Current Status of TARE (Trans Arterial Radioembolization) in Clinical Practice – A Review

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Abstract

Transarterial radioembolization has emerged over the last decade as an established locoregional therapy for the management of primary and metastatic liver cancers, with hepatocellular carcinoma accounting for majority of primary liver cancers. TARE began as a treatment for advanced HCC in a palliative setting in patients with intermediate and advanced stage unresectable HCC that over the years has evolved as a curative treatment option. This review discusses the current evidence of TARE in clinical practice, concept of radiation segmentectomy, radiation lobectomy, and its role in tumors other than hepatocellular carcinoma and on personalized dosimetry.

Keywords: Transarterial radioembolization; Radiation segmentectomy; Radiation lobectomy; Dosimetry

Introduction

Transarterial Radioembolization (TARE) has emerged over the last decade as an established locoregional therapy for the management of primary and metastatic liver cancers. Hepatocellular Carcinoma (HCC) accounts for majority of primary liver cancers (70% to 90%) with the single largest risk factor being cirrhosis of any etiology, and has been reported in about 70% to 90% globally in cirrhotic livers [1,2]. The underlying etiologies of cirrhosis are chronic Hepatitis B Viral (HBV) infection, Chronic Hepatitis C viral (HCV) infection, alcohol consumption [8%] and aflatoxin exposure. The other important risk factors are diabetes mellitus; non-alcoholic fatty liver disease (NAFLD), smoking and tobacco use [2-5]. Consistent with the global trend, NAFLD is increasingly being recognized in India as a cause of HCC and has been linked to obesity and type 2 diabetes [6].

HCC has a poor prognosis, with two-thirds of patients surviving for less than two years, and less than five per cent achieving a five year survival rate [7]. The therapeutic option and clinical outcomes are based on tumor characteristics such as size, number of lesions, vascular invasion, the child’s status of liver disease and overall performance status of the patient. The BCLC staging is the standard means for assessing the prognosis of patients with HCC and links the prognosis with treatment recommendations [8]. In a country like India, patients present predominantly in advanced stage of disease wherein curative treatment remains a challenge. Up to 13% HCC patients have extra-hepatic metastasis at the time of presentation [9,10]. Hence the therapeutic options for intermediate and advanced stage disease largely remain palliative. The reported median survival of patients with advanced unresectable HCC is only 2 to 3 months with best supportive care (BSC). Sorafenib, an oral multikinase inhibitor is the only drug that has demonstrated a survival benefit over BSC in advanced HCC. The recommended palliative treatment for BCLC stage B (intermediate stage disease) is Transarterial Chemoembolization (TACE) and stage C (advanced stage disease) is sorafenib [8].

