiation Dosimetry; FDA: Food and Drug Administration; PMA: Pre-Market Approval; HDE: Humanitarian Device Exemption.

used for radioembolization must be small enough (approximately 20 to 40 mm) to allow optimal access into the tumor nodules and deposition within the tumor plexus, without creating ischemia, but large enough to prevent the passage of microspheres through the capillary bed into the venous circulation leaving the liver.

Two types of microspheres loaded with 90Y are commercially available, one made of resin (SIR-Spheres; Sirtex Medical, Sidney, N.S.W., Australia) and an alternative made of glass (TheraSpheres, MDS Nordion, Toronto, Ont, Canada); the differences include the amount of activity contained in each microsphere and the number of microspheres injected in a single treatment (< 5 million to 10-30 million for glass and resin microspheres, respectively); however, their efficacy, toxicity and clinical outcome are similar (Table 1).

An HCC is a radiosensitive tumor[19] but external beam radiation therapy (EBRT) is not widely used due to severe liver toxicity [radiation induced liver disease (RILD)] when the dose absorbed by the liver is greater than 35 Gy[20,21] and lower doses, in order to spare the liver parenchyma, do not obtain a tumoricidal effect; an effective dose must exceed 70 Gy[22,23].

In both resin and glass microspheres, the primary mechanism of action is to the result of a localized radiotherapeutic effect (brachytherapy) rather than to microvascular embolization and tumor ischemia[24-26]. The radiation dose absorbed depends on the microsphere distribution within the tumor, mainly resulting from the arterial hepatic hemodynamic and tumor vascularization. In this way, tumors can be exposed to a higher radiation dose than with EBRT. In TARE, dosimetry planning, the administration and delivery of the radiation, modification of the dose on the basis of tumor and hepatic volume, and the knowledge required regarding radiation effects on tissue make this therapy a brachytherapy procedure as well.

TARE PROCEDURE

Patient selection

The specific technical aspects of the TARE procedure have recently been addressed by an International Working Group[27], and a detailed review of the methodological and technical aspects of the procedure was undertaken by Salem *et al*[28].

A multidisciplinary team consisting of professionals from interventional radiology, hepatology, medical, surgical and radiation oncology, and nuclear medicine is involved in selecting patients suitable for radioembolization. The patients are selected according to the following criteria.

Inclusion criteria: (1) confirmed diagnosis of unresectable HCC; (2) age > 18 years; (3) Eastern Cooperative Oncology Group performance status ⩽ 2; (4) adequate hematologic parameters (granulocyte count < 1.5 × 109/L, platelet count > 60 × 109/L), renal function (serum creatinine level < 2.0 mg/dL) and liver function (serum total bilirubin level < 2.0 mg/dL); and (5) the ability to undergo angiography and selective visceral catheterization. The majority of patients have a Child-Pugh score ⩽ 7 even though a Child-Pugh score > 7 is not an absolute contraindication.

Exclusion criteria: (1) any other liver-directed therapy planned for cancer treatment; (2) uncorrectable flow to the gastrointestinal tract; (3) lung shunting > 20% (resin microspheres) or estimated radiation doses to the lungs > 30 Gy (with a single administration) or 50 Gy (with multiple administrations); and (4) significant extrahepatic disease.

In cirrhotic patients, the tumor volume has to be ⩽ 50% of the total liver volume while, in patients with normal liver function, the tumor volume should not exceed 70% of the total liver volume.

Pre-treatment evaluation

All patients undergo pretreatment assessment, consisting of history, and a laboratory and imaging work-up, approximately 1/3 wk before the first planned treatment. Pretreatment cross sectional imaging is essential for treatment planning and post-treatment response assessment.

Treatment with 90Y microspheres is a 2-stage process involving an extensive work-up procedure to assess the appropriateness of the patient for treatment and to prepare the liver for radiation treatment, and the treatment procedure itself[29]. The pretreatment work-up includes.

Imaging work-up: Three-phase contrast computed tomography (CT) and/or gadolinium-enhanced magnetic resonance imaging (MRI) of the liver should be conducted for the assessment of tumor and non-tumor volume, portal vein patency and the extent of extrahepatic disease (Figure 1A and B).

Pre-treatment angiography: Given the high propensity for arterial variants and hepatic tumors to exhibit arteriovenous shunting, all patients being evaluated for 90Y must undergo pretreatment angiography (Figure 1C)[30]. This permits tailoring the treatment plan according to each patient's individual anatomy and helps to assess the possibility of any inadvertent spread of the microspheres to non-target organs; this can be mitigated by the prophylactic embolization of aberrant vessels to non-hepatic targets[30]. The superior mesenteric and celiac trunk angiograms provide the interventional radiologists an opportunity to study the hepatic vascular anatomy. The patency of the portal vein and the presence of arterio-portal shunting are also assessed. In some cases, prophylactic embolization of the gastroduodenal artery and right gastric artery is recommended as a safe and efficacious mode of minimizing the risks of hepatoenteric flow since this can lead to the inadvertent deposition of microspheres in the gastrointestinal tract causing severe ulcers which are highly symptomatic and difficult to manage[31]. Other vessels which need to be investigated and potentially embolized are the falciform, inferior esophageal, left inferior phrenic, accessory left gastric, supraduodenal and retroduodenal arteries. Diagnostic angiography is essential for ensuring that the blood supply to the tumor(s) has been adequately identified since incomplete identification of the blood supply to the tumor may lead to incomplete targeting and treatment. This facilitates accurate calculations of the target volume.

