Clinics in Oncology

Review Article
Published: 11 Jun, 2021

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

Sumati Sundaraiya[1] and Rajasekhar Perumalla[2]*

[1]Department of Nuclear Medicine, Apollo Proton Cancer Centre Chennai, India

[2]Department of Hepatobiliary and Transplant Surgery, Fortis Hospital, India

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, 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 ^{90}Yttrium (^{90}Y) - Microspheres are imported

OPEN ACCESS

Correspondence:
Sumati Sundaraiya, Department of Nuclear Medicine, Apollo Proton Cancer Centre, Chennai, Tamilnadu, India, Tel: +91-9445006784;
E-mail: s_sumati@yahoo.com

Received Date: *11 May 2021*
Accepted Date: *04 Jun 2021*
Published Date: *11 Jun 2021*

Citation:
Sundaraiya S, Perumalla R. Current Status of TARE (Trans Arterial Radioembolization) in Clinical Practice – A Review. Clin Oncol. 2021; 6: 1823.
ISSN: 2474-1663

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 MeV] allows uniform dose distribution delivering critical dose rate with lower long-term adverse effects. The exorbitant cost of the imported FDA approved ^{90}Yttrium- 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 ^{188}Rhenium (Re) labeled lipiodol or ^{131}Iodine (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. ^{188}Re based molecules have been studied and shown to be effective [12-17]. However the lack of phase III randomized controlled trials has precluded ^{188}Re-lipiodol for clinical use [16,17]. Another limitation is related to the low labeling yields and current shortage in the supply of ^{188}Re generators. On the other hand ^{131}I- 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. ^{131}I 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 beta-emitting ^{131}I-lipiodal 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 ^{131}I-Lipiodol are limited, on smaller sample size, predominantly in metastatic liver disease but also in HCC [18-21]. ^{166}Holmium Microspheres compared with ^{90}Y 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 undoubtful 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. SIRveNIB and SARAH comparing ^{90}Y-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 SIRveNIB 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 effects (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 ^{90}Y-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 ^{90}Y 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 ^{90}Y 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 ^{90}Y 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

T h ough 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 primaries 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 Bevazicumab in the recently conducted large randomized control trials (SIRFLOX, FOXFIRE and FOXFIRE Global), ^{90}Y 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 extrahepatic 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}Y 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-NENs 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 NETs. 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-NEN, 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 NEN 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 ^{90}Y-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, are safe and shows almost 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 ^{90}Y 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 ^{90}Y TARE (Theraspheres) 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 ^{99m}Tc-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 ^{99m}Tc-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.