TARE in Clinical Practice

TARE is a sophisticated procedure that requires technical expertise, multidisciplinary management and a considerable learning curve. The role of TARE clinically emerged in the patient population of intermediate HCC who predominantly presented with portal vein thrombosis making them unsuitable for TACE, even though super selective TACE is accepted in the presence of segmental portal vein thrombosis [11]. Until recently, TARE was mainly used in a palliative setting in inoperable advanced HCC cases with extensive portal vein thrombosis who had progressed on sorafenib or in intermediate stage diseases who had either failed TACE or were deemed unsuitable for TACE. The micron-range diameter particulate carrier 90Yttrium (90Y) - Microspheres are imported...
from either Australia or Canada. Its 64.1 h half life and high tissue penetration range (maximum range of 12 mm) of pure beta-emissions \(E_{\beta\max}=2.28 \text{MeV}\) allows uniform dose distribution delivering critical dose rate with lower long-term adverse effects. The exorbitant cost of the imported FDA approved ⁹⁰Yttrium- microspheres (SIR-spheres and Theraspheres) has been the foremost deterrent to the widespread use of TARE clinically especially in developing countries. This has lead nuclear medicine physicians in India to explore and adopt cheaper alternate isotopes such as ¹⁸⁸ReRhenium (Re) labeled lipiodol or ¹³¹Iodine (I) labeled lipiodol for TARE, notwithstanding each radiotracer having its own advantages and limitations. The above two radiotracers need lipiodol as a carrier for the radioactivity. ¹⁸⁸Re based molecules have been studied and shown to be effective [12-17]. However the lack of phase III randomized controlled trials has precluded ¹⁸⁸Re-lipiodol for clinical use [16,17]. Another limitation is related to the low labeling yields and current shortage in the supply of ¹⁸⁸Re generators. On the other hand ¹³¹I- lipiodol is highly radioactive and requires patients to be hospitalized in the therapy isolation ward for few days until the radiation exposure falls to permissible levels. ¹³¹I is a beta-emitting radionuclide with mean beta particle energy of 0.192 MeV and possesses a high energy gamma emission of 364 keV and has a long half-life of 8.02 days. Handling of high activities of ²⁰¹Thorium (Thorium) can also lead to a high radiation burden to the staff during the procedure. Therefore, though a cheaper option, radiation safety concerns remains a limitation. The available studies on TARE with ¹³¹I-Lipiodol are limited, on smaller sample size, predominantly in metastatic liver disease but also in HCC [18-21]. ¹⁷⁷Lutetium Microspheres compared with ⁹⁰Y has the advantage of possessing γ emission (81 keV) suitable for SPECT imaging and is highly paramagnetic enabling MRI imaging and quantification. It has a 26.8 h half-life, resulting in a high dose-rate [22,23].

TARE began as a treatment for advanced HCC in a palliative setting, with undoubtable benefit of being the only option apart from sorafenib, to treat tumor-related portal vein thrombosis (PVT). Several retrospective and large cohort studies showed an acceptable safety profile of TARE, effective for local control of the disease and long-term survival in patients with unresectable HCC limited to the liver in the intermediate and advanced stages [24-28]. In two phase III randomized control trials (RCT) i.e. SIReNIB and SARAH comparing ⁹⁰Y-resin microspheres TARE and sorafenib in patients with locally advanced HCC, no significant differences in the overall survival was demonstrated in the treated population (11.3 and 10.4 months in the TARE and sorafenib arms respectively, P=0.27 in SIReNIB and 8 months versus 9.9 months with P=0.18 in SARAH) nor in subgroup analyses. However, the tumor response rates (TRR) was significantly higher in the TARE arm and no differences in progression-free survival were observed. Fewer patients in the TARE group had serious adverse events (20.8%) than in the sorafenib group (35.2%) [29,30]. These trials were however pivotal since they were the first RCTs confirming the safety and efficacy of TARE in patients with locally advanced HCCs, is better tolerated than sorafenib and a clear superiority of TARE in inducing tumor response compared to sorafenib was confirmed [31].

Recent Trends in Clinical Practice

Over the years, TARE has evolved as a distinctive treatment option to treat early to intermediate stage disease with a curative intent, as a neoadjuvant treatment prior to resection and as a bridge to transplant or to downstage disease for liver transplantation.

TARE has shown a key advantage in the setting of bridge to transplant in the existing United Network for Organ Sharing (UNOS) implemented waiting periods for liver transplant. A comparative data analysis and two other case series comparing TARE and TACE have shown that downstaging from UNOS T3 to T2 disease was achieved in 31% of TACE and 58% of ⁹⁰Y-TARE patients. In this particular analysis TARE was also found beneficial in terms of survival. These results have confirmed the potential of TARE to downstage HCC patients to become eligible for transplants and other treatments such as resection and ablation [32,33].