99mTc-macroaggregated albumin scintigraphy: one of the most important complications related to TARE is the possible deposition of microspheres in extrahepatic sites, in particular into the lungs due to hepato-pulmonary shunts. Since doses to the lungs can represent a limitation of the 90Y injected activity, evaluation of the lung shunt is mandatory before TARE (Figure 1D). Just after the pre-treatment angiography 150-200 MBq of 99mTc labeled macroaggregated albumin (99mTc-MAA) are intra-arterially administered into the arterial branch selected for the treatment. Macroaggregated albumin particles, considered a surrogate of microspheres, can be used to simulate their distribution to the liver, lungs and, possibly, the extrahepatic abdominal organs. The lung shunt fraction is evaluated by means of antero-posterior planar or whole body scintigraphy while the 3D distributions of the microspheres inside the tumor and normal liver can be evaluated by acquiring single photon emission CT (SPECT) images[32]. Scintigraphy is usually performed within one hour after the injection of 99mTc-MAA in order to avoid redistribution of free technetium and MAA particles, causing false-positive extrahepatic findings.

The lung shunt fraction is obtained by planar 99mTc-MAA imaging as follows:

$$LSF = Total\ counts_{lungs}/(Total\ counts_{lungs} + Total\ counts_{liver})$$

where:

(Total counts)lungs is the geometric mean of the total counts in a region of interest (ROI) positioned on the lungs in the anterior and posterior views of the 99mTc-MAA scan.

(Total counts)liver is the geometric mean of the total counts in a ROI positioned on the liver in the anterior and posterior views of the 99mTc-MAA scan.

The dose absorbed in the lungs, due to the shunt, can be calculated using the following formula:

$$D\ (Gy)_{lungs} = A\ (GBq)_{injected} \times LSF \times 50/M\ (kg)_{lungs}$$

A radiation absorbed dose limit of 30 Gy per radioembolization treatment session is recommended[33]. The published upper limit for hepatopulmonary shunt fraction is 20% for resin-based microspheres (SIR-Spheres; Sirtex)[31].

90Y treatment

The 90Y treatment is carried out using well-known guidelines[27,28,34] based on the experience of more than 900 90Y infusions carried out over a 5-year period.

The tumor is approached under fluoroscopic guidance; the first part of the procedure is similar to the pretreatment angiography after which the activity vial is injected into the vessel feeding the tumor. The device for administering the 90Y is designed to minimize the radiation exposure of the personnel involved in the procedure. A physicist is present throughout the procedure to ensure that proper protocols are followed in order to minimize accidental radiation exposure. In some hospitals, immediately after the treatment, a

