Review Article Therapy.

Radio embolization for Hepatocellular Carcinoma.

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ABSTRACT:

Liver cancers are the fourth most common cause of cancer-related deaths. Based on annual projections, the World Health Organization estimates that in 2023 more than 1 million patients will die from liver cancer. In the United States, the proportion of deaths owing to liver cancer increased by 43%, from 7.2 to 10.3 deaths per 100,000, between 2000 and 2016, with a 5-year survival rate of 18%. Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Only 20–30% of HCC patients are diagnosed at an early stage and more than 70% of patients are diagnosed with non resectable disease and have poor overall prognosis [1,2].

HCC has many causes, including hepatitis B virus, hepatitis C virus, excessive alcohol consumption, obesity, diabetes, and exposure to aflatoxins. The prevalence of these causes and their contribution to the course of disease can be influenced by additional factors such as geographic region, ethnicity, race, and age. The prognosis for HCC is poor, with an overall 5-year survival from diagnosis of less than 20%. Without treatment, patients with advanced HCC usually survive less than 6 months [3,4,5,6].

Treatment options for patients with HCC depend on the presence or extent of underlying liver disease, the stage at which HCC is diagnosed, and tumour characteristics. Patients with early-stage HCC may be treated with potentially curative surgical treatments such as resection, ablation, and liver transplantation. For non resectable intermediate-stage HCC trans-arterial chemoembolization (TACE) is generally the treatment of choice. However, FDA has approved **Sorafenib**, an angiogenesis inhibitor as a systemic therapy for non resectable HCC. **Sorafenib** provides a survival benefit for patients with advanced HCC and patients with non resectable intermediate HCC who are ineligible for TACE or who show progression despite loco regional therapies. **Regorafenib**, another systemic multi kinase inhibitor drug has been approved for patients with HCC previously treated with **Sorafenib**. However, the efficacy of **sorafenib** and **regorafenib** are still limited, with median overall survival (OS) of less than 11

months, and are associated with substantial adverse effects [7,8,9,10,11,12,13].

Radio embolization is another treatment option for treatment of non resectable hepatocellular carcinoma. Radio embolization defines procedures in which intra-arterially injected radioactive microspheres are used for internal radiation purposes. It is called selective internal radiation therapy or SIRT and is a form of brachytherapy for liver tumours in which the source of radiation has to access the network of tumour neo vessels after being injected into the hepatic arteries. It has to be emphasized that both the beneficial and deleterious effects of radio embolization originate from the radiation delivered by the isotope and the not well-understood effects of micro embolization, but not by ischemia due to vessel occlusion. Since there is no significant vessel occlusion thus this treatment is suitable for patients with portal vein thrombosis (PVT), which is a contraindication to TACE. Once delivered, the microspheres largely remain in the tumour, where radiation is delivered within a limited range, and sparing normal surrounding liver tissue from damage. The volume of irradiated liver tissue depends on the artery or arteries in which microspheres are injected. Radio embolization differs substantially from TACE. In TACE, medium and large arteries are occluded with particles 3–10 times larger than those used in radio embolization resulting in tumour ischemia that causes the antitumor effect, with drug delivery potentially enhancing tumour cell killing [15,16,17,18].

Radio embolization uses the commercially available microspheres that are made of resin (SIR-Spheres,) or glass (Thera Sphere,) and labelled with Yttrium 90 (Y-90). Resin Microspheres (SIR-Spheres) consist of biocompatible polymer resin microspheres of a median diameter of 32.5 m (range between 20 and 60 um). The resin microspheres are small enough to become lodged in the arterioles within the growing rim of the tumour but are too large to pass through the capillaries and into the venous system. Glass microspheres (Thera sphere) are 20–30 um in diameter. Glass microspheres are minimally embolic and do not occlude macro vessels with potential benefit in less perfused tumours. Glass microspheres penetrate and lodge within the tumour arteriolar capillaries, where they emit lethal beta radiation that is localized to the tumour tissue. Y-90 is pure beta-emitting isotope with no primary gamma emission. It has high-energy (maximum energy of the beta particles is 2.27 MeV with a mean of 0.93 MeV), short half-life (2.67 days), and a short tissue penetration (mean 2.5 mm and maximum 11 mm), making it ideal for internal radiation of the tumour sparing the adjacent normal liver tissue. In resin microspheres the isotope is attached to the surface while in the glass microspheres it is incorporated into the glass matrix [20,20,21].