A systematic review in 2016 and meta-analysis of 5 studies with unresectable HCC who underwent TACE or ⁹⁰Y TARE showed no significant survival differences between the groups with similar partial and complete response rates [34-36]. In the phase II PREMIERE trial in 2016, comparing the time to progression (TTP) in 45 BCLC A and B patients randomized to TACE or ⁹⁰Y TARE showed a significantly longer median TTP in the TARE group as compared to TACE (26 months vs. 6.8 months, P value =0.001). The study however did not demonstrate any survival benefit suggesting that local control is insufficient for survival improvement in cirrhotic patients with competing risks of death. It was however inferred that the prolonged TTP and improved local control following TARE could decrease transplant list drop-out and lead to improved quality of life [37,38]. In this and few other studies, TARE has been shown to effectively prevent tumor progression during the usual 6- to 1-year waiting period for an appropriate donor liver. TARE has also been show to downstage the disease in HCC patients who do not meet the Milan criteria to the point of meeting these criteria. In the setting of liver resection (LR) in advanced HCC not meeting the criteria for radical resection, TARE with ⁹⁰Y can serve as a safe bridge to LR by treating tumors and promoting hypertrophy of the future liver remnant.

In recent years, the concept of radiation segmentectomy by super selective radioembolization of a calculated lobar dose into a segmental vessel to ablate an entire vascular territory has gained importance in the setting of bridge to transplant/liver resection. This is largely for treatment of patients with small lesions confined to ≤2 liver segments who may not be suitable for tumor resection or ablation or in those where ablation is not feasible given the tumor size or the proximity to adjacent structures such as the biliary tree or vasculature. The promising results of the above approach is due to the ability to escalate doses >200 Gy via infusion of a calculated dose into a segmental tumor feeding vessel resulting in tumor ablation while minimizing radiation to the normal liver parenchyma. These promising results have shown higher objective tumor response rates with longer time to disease progression (median TTP - 33.1 months) and median OS as 6.7 years, with 5-year overall survival probability of 75% which appears to be comparable with the 5-year survival for patients undergoing other curative treatment options. In about a third of patients who underwent transplant following radiation segmentectomy, the tumors revealed 90% to 100% pathological necrosis in all patients with improved necrosis when the dose exceeded 190 Gy. The outcomes for radiation segmentectomy compared to segmental TACE showed overall higher response rates for radiation segmentectomy (84% vs. 58%) with higher median PFS (564 vs. 271 days) and local control rates (92% vs. 70%). However, the OS rates were not different between the two groups. Results have demonstrated long TTP and long-term overall survival (OS) rates for patients with limited tumor burden and preserved hepatic function [39-43].
The other approach is that of radiation lobectomy which leads to volumetric decreases of the treated lobe of liver by inducing both tumor control and liver parenchymal atrophy. In a neoadjuvant setting, this approach can serve as a bridge to hepatic resection for select patients with inadequate future liver remnant (FLR) by inducing hypertrophy of contralateral lobe along with local tumor control. While it is similar to the traditional portal vein embolization which redirects blood flow from the fibrotic radiation-treated hepatic lobe to subsequent FLR hypertrophy for facilitating surgical resection, with comparable 5-year survival rates. There is the additional benefit of concomitant tumor control during the time interval to hypertrophy that is not seen following portal vein embolization. Though a promising approach, further studies are needed to compare long term outcomes of portal vein embolization and radiation lobectomy [44-48]. Therefore in recent years, TARE techniques leading to radiation segmentectomy and lobectomy have gained importance in the clinical setting to treat HCC’s with a curative intent.

**TARE in Tumors other than HCC**

Though a vast amount of data on TARE is available in the treatment of metastatic liver disease, commonly in colorectal liver metastases (CRLM) with predominant hepatic disease, it is still underutilized by the medical oncologists in our country considering the amount of approved molecular targeted therapies that are currently available lead by a plethora of drug trials. Monoclonal antibodies directing epidermal growth factor receptors (EGFR) and vascular endothelial growth factor (VEGF) are main biologic agents currently used in the treatment of metastatic colorectal cancer (CRC), which combined with conventional chemotherapeutic agents, is the standard therapy for patients with metastatic CRC. Development of resistance to these target agents are however a limitation in clinical practice.