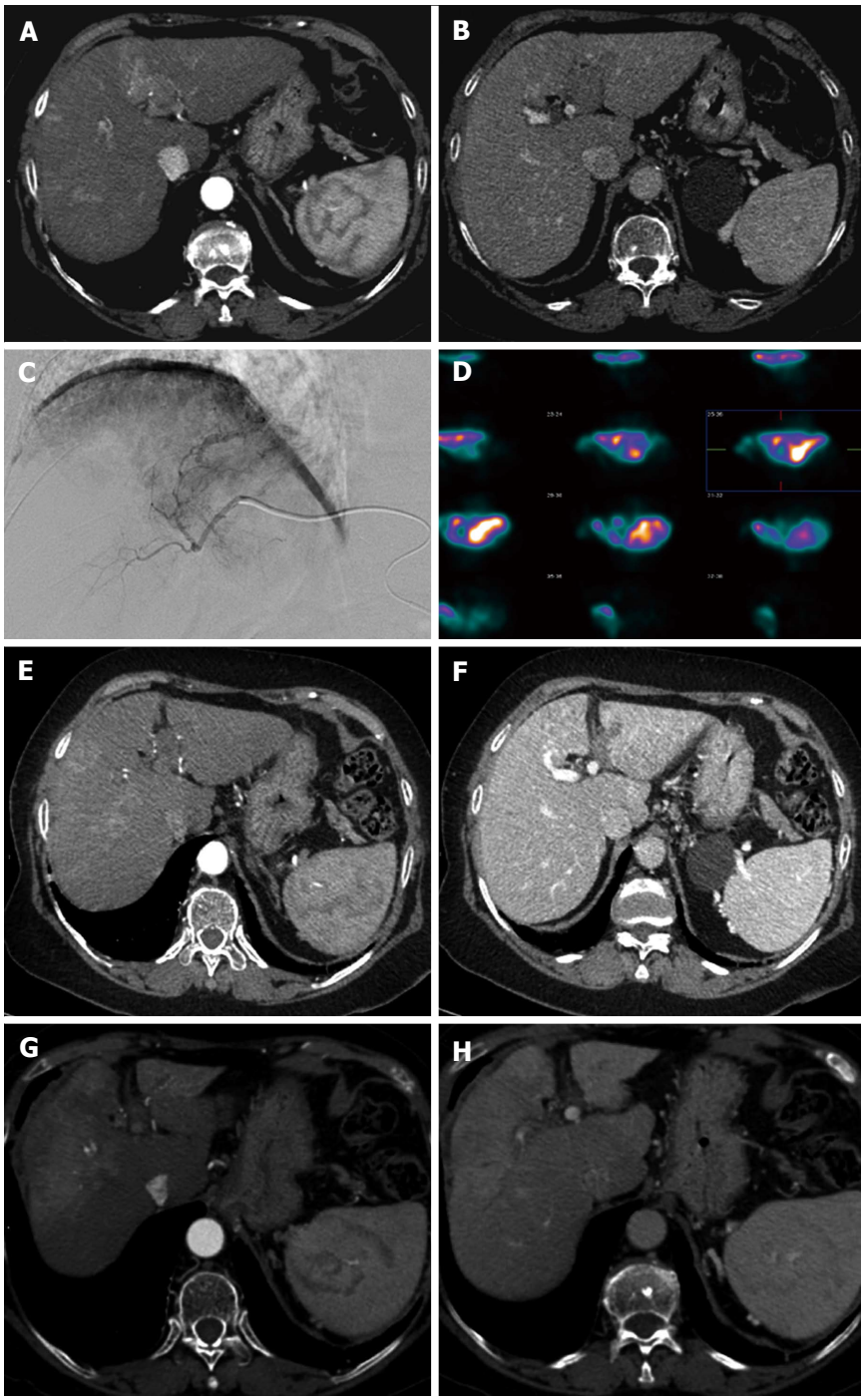

Figure 1 Treatment with Yttrium-90 and response of infiltrative hepatocellular carcinoma. A and B: The pretreatment computed tomography (CT) showing infiltrative hepatocellular carcinoma in the Ⅳ segment with associated tumor thrombosis of the left portal branch as visualized in the arterial phase and in the portal-venous phase; C: The pretreatment angiogram carried out with selective catheterization of the left hepatic artery, arising from the left gastric artery, confirms the hypervascularization of the venous thrombus; D: The pretreatment 99mTc-MAA single photon emission computed tomography images showing the corresponding uptake of MAA in the region of interest (tumor thrombus); E and F: The CT performed 1 mo after treatment showing both a significant decrease of the enhancement of the portal venous thrombus and a reduction in the enlargement of the portal branch as a sign of response, better visualized at 1 year (G and H). Note the significant "shrinkage" of the left lobe and the compensatory hypertrophy of the contralateral hepatic lobe. 99mTc-MAA: 99mTc labeled macroaggregated albumin.

Bremsstrahlung (gamma) scan or positron emission tomography-CT is performed to evaluate 90Y distribution.

DOSIMETRY

The main goal of TARE is to deliver a curative therapeutic dose to the tumor while sparing normal tissues[35]. Personalized treatment planning is desirable for TARE and can be carried out using 99mTc-MAA SPECT images and volumes obtained from CT scans. The image fusion of the CT and the SPECT images can help in the delineation of volumes involved in the treatment.

An important limitation of TARE is the dose to the normal liver because an excessive dose to the normal

parenchyma could induce radiation hepatitis and liver failure[36]. The spatial distribution of the microspheres is crucial and may be very different for the two types of spheres. When using resin microspheres, the dose absorbed by the normal liver should be kept lower than 40 Gy to minimize the risk of liver failure, especially in patients having compromised liver function[36]. Although personalized dosimetry would be the best approach to TARE, it has not been standardized and is often not attainable.

For these reasons, the majority of TARE treatments are performed calculating the injected activity based on empiric formulas suggested by the manufacturers instead of following scrupulous dosimetric formalism. In the following paragraphs, the standard methods for activity assessment have been briefly described for both glass and resin microspheres.

Glass microspheres

The activity determination for glass microspheres, proposed by the manufacturer (TheraSphere 90Y Glass Microspheres Users Manual. BTG cercare nuovo indirizzo), is based on a nominal target dose (80-150 Gy) to the treated mass (M), which can be measured by CT images. This approach assumes a uniform distribution of the microspheres throughout the treated volume, including the tumor and the normal parenchyma:

$$A\ (GBq)_{glass} = D\ (Gy) \times M\ (kg)/50$$

Lung dose should be kept to less than 30 Gy for a single injection and less than 50 Gy as a cumulative dose for multiple injections[37].

Using the above formula, the dose delivered to the tumor is not known; however, going on the assumption that tumors have an higher vascularity as compared to the normal parenchyma, it is reasonable to predict that the prescribed dose be at least that which is absorbed by the tumor in order to prevent liver fibrosis.

Resin microspheres

Two methods are proposed by SIRTEX to determine the activity of 90Y to be injected: the empiric method and the body surface area (BSA) method [38].

The empiric method suggests a standard amount of activity based on tumor involvement only, considering three varying degrees of tumor involvement.

Tumor $\leqslant$ 25% of the total mass of the liver by CT scan = 2 GBq whole-liver delivery.

Tumor $\geqslant$ 25% but $\leqslant$ 50% of liver mass by CT scan = 2.5 GBq whole-liver delivery.

Tumor $\geqslant$ 50% of liver mass by CT scan = 3 GBq for whole liver delivery.

It is important to point out that this method is not recommended by the scientific community[39].

The BSA method is a variant of the empiric method which calculates the injected activity, taking into account the patient's BSA and the fraction of liver volume involved by the tumor:

$$A\ (GBq) = (BSA - 0.2) + V_{tumor}/(V_{tumor} + V_{normal\ liver})$$

Where: BSA (m^2) = 0.20247 $\times$ height (m) 0.725 $\times$ weight (kg) 0.425.

The BSA formula is considered safe for patients with compromised liver function or for particularly small patients. A reduction of the amount of activity up to 20% is recommended for lung shunts greater than 15%.