References

1. Kumar A, Acharyay SK, Singhz SP, Saraswat VA, Arora A, Dusejak A, et al. The Indian National Association for Study of the Liver (INASL) consensus on prevention, diagnosis and management of hepatocellular carcinoma in India: The Puri recommendations. J Clin Exp Hepatol. 2014;4(Suppl 3):S3-S26.
2. Herbst DA, Reddy KR. Risk factors for hepatocellular carcinoma. Clin Liver Dis. 2012;1(6):180-2.
3. Nayak NC. Hepatocellular carcinoma--a model of human cancer: Clinico-pathological features, etiology and pathogenesis. Indian J Pathol Microbiol. 2003;46(1):1-16.
4. Yang WS, Va P, Bray F, Shan Gao, Jing Gao, Hong-Lan Li, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: A meta-analysis of prospective cohort studies. PLoS One. 2011;6(12):e27326.
5. Wang C, Wang X, Gong G, Weili Qiu, Yi Chen, Guoping Li, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: A systematic review and meta-analysis of cohort studies. Int J Cancer. 2012;130(7):1639-48.
6. Duseja A, Sharma B, Kumar A, Kapil S, Das A, Dhiman RK, et al. Nonalcoholic fatty liver in a developing country is responsible for significant liver disease. Hepatology. 2010;52(6):2248-9.
7. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine (Baltimore). 2017;96(9):e5904.
8. De Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol. 2012;56(Suppl 1):S75-87.
9. Kumar R, Saraswat MK, Sharma BC, Sakhuja P, Sarin SK. Characteristics of hepatocellular carcinoma in India: A retrospective analysis of 191 cases. QJM. 2008;101(6):479-485.
10. Paul SB, Chalamalasetty SB, Vishnubhatla S, Madan K, Gamanagatti SR, Batra Y, et al. Clinical profile, etiology and therapeutic outcome in 324 hepatocellular carcinoma patients at a tertiary care center in India. Oncology. 2009;77(3-4):162-71.
11. Silva JP, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, et al. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: A systematic review and meta-analysis. HPB (Oxford). 2017;19(8):659-66.
12. Lepareur N, Lacceuille F, Bouvry C, Hindre F, Garcion E, Cherel M, et al. Rhenium-188 labeled radiopharmaceuticals: Current clinical applications in oncology and promising perspectives. Front Med (Lausanne). 2019;6:132.
13. Lambert B, Bacher K, De Keukeleire K, Smeets P, Colle I, Jeong JM, et al. 188Re-HDD/Lipiodol for treatment of hepatocellular carcinoma: A feasibility study in patients with advanced cirrhosis. J Nucl Med. 2005;46(8):1326-32.
14. Sundram F, Chau TCM, Onkhuudai P, Bernal P, Padhy AK. Preliminary results of transarterial rhenium-188 HDD Lipiodol in the treatment of inoperable primary hepatocellular carcinoma. Eur J Nucl Med Mol Imaging. 2004;31(2):250-7.
15. Kumar A, Bal C, Srivastava DN, Acharya SK, Thulkar SP, Sharma S, et al. Transarterial radionuclide therapy with Re-188-HDD-lipiodol in case of unresectable hepatocellular carcinoma with extensive portal vein thrombosis. Eur J Radiology Extra. 2005;56(2):55-9.
16. Bernal P, Raoul JL, Vidmar G, Sereegotov E, Sundram FX, Kumar A, et al. Intra-arterial Rhenium-188 Lipiodol in the treatment of inoperable hepatocellular carcinoma: Results of an IAEA-sponsored multination study. Int J Radiat Oncol Biol Phys. 2007;69(5):1448-55.
17. Padhy AK, Dondi M. A report on the implementation aspects of the International Atomic Energy Agency's first doctoral coordinated research project, "Management of liver cancer using radionuclide methods with special emphasis on trans-arterial radio-conjugate therapy and internal dosimetry. Semin Nucl Med. 2008;38(2):S5-12.
18. Mulcahy MF, Lewandowski RJ, Ibrahim SM, Sato KT, Ryu RK, Atassi B, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer. 2009;115(9):1849-58.
19. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103(3):324-31.
20. Murthy R, Xiong H, Nunez R, Cohen AC, Barron B, Szklaruk J, et al. Yttrium-90 resin microspheres for the treatment of unresectable colorectal hepatic metastases after failure of multiple chemotherapy regimens: Preliminary results. J Vasc Interv Radiol. 2005;16(7):937-45.
21. Bhargavi V, Subbana I, Kallur KG, Patel A, Swamy S, Patil S. Transarterial radioembolization with Iodine-131-Lipiodol for hepatic metastases from gastrointestinal malignancies – Experience in tertiary care oncology center in India. South Asian J Cancer. 2019;8(1):31-4.
22. Seevinck PR, Van De Maat GH, De Wit DC, Vente MAD, Nijsen JFW, Bakker CJG. Magnetic resonance imaging-based radiation-absorbed dose estimation of166Ho microspheres in liver radioembolization. Int J Radiat Oncol Biol Phys. 2012;83(3):e437-44.
23. Van De Maat GH, Seevinck PR, Bos C, Bakker CJG. Quantification of holmium-166 loaded microspheres: Estimating high local concentrations using a conventional multiple gradient echo sequence with S 0-fitting. J Magn Reson Imaging. 2012;35(6):1453-61.
24. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: A European evaluation. Hepatology. 2011;54(3):868-78.
25. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: A comprehensive report of long-term outcomes. Gastroenterology. 2010;138(1):52-64.
26. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al.

Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: A phase 2 study. Hepatology. 2013;57(5):1826-37.

27. Cho YY, Lee M, Kim HC, Chung JW, Kim YH, Gwak GY, et al. Radioembolization is a safe and effective treatment for hepatocellular carcinoma with portal vein thrombosis: A propensity score analysis. PLoS One. 2016;11(5):e0154986.

28. Jia Z, Jiang G, Tian F, Zhu C, Qin X. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Saudi J Gastroenterol. 2016;22(5):353-59.

29. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective internal radiation therapy versus Sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol. 2018;36(19):1913-21.

30. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624-36.

31. Sposito C, Mazzaferro V. The SIRveNIB and SARAH trials, radioembolization *vs.* sorafenib in advanced HCC patients: Reasons for a failure, and perspectives for the future. Hepatobiliary Surg Nutr. 2018;7:487-9.

32. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: Chemoembolization versus radioembolization. Am J Transplant. 2009;9(8):1920-8.

33. Abdelfattah MR, Al-Sebayel M, Broering D, Alsuhaibani H. Radioembolization using yttrium-90 microspheres as bridging and downstaging treatment for unresectable hepatocellular carcinoma before liver transplantation: Initial single-center experience. Transplant Proc. 2015;47(2):408-11.

34. Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, Sharma R, et al. Unresectable hepatocellular carcinoma: Radioembolization *vs.* Chemoembolization: A systematic review and meta-analysis. Cardiovasc Interv Radiol. 2016;39(11):1580-88.

35. Ni JY, Xu LF, Wang WD, Sun HL, Chen YT. Conventional transarterial chemoembolization *vs.* microsphere embolization in hepatocellular carcinoma: A meta-analysis. World J Gastroenterol. 2014;20(45):17206-17.

36. Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis. Biosci Trends. 2015;9(5):289-98.

37. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151(6):1155-63.e2.

38. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol. 2013;11(10):1358-65.e1.

39. Riaz A, Gates VL, Atassi B, Lewandowski RJ, Mulcahy MF, Ryu RK, et al. Radiation segmentectomy: A novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys. 2011;79(1):163-71.

40. Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014;60(1):192-201.

41. Lewandowski RJ, Gabr A, Abouchalh N, Ali R, Al Asadi A, Mora RA, et al. Radiation segmentectomy: Potential curative therapy for early hepatocellular carcinoma. Radiology. 2018;287(3):1050-58.

42. Padia SA, Johnson GE, Horton KJ, Ingraham CR, Kogut MJ, Kwan S, et al. Segmental Yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: Results of a single-center, retrospective, propensity score–matched study. J Vasc Interv Radiol. 2017;28(6):777-85.e1.

43. Biederman DM, Titano JJ, Korff RA, Fischman AM, Patel RS, Nowakowski FS, et al. Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. J Vasc Interv Radiol. 2018;29(1):30-7.e2.

44. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: Evolution of a new standard of care. J. Vasc Interv Radiol. 2005;16:779-90.

45. Gaba RC, Lewandowski RJ, Kulik LM, Riaz A, Ibrahim SM, Mulcahy MF, et al. Radiation lobectomy: Preliminary findings of hepatic volumetric response to lobar Yttrium-90 radioembolization. Ann Surg Oncol. 2009;16(6):1587-96.

46. Roxburgh P, Evans TRJ. Systemic therapy of hepatocellular carcinoma: Are we making progress? Adv Ther. 2008;25(11):1089-1104.

47. Vouche M, Lewandowski RJ, Atassi R, Memon K, Gates VL, Ryu RK, et al. Radiation lobectomy: Time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013;59(5):1029-36.

48. Kudo M. Early detection and curative treatment of early-stage hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2005;3(10 Suppl 2):S144-8.

49. Vogel A, Cervantes A, Chau I, Daniele B, Llovet, J, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv238-iv255.

50. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103(3):324-31.

51. Saxena A, Bester L, Shan L, Perera M, Gibbs P, Meteling B, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol. 2014;140(4):537-47.

52. Kennedy AS, Ball D, Cohen SJ, Cohn M, Coldwell DM, Drooz A, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. J Gastrointest Oncol. 2015;6(2):134-42.

53. Pennington B, Akehurst R, Wasan H, Sangro B, Kennedy AS, Sennfält K, et al. Cost-effectiveness of selective internal radiation therapy using yttrium-90 resin microspheres in treating patients with inoperable colorectal liver metastases in the UK. J Med Econ. 2015;18:797-804.

54. Van Hazel GA, Heinemann V, Sharma NK. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) *vs.* mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(15):1723-31.

55. Virdee PS, Moschandreas J, Gebski V, Love SB, Francis EA, Wasan HS, et al. Protocol for combined analysis of FOXFIRE, SIRFLOX, and FOXFIREGlobal randomized phase III trials of chemotherapy +/- selective internal radiation therapy as first-line treatment for patients with metastatic colorectal cancer. JMIR Res Protoc. 2017;6(3):e43.

56. Chauhan N, Mulcahy MF, Salem R, Al B Benson III, Boucher E, Bukovcan J, et al. TheraSphere Yttrium-90 glass microspheres combined with chemotherapy versus chemotherapy alone in second-line treatment of patients with metastatic colorectal carcinoma of the liver: Protocol for the EPOCH phase 3 randomized clinical trial. JMIR Res Protoc.