As per the 2016 ESMO clinical guidelines, TARE as a locoregional therapy is positioned as a third-line option in patients with liver dominant disease following first and second lines of chemotherapy or in combination with chemotherapy as a salvage setting [49]. The role of TARE in this setting is with the belief that local tumor control will translate into overall survival. Few prospective and large retrospective studies demonstrate consistent results with TARE worldwide with median overall survival in patients with chemotherapy-insensitive CRC metastases of approximately 9 to 12 months in the most recent results with objective response rates between 24% to 41% [50-53].

The efficacy of TARE as first-line therapy has been studied in 3 large multicentric randomized control trials (SIRFLOX Study followed by the FOXFIRE and FOXFIRE Global) when added to first-line chemotherapy for the treatment of metastatic CRC [54,55]. Though a promising result was expected from the combined data from these studies, they actually were rather disappointing. Despite an improved response within the liver and liver PFS, there was no difference in the OS. Further sub-analysis showed that for right-sided primary tumors, which had a poorer prognosis, there was a 4.9-month improvement in OS for those treated with systemic chemotherapy plus TARE compared with those treated with systemic therapy alone, whereas for left-side primary there was no difference.

These studies however had shortcomings including a shifting design of the trial and other confounding factors. But despite these, a substantial benefit was seen for PFS in the liver, and this increase was statistically highly significant (median liver-specific PFS in the arm that received TARE plus chemotherapy was 20.5 months compared with 12.6 months in the control arm who received chemotherapy alone with HR, 0.69; 95% CI, 0.55-0.90; P=0.002). In summary, when added to FOLFOX chemotherapy with or without Bevacizumab in the recently conducted large randomized control trials (SIRFLOX, FOXFIRE and FOXFIRE Global), 

\[ ^{90} \text{Y} \text{TARE} \] significantly improved the radiological response and liver-specific PFS with no change in PFS at any site. The biggest message however from these studies was the safety of the procedure and alleviation of concern that TARE would damage the liver and hamper chemotherapy. Moreover, development of new lung or bone metastasis was a failure of the endpoint, indicating it was perhaps because of progression of extrhepatic disease and that it was indeed a failure of the systemic chemotherapy [54,55]. Based on the above data, TARE is therefore currently not recommended as first-line therapy for patients with non-resectable CRLM, although when added earlier, the chances of liver toxicity that may be compounded due to further chemotherapies may be reduced.

The phase III EPOCH randomized control trial is currently underway using Therasphere 

\[ ^{90} \text{Y} \text {Glass Microspheres} \] that may contribute toward the establishment of the role of TARE combined with oxaliplatin or irinotecan-based chemotherapy in the second-line treatment of metastatic CRC of the liver versus chemotherapy alone [56].

TARE is frequently also used to treat neuroendocrine (NET) liver metastatic disease and intrahepatic cholangiocarcinoma. NET’s are well arterialized tumors and thus suitable for transarterial therapies similarly to HCC, with the predominant goal of treatment being control of symptoms. Surgical resection is preferred if greater than 90% of the disease can be safely removed. However, only 5% to 15% of patients with liver metastases are surgical candidates and nearly 50% recur after resection [57,58]. Somatostatin analogues (SSAs) are usually recognized as the first line of therapy in advanced GEP-NEt’s due to their favorable safety profile and established benefit on PFS [59]. There are no randomized control trials of TARE in this setting. A number of retrospective as well as few prospective studies have demonstrated efficacy and safety of TARE in metastatic NET’s. The largest retrospective study so far including 148 patients from ten institutions in a salvage setting of metastatic NET reported encouraging results of extremely high response rates (any response in 95.1% of patients and progressive disease in only 4.9% of the patients) and median OS of 70 MO after initial TARE [60]. Treatment related toxicity was very low, with no radiation-induced liver disease (RILD) seen even in the 33 patients receiving retreatment of the same liver lobe(s). Both systemic and locoregional therapies including radiolabeled somatostatin receptor analogues (PRRT) are now available in the setting of disease progression after SSAs. However, considering the often long life expectancy of patients with GEP-NEt, the optimal timing of treatments is crucial. Locoregional therapies may be considered in patients with metastatic disease limited to the liver or in case of evidence of disease progression limited to the liver wherein they are recognized to be very effective in symptom control [61]. Considering the lack of randomized and controlled trials comparing locoregional treatments of liver metastatic NET patients, clinical judgment remain key to set the most appropriate therapeutic pathway. Prospective data may ultimately lead to a more personalized and optimized treatment.