Dosimetric approach

The empiric methods suggested by both manufacturers do not represent a real dosimetric approach to the treatment because the distribution of the 90Y microspheres and the uptake ratio between the tumor and the normal parenchyma are never considered, thus preventing any accurate dosimetric evaluation.

A dosimetric approach based on Medical Internal radiation Dosimetry (MIRD) formalism was proposed by SIRTEX as a "partition model" and has been formalized with MIRD equations by Gulec *et al*[40]. The MIRD formalism is based on the determination of the fraction of activity (fractional uptake) which is trapped by the tumor, normal liver and lungs, respectively, by the masses of each compartment which are calculated using CT images. The fractional uptake, representing the fraction of activity reaching each compartment, is measured by 99mTc-MAA SPECT images, calculating the tumor to liver ratio and the lung shunt fraction. Because the dose to the normal parenchyma is the most important limiting factor, the administered activity can be calculated as the activity delivering the selected nominal dose to the liver, as follows:

$$A\ (GBq)_{injected} = D\ (Gy)_{liver} \times M\ (kg)_{liver}/50$$

where:

A(GBq) is the 90Y injected activity;

D(Gy) is the nominal dose to the liver;

M(Kg) is the liver mass;

and 50 is a constant which depends on the physical characteristics of 90Y.

Once the fraction of activity reaching each compartment/tissue is measured, the corresponding absorbed dose is evaluated using the following formula:

$$D\ (Gy)_{tissue} = 50 \times A\ (GBq)_{tissue}/M\ (kg)_{tissue}$$

The 99mTc-MAA particles are considered a surrogate of the microspheres, and their distribution inside tissues is representative of the microsphere distribution. It is very important to point out that, using 99mTc-MAA SPECT images, it is possible to carry out provisional dosimetry before the 90Y infusion, although it presents several limitations. In particular, the major limitations of this approach are the different size and specific gravity of 99mTc-MAA and the 90Y microspheres, the different volume and velocity of injection, the reproducibility of the exact site of injection and the hemodynamic conditions inside the tumor which can be considerably different

between the 99mTc-MAA and the 90Y treatments. Furthermore, the MIRD approach assumes the uniform distribution of the microspheres and measures average doses while, especially in tumor masses, the dose is strongly dependent on heterogeneous vessel density.

However, despite the limitations listed above, the higher mean dose absorbed by the tumor masses, calculated with 99mTc-MAA SPECT images, was predictive of a better tumor response in patients affected by HCC for both resin[41] and glass microsphere[35] treatments.

Furthermore, the intrinsic differences between the two types of microspheres and, in particular, their different numbers and specific activities, are responsible for the different distribution of the microspheres inside the tissues, more uniform for resin than for glass microspheres. Consequently, the published data regarding dosimetry have reported higher values of the tumor dose response for glass microspheres than for resin microspheres[42].

POST-TREATMENT ASSESSMENT AND FOLLOW-UP

To monitor tumor response and to identify any toxicity, clinical, laboratory and radiologic follow-ups are necessary. A regular follow-up includes liver function tests, a complete blood count, tumor marker analysis and cross-sectional imaging (CT and/or MRI) one month post-treatment and then every three months.

Imaging after TARE is required to monitor the tumor response but it is not always easy to interpret. Imaging usually shows a change in both the appearance of the tumor and the surrounding liver. Since the effect of the radiation may not be manifested until after 30 d, imaging at 1 mo after the procedure is usually not representative of the tumor response (Figure 1E and F). However, a common early feature is the appearance of rim enhancement surrounding the lesion; this is an early sign of a fibrotic capsule and it is fundamental not to erroneously consider it as a residual tumor[43]. Instead, in a period ranging from 8 to 12 wk after TARE (Figure 1G and H), there is noticeable tumor shrinkage and the parenchyma also becomes atrophic as a consequence of hepatic fibrosis and capsular retraction of the treated area; atrophy of the treated area induces a compensatory hypertrophy of the contralateral lobe especially after lobar procedures (rather than after a segmental or subsegmental approach). Another common feature is the appearance of transient perfusion abnormalities in the treated area, which should be differentiated from residual or recurrent tumors. Furthermore, transient hypoattenuating perivascular edema near the hepatic and portal veins can also be observed on imaging.

Computed tomography is capable of identifying changes in the size of the lesions, alterations in vascularity and enhancement; the appearance of new intra or extrahepatic lesions are well defined with this technique but may limit the capability of documenting the tumor necrosis.

Magnetic resonance imaging, especially using diffusion-weighted imaging (DW-MRI) and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid imaging (Gd-EOB-DTPA-MRI) identifies necrosis and cell death[44] earlier (6-8 wk post-procedure in some cases) and better than CT[34,45].

Regarding the assessment of treatment response, the clinical studies conducted have mainly used modified Response Evaluation Criteria in Solid Tumors[46] or the European Association for the Study of the Liver (EASL) criteria, the former measuring the diameter and the latter the area of the enhancing tumor[47].

RESPONSE AND SURVIVAL ACCORDING TO TUMOR STAGES

Tumor response after treatment

The benefits of 90Y TARE in patients with HCC have been widely described[48-53]. Current data report a response rate which varies among published studies, mainly due to the heterogeneous populations enrolled (Table 2).