2019;8(1):e11545.

57. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery. 1990;108(6):1091-6.

58. Elias D, Lasser P, Ducreux M, Duvillard P, Ouellet JF, Dromain C, et al. Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: A 15-year single center prospective study. Surgery. 2003;133(4):375-82.

59. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-63.

60. Kennedy AS, Dezarn WA, McNeillie P, Coldwell D, Nutting C, Carter D, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: Early results in 148 patients. Am J Clin Oncol. 2008;31(3):271-9.

61. Memon K, Lewandowski RJ, Riaz A, Salem R. Chemoembolization and radioembolization for metastatic disease to the liver: Available data and future studies. Curr Treat Options Oncol. 2012;13(3):403-15.

62. Geisler J, Auernhammer C, Zech C, Bartenstein P, Hacker M, Haug A. Toxicity of sequential treatment with radioembolization and PRRT in hepatic metastasized neuroendocrine tumors. J Nucl Med. 2012;53(Suppl 1):1189.

63. Braat AJAT, Ahmadzadehfar H, Kappadath SC, Stothers CL, Frilling A, Deroose CM, et al. Radioembolization with 90Y resin microspheres of neuroendocrine liver metastases after initial peptide receptor radionuclide therapy. Cardiovasc Intervent Radiol. 2020;43(2):246-253.

64. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet. 2005;366(9493):1303-14.

65. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: A meta-analysis of two randomised trials. Ann Oncol. 2014;25(2):391-8.

66. Ibrahim SM, Mulcahy MF, Lewandowski RJ, Sato KT, Ryu RK, Masterson EJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: Results from a pilot study. Cancer. 2008;113:2119-28.

67. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: A preliminary assessment of this novel treatment option. Ann Surg Oncol. 2010;17(2):484-91.

68. Rafi S, Piduru SM, El-Rayes B, Kauh JS, Kooby DA, Sarmiento JM. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: Survival, efficacy, and safety study. Cardiovasc Intervent Radiol. 2013;36(2):440-8.

69. Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS, et al. Modified response evaluation criteria in solid tumors and European Association for the Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. J Vasc Interv Radiol. 2014;25(2):256-65.

70. Mouli S, Memon K, Baker T. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: Safety, response, and survival analysis. J Vasc Interv Radiol. 2013;24(8):1227-34.

71. Al-Adra DP, Gill RS, Axford SJ, Shi X, Kneteman N, Liau SS, et al. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis. Eur J Surg Oncol. 2015;41(1):120-7.

72. Rayar M, Sulpice L, Edeline J, Garin E, Sandri GBL, Meunier B, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. Ann Surg Oncol. 2015;22(99):3102-8.

73. Lau WY, Kennedy AS, Kim YH, Lai HK, Lee RC, Leung TWT, et al. Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres. Int J Radiat Oncol Biol Phys. 2012;82:401-7.

74. Liu DM, Westcott M, Garcia-Monaco R, Abraham R, Gandhi R. Down and dirty with dosimetry - A practical understanding and approach to radioembolization. Endovascular today. 2016;15:70-76.

75. Gnesin S, Canetti L, Adib S, Cherbuin N, Monteiro MS, Bize P, et al. Partition model-based 99mTc-MAA SPECT/CT predictive dosimetry compared with 90Y TOF PET/CT post treatment dosimetry in radioembolization of hepatocellular carcinoma: A quantitative agreement comparison. J Nucl Med. 2016;57:1672-78.

76. Kim SP, Cohalan C, Kopek N, Enger SA. A guide to ^{90}Y radioembolisation and its dosimetry. Phys Med. 2019;68:132-45.

77. Abraham R, Lewandowski, Gandhi RT, Liu DM. What's New in Y-90? Technical and procedural innovations in Y-90 radioembolization including existing and investigational next-generation technologies. Endovascular today. 2019;18:49-60.

78. Morán V, Prieto E, Sancho L, Rodríguez-Fraile M, Soria L, Zubiria A, et al. Impact of the dosimetry approach on the resulting ^{90}Y radioembolization planned absorbed doses based on ^{99m}Tc-MAA SPECT-CT: is there agreement between dosimetry methods? EJNMMI Phys. 2020;7;72.

79. Garin E, Lenoir L, Rolland Y, Edeline J, Mesbah H, Laffont S, et al. Dosimetry based on 99mTc-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with 90Y-loaded glass microspheres: preliminary results. J Nucl Med. 2012;53(2):255-63.