In our experience, the result of TARE in metastatic liver NET’s has been variable, which may be accounted for the variable biology of NET. Pancreatic NET’s are known to have markedly poor...
prognosis when compared to non pancreatic NETs. TARE with 90Y-microspheres is safe with high response rates, even with extensive tumor burden of the liver.

There are also reports suggesting combined PRRT and locoregional therapies when extrahepatic NET metastases are present. The concerns are related to the possible added toxicity to the liver from excessive radiation, but in a cohort of 20 patients, sequential treatment with TARE and PRRT was found to be safe [62]. As per published reports, TARE in progressive NET liver metastasis after initial PRRT resulted in a disease control rate of 91% at 3 months according to RECIST 1.1, clinical response in 65% of symptomatic patients and a long median OS of 3.4 years (41 months). Intrahepatic tumor load >75%, and the presence of extrahepatic disease prior to treatment were negative prognostic markers for OS. Occurrence of radiation induced liver disease after treatment was limited (5%) [63].

Intrahepatic cholangiocarcinoma (ICC) currently represents the second most common primary hepatic cancer with a dismal prognosis, even for patients undergoing surgery with 5-year overall survival rate being less than 5% [64]. The treatment options for advanced and inoperable ICC are limited, with cisplatin and gemcitabine being an established effective first-line systemic treatment [65]. Numerous studies have demonstrated that TARE can be used effectively in carefully selected patients with ICC, and are safe and shows similar response rates as TACE even though higher rates of partial and stable response have been reported with TARE. Few prospective studies in a small group of unresectable ICC patients using both the glass beads and resin microspheres refractory to chemotherapy have shown median overall survival ranging between 9.3 to 16.3 months (66 to 70). The largest prospective study showed median overall survival of 14.3 months in solitary lesion and 6.1 months in infiltrative lesion. Median overall survival for intra arterial therapies was 13 months, which is higher than median overall survival of 11 months for systemic chemotherapy [68]. A systematic review by Al-Adra et al. in a total of twelve studies (n=5 retrospective; n=7 prospective) including 298 patients summarizes current clinical evidence available for the efficacy and toxicity of 90Y TARE. The primary outcomes i.e. overall weighted medial survival and radiological response was 15.5 months (7 to 22.2 months) and 28% partial response and 54% stable disease rates [71]. There are also data now supporting the use of TARE for downstaging unresectable ICC to allow for secondary resection, an indication previously validated for patients with HCC [72].

As surgery remains the only curative therapy for ICC, a retrospective trial including 45 patients with unresectable ICC who received 90Y TARE (Therasphere) combined with systemic chemotherapy were compared to a total of 54 patients who underwent primary resection. No grade III/IV complications were observed in any patients. The tumors showed significant volume reduction (295 (range, 90 to 1,250) vs. 168 (range, 46 to 535) mL; P=0.02) during the median follow-up of 15.6 months (range, 4 to 40.7 months), and became resectable in seven patients. Six of these patients (85.7%) survived the postoperative period and one (14.3%) died 6.5 months after surgery with a median overall recurrence-free survival of 19.1 months [72].