In an early study[54], a 50% reduction in tumor volume was reported in 19 (26.7%) out of 71 patients after the first treatment. More recently, a German multicenter study[55] (carried out on 108 patients) reported complete response (CR) in 2 (3%) patients, partial response in 23 (37%) and stable disease in 33 (53%) patients 3 mo after treatment, using the EASL criteria.

In a European prospective study involving 52 patients with a median follow-up of 36 mo, Mazzaferro *at al*[56] reported an objective response and a disease control rate of 40.4% and 78.8%, respectively, according to the EASL response criteria; there was a CR in 5 patients (9.6% of cases).

TARE in intermediate- and early-stage patients

According to the BCLC staging system recommendation, in the intermediate stages, TACE is the first-line therapy for asymptomatic patients with multinodular unresectable HCC[6,57-59]. However, these data come from trials which enrolled a large number of patients in the early stage or patients in the intermediate stage but with single-lobe involvement. Moreover, the TACE procedure was performed with very different modalities all over the world; the above-mentioned reasons explain the wide differences in the 2-year survival rates observed in prospective randomized trials (24%-63%) as well as in retrospective series (11%-47%)[8].

Patients in intermediate-stage HCC who are treated with TARE as a first-line therapy are generally patients with a normal performance status for whom TACE is not suitable due to voluminous disease with more than 5 nodules in both lobes or a single large nodule. In these patients (BCLC-B stage), survival was approximately 15.4-16.6 mo[8], not very different from the median overall survival (OS) of 15.6-17.4 mo observed in patients treated

Table 2 Outcomes after transarterial radioembolization from recent studies (modified from Kim *et al*[89])

Ref.	No. of patients	Response rate	Survival (mo)	Prognostic factors
Carr *et al*[48]	65	OR = 38%	Okuda *et al*[90] I : 21 Okuda *et al*[90] II : 10	
Salem *et al*[50]	43	PR = 47%	Okuda *et al*[90] I : 24 Okuda *et al*[90] II : 13	Main PVTT; AFP > 400 ng/mL tumor burden > 25%
Sangro *et al*[91]	24	PR = 24%; SD: 64%	7	
Young *et al*[80]	41		Okuda *et al*[90] I : 21.7 Okuda *et al*[90] II : 14.2	
Kulik *et al*[92]	71	PR = 42%; SD: 35%	15.5	
Salem *et al*[63]	123	RR = 72%	20.5	Sex (female); Child-Pugh class; UNOS
Sangro *et al*[8]	325		12.8	ECOG; nodules > 5; INR > 1.2; extrahepatic disease
Mazzaferro *et al*[56]	52	CR = 9.6%; OR = 40.4%	15	Response; Child Pugh class

PVTT: Portal vein tumour thrombosis; AFP: Alpha-fetoprotein; OR: Odds ratio; PR: Partial response; RR: Response rate; CR: Complete response; SD: Stable disease; UNOS: United Network of Organ Sharing; ECOG: European Cooperative Oncology Group; INR: International Normalized Ratio.

Table 3 Comparison of response and median survival after transarterial radioembolization and transarterial chemoembolization from recent studies (modified from Lau *et al*[93])

Ref.	Treatment	*n*	OS (mo)	TTP (mo)	Response (CP/PR) % WHO/RECIST criteria	RR (CP/PR) % EASL criteria	Downstaged/ LT %	Mean days in hospital per treatment
Lewandowski *et al*[69]	TARE (TheraSphere[1])	43	35.7	33.3	61	86	58[a]	0[a]
	TACE	43	18.7	18.2	37	71	31	3
Kooby *et al*[88]	TARE (SIR-Spheres[2])	27	6	NR	11	NR	NR	1.7[a]
	TACE	44	6		6			6
Carr *et al*[68]	TARE (TheraSphere[1])	99	11.5	NR	41	NR	NR	NR
	TACE	691	8.5		60			
Salem *et al*[63]	TARE (TheraSphere[1])	123	20.5	13.3	49	72	25	0[a]
	TACE	122	17.4	8.4	46	69	36	1.8

[1]BTG International Canada Inc., Ottawa, Ontario, Canada; [2]Sirtex Medical, North Sydney, Australia. [a]$P < 0.05$, response and median survival after transarterial radioembolization *vs* transarterial chemoembolization. OS: Overall survival; TTP: Time to tumor progression; CP: Complete response; PR: Partial response; RR: Response rate; WHO: World Health Organization; RECIST: Response Evaluation Criteria in solid tumors; TARE: Transarterial radioembolization; TACE: Transarterial chemoembolization; EASL: European Association for the Study of the Liver; LT: Liver transplantation; NR: Not reported.

with TACE[60-62]. Survival was even better after TARE than after TACE in patients who were ideal candidates for TACE as reported by Sangro *et al*[8] with a median OS of 22.8 mo in patients with 1-5 nodules and 23.2 mo for those with unilobar disease.

It has been widely reported that TACE is not effective for large tumors, especially for tumors > 5 cm[10] or in the presence of multiple satellite nodules; in this setting, TARE could be the first line treatment.

Numerous studies have compared TARE to TACE in matched patient cohorts; Table 3 summarizes the largest and the most noteworthy series reported in the literature.