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METHODOLOGY:

The decision to treat patient with radio embolization should be decided by multidisciplinary team consisting of hepatologists, oncologists, surgeons, interventional radiologists and nuclear medicine physicians. Potential patients

with non resectable HCC should be carefully evaluated before making the decision of radio embolization. Pre-treatment evaluation includes medical history, physical examination, the presence of cirrhosis, etiology of HCC, evidence of portal hypertension, and prior treatment such as radiofrequency ablation, hepatic resection, chemotherapy, or radiation therapy. Baseline investigation including full blood count, liver function tests, CT chest and abdomen and liver MRI should be all reviewed [22]. This is followed by diagnostic angiography with injection of 99mTc-MAA and scintigraphic imaging to identify vascular anatomy, HCC feeding vessels, aberrant vessels and extrahepatic collateral vessels feeding extrahepatic organs (especially the gastrointestinal tract), and the presence of intrahepatic or intra-tumoral arterio-portal shunting; and, in case of PVT, the presence of bypassing blood flow through collateral vessels. Aberrant hepatic vessels and extrahepatic collaterals were coil embolized to prevent the shunting of the radiolabelled microspheres to the gastrointestinal tract or pancreas. 99mTc-MAA is then injected with the delivery catheter in the intended position for radiolabelled microsphere infusion. Single-photon emission tomography (SPECT) images were acquired to evaluate the 3D distributions of the microspheres inside the tumour and surrounding liver. Imaging is usually performed within one hour after 99mTc-MAA injection to assess pulmonary shunt and extrahepatic extravasation [23]. Significant extrahepatic extravasation on MAA scan is a contraindication to radio embolisation. The percentage of lung shunt can be calculated by drawing ROIs over both lungs and the liver, and by using the geometrical mean of anterior and posterior total counts of lung and abdominal planar images. The accepted safe radiation dose to the lung is less than 30 Gy in a single procedure and less than 50 Gy in total over multiple procedures [24,25].

Within 1 week after MAA scan, microspheres are administered following the same route used for MAA. Small (25-35 μm) radio-labelled particles are delivered into the smallest intra-tumour blood vessels through injecting the microspheres in medium and large arteries aiming to deliver maximum short-range irradiation to the tumour and minimizing irradiation to the rest of the liver and extrahepatic organs.

EFFICACY:

Radio embolization usually induces tumour regressions of varying degrees in targeted lesions, with most series reporting response rates of 25–50%. Despite glass and resin microspheres differ in several characteristics the results and the clinical outcomes are very similar for both [21].

Y-90 SIRT has been shown to increase median overall survival (OS) in patients with HCC. A meta analysis including 21 studies assessing the OS after radio embolization and time to progression (TTP), showed pooled post radio embolization OS of 63% (95% CI: 56-70%) and 27% (95% CI: 21-33%) at 1- and 3-years respectively in intermediate stage HCC. Whereas OS was 37% (95% CI: 26-50%) and 13% (95% CI: 9-18%) at the same time intervals in patients with sufficient liver function but with an advanced HCC because of the presence of portal vein thrombosis. When an intermediate and advanced case-mix was considered, OS was 58% (95% CI: 48-67%) and 17% (95% CI: 12-23%) at 1- and 3-years respectively. As for TTP, only four studies reported data:

the observed progression probability was 56% (95% CI: 41-70%) and 73% (95% CI: 56-87%) at 1 and 2 years respectively [26,27,28].

A study by Nguyen et al., demonstrated that SIRT administered to 97 patients with non resectable HCC resulted in a median survival of 23.9 months, with a 3-year survival of 31% [23].

Salem et al., reported a median survival of 20.5 months and 3-year survival of 25% in 123 patients who underwent SIRT. **Mantry et al**., reported a median survival of 13.1 months in 111 patients treated with SIRT [29,30].

In the ENRY study, a prospective European multicentre trial of Y-90 resin SIRT including 325 patients with non resectable HCC, the median OS was 12.8 months (95% CI: 10.9–15.7) [26].