**Dosimetric Considerations**

The standard methods of dosimetric calculations have been based on Body Surface Area (BSA model) as specified by commercial vendors for SIR-Spheres resin microspheres and the Medical Internal Radiation Dose (MIRD) model for glass microspheres (Therasphere). Both models are suboptimal; BSA model takes into account the theoretical normal liver volume relative to BSA with increase in activity for increasing tumor burden. It does not take into account the actual activity or its distribution into the liver and tumor and generally results in lower overall amount of calculated activity for the tumor lesions. The larger number of particles however results in more uniform distribution of the radioactivity within the liver and the tumor. Despite its limitation, the BSA method has been effectively utilized for resin microspheres in several randomized controlled trials [74]. On the other hand, MIRD method is utilized primarily for glass microspheres with a recommended dose between 80 GY to 150 GY to the liver which takes into account the liver mass and may result in potentially high doses of radioactivity within the tumor [74].

Recent trends in the dosimetric estimations for TARE are moving from the above vendor recommended standard methods towards partition model which takes into account the compartmentalization and preferential uptake of particles into the hepatic arterial supply. The partition model is therefore more accurate and personalized model based on the Tumor-to-Normal liver (T/N) uptake ratio on the pretreatment 99mTc-MAA (macroaggregates of albumin) scans incorporating the tumor volume, liver volume, lung shunt fraction and tumor to normal liver ratio uptake and vascular anatomy. The only caveat to this method is that the calculation is laborious and the model assumes a more uniform and homogenous distribution of injected activity in all compartments i.e. the tumor, normal liver and lungs, which generally is not the case [75,76].

Several dose calculation software systems are available that allows for automated volume segmentation, measurement of hepatic volumes and tumor volumes, calculation of lung shunt fraction, pre and post-implantation dose calculation, dosimetry comparison, voxel-based dosimetry and measurement of treatment response. With the help of these treatment planning software systems, it is possible to measure the pretreatment distribution of Y-90 radiomicrospheres in different compartments, corresponding doses to different structures and post-implantation dosimetry to evaluate the actual dose delivered to different tumors and normal liver tissue [77,78]. The intent of dosimetry is to target and optimize the deposition of radioactivity to the tumor while minimizing the amount of radiation dose to the native liver parenchyma. When radiation segmentectomy is intended, complete ablation and necrosis of the entire vascular territory is desired, and a higher radiation dose is planned to the target region in the liver that is not limited by optimal dose to the tumor.

In 2013, Garin et al. [79] showed that dose intensification with tumor dose >205 GY of glass Y-90 microspheres lead to better outcomes for HCC with macrovascular invasion using 99mTc-MAA SPECT/CT based personalized dosimetry with improved Overall Survival (OS). The investigators evaluated the impact of the above dosimetry in predicting treatment response, toxicity and survival in 71 patients with inoperable HCC treated with glass microsphere radioembolization and demonstrated median tumor doses of 342 Gy and 191 Gy for responding and non-responding lesions respectively. The TTP and median OS were 5.5 months and 11.5 months respectively, in patients with a tumor dose <205 GY and 13.0 and 23.2 months respectively in patients who received tumor dose >205 GY [79]. Based on this dosimetry, select patients including those with large lesions or PVT were able to undergo treatment intensification resulting in good clinical outcomes and without added toxicity.
Conclusion

TARE is an excellent locoregional treatment for patients with advanced liver malignancies. While some guidelines like EASL does not recommend its use, others such as ESMO recognizes the same in the therapeutic armamentarium. The negative phase III trials and the limited prospective data are the major reasons for the negative view on TARE, although the limitations of the above trials are well recognized. Despite this, TARE has been recognized as an established treatment in clinical practice and is the only choice in BCLC – B disease with macrovascular invasion that offers patients with improved quality of life can stabilize or prolong tumor progression to improve overall outcomes. What began as a palliative treatment for patients with unresectable liver malignancies has evolved over the years as a curative treatment option as a neoadjuvant treatment prior to resection, as bridge or downstaging disease for liver transplantation. Radiation segmentectomy in early stage disease and radiation lobectomy are gaining importance allowing patients to be amenable to curative resections. It has also been recognized that higher radiation doses improve clinical outcomes. Personalized dosimetry is now possible for dose intensification and single-session treatment and continued personalization of tumor therapy will be continued in our clinical practice.

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