In a recent study, Salem *et al*[63], comparing TARE and TACE in the entire cohort of patients achieved a median OS for TACE and TARE patients (53% intermediate-stage HCC and 35% early-stage HCC) which did not significantly differ (17.4 mo for the TACE group and 20.5 mo for the TARE group); moreover the same study, analyzing only the survival of the BCLC B group, showed similar results between TARE and TACE (17.5 mo *vs* 17.2 mo, $P = 0.42$). Lance *et al*[64], in a recent retrospective study, did not report any significant differences in survival when comparing 38 patients treated with TARE and 35 treated with TACE (median 8.0 mo *vs* 10.3 mo, $P = 0.33$, respectively).

However, significant data regarding comparison between TARE and TACE are lacking because of the well-known heterogeneity of the BCLC-B stage, which includes different tumor characteristics in terms of tumor number and size[65]; at the moment, in fact, the data available are not sufficient to demonstrate a significant difference between these two therapies. In order to power a head-to-head equivalence trial with TACE having overall survival as the main endpoint, more than 1000 patients would have to be recruited, and this would represent too large a sample, even for a multicenter study[63].

Moreover, it is also necessary to evaluate the cost-effectiveness of these two therapies considering, on the one hand, the higher cost of TARE and, on the other hand, the longer hospital stay and the cumulative charges involved in repeated TACE procedures.

The shorter time to tumor response and the longer time to tumor progression after TARE as compared to TACE are two important considerations; these data suggest a potential advantage of using TARE as a bridge therapy in patients waiting for liver transplantation

(LT)[63].

In fact, in the early stage, 90Y treatment is most usually employed as a bridge to liver transplantation. Riaz *et al*[66] have recently demonstrated that none of the 15 patients treated with TARE prior to LT progressed from United Network for Organ Sharing T2 to T3, and 8 out of 10 were downstaged from the T3 to the T2 stage; moreover, histology showed 100% necrosis in 89% of the lesions < 3 cm and 65% of the lesions 3-5 cm in size. The same authors and others had previously analyzed[67,68] similar data in patients treated with TACE prior to LT, showing 35%-57% complete necrosis in lesions < 3 cm and 17%-42% in lesions 3-5 cm in size[9,67]. A retrospective analysis by Lewandowski *et al*[69] showed that TARE achieved better downstaging than TACE (58% *vs* 31%, $P = 0.023$) in patients with HCC beyond the Milan criteria, among which as many as two-thirds were downstaged.

Gramenzi *et al*[70] have very recently reported that, among the patients treated with TARE in the series analyzed, two patients were successfully downstaged, free from HCC recurrence and listed for LT.

TARE in advanced stage patients

Sorafenib is the mainstay for treating advanced HCC, defined by the presence of vascular invasion, extra-hepatic disease or deteriorated performance status in a patient with at least partially preserved liver function; it has been shown to improve survival in these patients with or without portal vein tumor thrombosis (PVTT)[12,13]; however, it is not without severe side effects.

Patients in the advanced stage treated by radioembolization have median overall survivals ranging from 6-10 mo[71] very similar to the 6.5-10.7 mo of the SHARP and Asia-Pacific populations. Due to the lack of significant macroembolic effect causing liver decompensation, PVTT is not a contraindication for radioembolization; however, prognosis is closely correlated to the PVTT extension; in fact, patients with main PVTT have a poor prognosis (OS ranging from 3 to 6 mo) as compared to the patients with segmentary or lobar PVTT (OS ranging from 10 to 14 mo). Patients with PVTT and Child-Pugh B have a median survival of 2-5 mo due to liver decompensation[72].

Currently, there is increasing evidence that TARE can be delivered safely and effectively in patients with lobar or segmentary PVTT. Table 4 reports several studies with a median OS rate of approximately 10 mo. Therefore it is evident that TARE in BCLC-C stage patients with PVTT could be an alternative to sorafenib but a phase Ⅲ trial comparing TARE with sorafenib in locally advanced HCC would be necessary to define the role of these two therapeutic strategies in advanced-stage HCC.

However, to date, only one retrospective series with a propensity analysis[70] has compared the outcomes of two groups of patients treated with TARE and Sorafenib, and it showed that these therapies provided similar survival; the median OS of the Sorafenib arm was 13.1 mo (95%CI: 1.2-25.9) and of the TARE arm 11.2 mo (95%CI: 6.7-15.7; $P = 0.392$) but only in the TARE arm were 2 patients fully downstaged to LT.

Even if liver failure or intrahepatic tumor growth are the reasons for nearly 90% of deaths among HCC patients, the presence of extrahepatic disease has however been demonstrated to have a negative impact on survival after TARE; the median OS was 7.4 mo in a European series[72] and 5.4 mo in a United States series[71]. Evaluating this aspect, the fundamental aim of the emerging studies was the combination of TARE and sorafenib[73,74]. There was only one study which evaluated the combination of TARE with sorafenib published by Kulik *et al*[75]; this randomized study compared the safety of combining TARE with sorafenib to TARE alone in 20 patients intended for LT; seventeen patients underwent liver transplantation, 9 patients in the TARE group and 8 in the other arm. This study showed that the combination of sorafenib and TARE did not appear to influence complete pathological necrosis and had similar survival rates (70% and 72% at 3 years); moreover, the combination was associated with more peri-transplant biliary complications and potentially trended towards more acute rejections.

SAFETY, TOLERABILITY AND TOXICITY

The safety of TARE in HCC has been well documented in the literature[54,76,77]. In fact, this therapy has excellent tolerability and a low incidence of complications resulting from the irradiation of non-target tissues, including the non-tumor liver compartment. The incidence of complications can be additionally reduced by patient selection and by rigorous pretreatment assessment, including dosimetry models and the thoroughness of the technique applied[66].