OS varies significantly by disease stage, performance status, liver health, and tumour burden. A sub-analysis of the ENRY database was conducted to evaluate the clinical outcomes among elderly patients (70 years or older) compared with younger patients. Radio embolization was as well tolerated and effective in the elderly as it was in younger patients with non resectable HCC [31].

A head-to-head comparison of Y-90 resin SIRT and **Sorafenib** for HCC, (phase 3 SARAH trial), did not show a significant difference in OS between the two groups, but patients who were treated with Y-90 resin had significantly fewer side effects and higher quality of life [32].

Similar results were reported from a multicentre clinical trial, comparing Y-90 with standard dose (400 mg bid) **Sorafenib**. The OS was similar in the two groups (Y-90: 8.54 months, **Sorafenib**: 10.58 months), and again less serious side effects in the Y-90 arm (27%) than in the **Sorafenib** arm (>50%). In addition, the tumour response rate was substantially better in the Y-90 arm (16.5%) than in the **Sorafenib** arm (1.7%) [33].

TACE is the standard of care and first-line treatment for intermediate-stage non resectable HCC [7,9].

A study comparing SIRT to TACE (SIRTACE), showed a single treatment session with Y-90 resin appeared to be as safe, and had a similar impact on quality of life, as multiple sessions of TACE, predicting that SIRT might be an option for patients eligible for TACE. Several studies comparing the relative efficacy of SIRT and TACE showed that SIRT is as effective, if not more effective, in inducing a radiological response and improving survival than TACE. A meta-analysis including 10 articles showed SIRT has statistically significant benefit as compared to TACE in terms of longer progression-free survival rate, but both SIRT and TACE showed similar overall survival [36]. These studies illustrated better quality of life outcomes in patients undergoing SIRT rather than those undergoing TACE, although more patients presented with advanced disease[34,35].

SAFETY:

Side effects are not common after radio embolization. Fatigue, abdominal pain, nausea, vomiting, anorexia, diarrhoea, fever, chills, and weight loss are minor side effects. The dominant side effect reported for SIRT is fatigue [29].

Major complications for SIRT are rare and generally result from irradiation of non target tissue rather than from embolic effects [31].

Cholecystitis, gastritis, duodentitis, pancreatitis, radiation pneumonitis, and radio embolization-induced liver disease

are more serious side effects. REILD (radio embolization-induced liver disease) is a form of sinusoidal obstruction that may happen 4–8 weeks after radio embolization. It manifests as jaundice, mild ascites, and a moderate increase in liver enzymes. It is not common, but has been reported and is probably more common in patients who had systemic treatment [37]. Most studies reported no treatment-related mortality [29,38].

DOSIMETRY:

One of the main factors that determine tumour response is the amount of radiation delivered to the tumour. The biological effects of radio embolization are mediated by the absorbed dose. The absorbed dose depends on the amount of Y-90 activity that is injected, the hemo dynamics of the hepatic artery blood flow, and the vascular density inside the tumours [39].

The total dose of radiation delivered to the tumour could be predicted from the dose estimates provided by the pre-treatment 99mTc-MAA scintigraphy [40].

However, accurate dosimetry can not be predicted in radio embolization due to the heterogeneity of the vascular supply and haemo dynamics within the tumour that may differ in the pre-treatment 99m Tc-MAA scintigraphy and the actual radio embolization. Hence estimates reflect the average dose delivered rather than the actual dose.

After injection of the microspheres, they accumulate in the tumour in at least a 3:1–20:1 ratio compared with the normal liver, and are more located in the periphery of tumour where the absorbed radiation dose can be well beyond 500 Gy. Radiation causes irreversible cell damage in tumour and ultimately leads to compromised tumour growth and tumour. Tumour response was associated with higher calculated mean absorbed doses for both glass and resin microspheres. However, a cut-off point has not been established for the estimated absorbed dose in the tumour that may lead to a tumour response, although there is a general agreement by experts that 120 Gy would suffice and it has even been reported that the lowest dose needed to produce an objective tumour response with glass spheres is 40 Gy [41,42,43,44,45].

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