The main complications occurring after radioembolization can be broadly classified into the following groups: postradioembolization syndrome, hepatic dysfunction, biliary sequelae, gastro-intestinal (GI) ulceration, radiation pneumonitis and lymphopenia[66]. The majority of current reports in the literature use the Common Toxicity Criteria of Adverse Events 3.0.

The most common side effect is postradioembolization syndrome; its incidence ranges from 20% to 55%[50,78]. Postradioembolization syndrome consists of the following clinical symptoms: fatigue (54%-61%), nausea and vomiting (20%-32%), fever (3%-12%), abdominal discomfort (23%-56%), cachexia and anorexia[8,71]. The degree of symptoms is reported to be less severe when compared to TACE[71] and, after TARE, they are generally transient.

RILD is defined by the presence of jaundice, mild ascites, a marked increase in bilirubin and alkaline phosphatase, no change in transaminase levels and liver function tests, the latter ranging from 15% to 20%[36]. It is described as a form of sinusoidal obstruction syndrome which usually occurs 4-8 wk after TARE[36]; Sangro *et al*[36], who described it for the first time, performed in some patients affected by suspected

Table 4 Response and median survival after transarterial radioembolization in hepatocellular carcinoma with or without portal vein tumour thrombosis from recent studies (modified from Okuda *et al*[90])

Ref.	PVTT	*n*	Response (CR/PR) % WHO/RECIST criteria	RR (CR/PR) % EASL criteria	OS
Salem *et al*[71]	Child-Pugh A	116	52	69	17.2
TheraSphere[1]	No PVTT	81	53	77	22.1
no EHS	PVTT (mixed)	35	50	50	10.4
	First-order	19	58	58	16.6
	Main	16	40	40	7.7
	Child-Pugh B	122	39	52	7.7
	No PVTT	65	47	67	14.8
	PVTT (mixed)	57	28	32	5.6
	First-order	27	28	40	6.5
	Main	30	28	24	4.5
Hilgard *et al*[55]	All patients	108	15	40	16.4
TheraSphere[1]	No PVTT	75	NR	NR	16.4
30% EHS	PVTT [mixed: main (12); first/second order (12); unknown (9)]	33			10
Sangro *et al*[8]	All patients	325	NR	NR	12.8
SIR-Spheres[2]	No PVTT	249			15.3
9% EHS	PVTT [mixed: main (32); first order (44)]	76			10.7/9.7
Iñarrairaegui *et al*[94]	PVTT [mixed: main (6); first/second order (19)]	25	NR	NR	10
TheraSphere[1] and SIR-Spheres[2]					
Tsai *et al*[95]	PVTT	22	NR	NR	7
TheraSphere[1] and SIR-Spheres[2]	Main	12			4.4
13% EHS	First order	10			7
Woodall *et al*[96]	No PVTT	20	NR	NR	13.9
TheraSphere[1]	PVTT [mixed: main (10)]	15			3.2
Kulik *et al*[92]	All patients	108	42	70	NR
TheraSphere[1]	No PVTT	71			15.4
12% EHS	PVTT main	12			4.4
	First order	25			9.9

[1]BTG International Canada Inc., Ottawa, Ontario, Canada; [2]Sirtex Medical, North Sydney, Australia. PVTT: Portal vein tumor thrombosis; CR: Complete response; PR: Partial response; WHO: World Health Organization; RECIST: Response Evaluation Criteria in solid tumors; RR: Response rate; EASL: European Association for the Study of the liver; EHS: Extrahepatic disease; NR: Not reported; OS: Overall survival; Main: Main portal vein trunk; First order: Right and/or left portal vein; Second order: Segmental branches of portal vein.

RILD the liver biopsy that showed extensive sinusoidal congestion affecting perivenular areas with focal hepatic atrophy, areas of necrosis around central veins with fresh thrombosis, and some cholestasis in periportal areas. These findings were consistent with hepatic veno-occlusive disease. RILD ranges from 0%-4%[18]; however, it is difficult to establish the actual incidence of this complication, mainly due to the fact that the majority of published series report the changes in laboratory tests over different periods of time (from 30 d to the entire follow-up period).

The incidence of biliary sequelae after radioembolization is less than 10%[66]. These complications may result from the microembolic effect of the therapy or radiation-induced injury to the biliary structures. The majority of biliary complications are not manifested clinically; clinical correlation with imaging findings is recommended.

According to Atassi *et al*[79], < 2% of patients required drainage of bilomas, treatment of abscesses and cholecystectomies. However, the treatment is not recommended in patients with main biliary duct obstruction or stenting. Radiation cholecystitis requiring surgical intervention occurs in less than 1% of cases[66].

Transarterial radioembolization can lead to severe toxic effects as a result of the non-targeted distribution of 90Y-microspheres, such as radiation-induced gastroduodenal ulcerations (less than 5% if proper percutaneous techniques are used)[66]. Severe epigastric pain after treatment should be aggressively managed as early management could prevent more serious complications from occurring. Endoscopy may be required to confirm the diagnosis. Cases refractory to proton pump inhibitors may require surgical management. As opposed to a normal ulcer which develops at the mucosal surface, 90Y-induced ulcers originate from the serosal surface. This may theoretically decrease the ability of the ulcer to heal and complicate the surgical field from scars/adhesions should surgery be required. Pretreatment angiography is essential to identify vessels which may supply the GI tract. However, gastrointestinal toxicities can be avoided by using meticulous techniques.

Pneumonitis is a rare event due to the mandatory quantification of pretreatment lung shunting[36,37]. Monitoring of the development of pneumonitis is necessary if the lung shunt fraction is greater than 13%[37]. If standard dosimetry models are used, the incidence of radiation pneumonitis is well below 1%[66]. Radiation pneumonitis manifests as a restrictive ventilatory dysfunction. It is radiologically seen as having a bat-wing appearance on chest CT. Lung doses less than 30 Gy per treatment and less than 50q Gy cumulatively are recommended.

Mild to moderate lymphopenia may be experienced in patients after TARE, but an association with increased susceptibility to infections has not been demonstrated[48].

Other side effects to be expected after treatment are a transient elevation in liver function tests, specifically in alkaline phosphatase, bilirubin and alanine transferase levels[36,80].

In a retrospective analysis involving 325 patients conducted on the database of the European Network on Radioembolization with 90Y resin microspheres study group[81], the clinical outcomes of elderly as compared to younger patients were evaluated. The authors showed that TARE was equally well tolerated in all cohorts and that the common procedure-related AEs were of mild-to-moderate intensity and of short duration. Moreover, in the elderly cohort ($\geqslant$ 75 years), no AEs were of grades $\geqslant$ 3. The difference in the occurrence of severe AEs was not statistically significant in the two cohorts. Gastrointestinal ulceration was predominantly mild or moderately severe in both the younger and the elderly patients (P = 0.320); severe increases in total bilirubin (to grade $\geqslant$ 3) at 3 mo as compared to baseline were observed in 4.3% and 6.9% of the elderly and the younger populations, respectively (P = 0.432) and in 4.2% of the very elderly population. A greater number of elderly patients experienced hypoalbuminemia (P = 0.018) and elevated alanine transaminase (P = 0.015) at 3 mo, although these changes were mild (grades 1-2).

CONCLUSION

Three categories of patients are potential candidates for Y-TARE: (1) patients in the intermediate stage who are not good candidates for TACE due to numerous or bulky tumors; (2) patients in the advanced stage with solitary HCC tumors and segmental or lobar PVTT; and (3) patients with HCC in potential downstaging for a radical approach.

Indeed, the European Society for Medical Oncology[82], the European Society of Digestive Oncology[83], and the National Comprehensive Cancer Network have recently included 90Y-TARE in their guidelines as a "bridge" option before other treatment modalities (partial hepatectomy, LT) as the principal therapy for patients with diffuse intrahepatic tumor spread or as an alternative to TACE in selected patients with contraindications for TACE[81,83]. Moreover, the Consensus Recommendations of the National Cancer Institute Clinical Trials Planning Meeting[84] stated that TARE may be used in selected patients with HCC without extrahepatic disease who are amenable to radical therapies.

Nevertheless, the American Association for the Study of Liver Disease[85], EASL and the European Organization for Research and Treatment of Cancer do not include TARE in their guidelines.

For this reasons, relevant clinical trials are now underway to establish the precise role of TARE in the treatment of HCC, in particular multicenter RCTs regarding both the intermediate and the advanced stages of HCC.

The PREMIERE trial (NCT00956930), a United States randomized trial, compares TARE with radiofrequency ablation, TACE or their combination in patients with unresectable HCC and well preserved liver function. To date, as described above, no significant differences between TACE and TARE have been found in terms of survival rates, but TARE seems to be significantly better tolerated regarding post-procedural abdominal pain, length of hospital stay and post-embolization syndrome.

Two important multicenter randomized-controlled trials in advanced-stage patients are the Asia-Pacific SIRveNIB trial (NCT 01126645) and the European SORAMIC trial (NCT01126645); they compare TARE and Sorafenib in HCC patients without extrahepatic disease who are not suitable for TACE and also in HCC patients with extrahepatic disease. The trials are ongoing but preliminary results report that TARE should be considered as good an option as sorafenib in the same setting of patients. The YES-P trial (NCT 00537514) has recently begun; it is a large prospective randomized clinical trial comparing TARE with glass microspheres (TheraSphere®) *vs* sorafenib for the treatment of advanced HCC with PVTT, involving up to 25 sites in Europe, Asia and North America.

Another important aspect to evaluate is the quality of life after TARE; Salem *et al*[86] have recently compared the quality of life (QoL) of HCC patients treated with TACE (29 patients) *vs* those treated with TARE (27 patients), using the FACT-Hep questionnaire (a 45-item self-report instrument specifically designed with patient and clinician input to measure health-related QoL in patients with hepatobiliary cancer)[87].

They did not observe any significant differences in overall FACT-Hep health-related QoL scores between the two groups, even if the TARE group had significant improvement in several aspects of QoL as compared to the TACE group. Currently, there is only one ongoing European randomized trial, the SIRTACE study (NCT00867750), which analyses the quality of life after TACE and TARE.

Finally, it is very important not to forget the cost of the TARE procedure; a recent study by Kooby *et al*[88], comparing the costs of TARE to those of TACE, has demonstrated that the first is less expensive than multiple TACE sessions, especially if drug-eluting beads are used.

In conclusion, regarding TARE treatment, a multi-disciplinary team of experts is necessary to ensure the best patient selection and to obtain optimal results; this is possible only in tertiary level centers having certified expertise, after thorough training of the staff.

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