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The Influence of Additional Treatments, Injected Activity and Mean Dose to the Tumor on the Overall Survival of Patients Undergoing Transarterial Radioembolization (TARE)

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Abstract: We present our preliminary experience with transarterial radioembolization (TARE) with Yttrium-90, and investigate the influence of additional treatments, injected activity, mean dose to the tumor on overall survival (OS). Our database was interrogated to retrieve patients who had undergone TARE with Yttrium-90 (90Y) glass or resin microspheres. The following information were searched: 1) type of pathology; 2) sex; 3) age; 4) administered activity; 5) mean dose to the tumor; 6) additional treatments; 7) OS. The OS of the different groups of patients were compared ($p<0.05$). A bivariate correlation ($p<0.05$) was used to investigate the association between injected activity and OS, and between mean dose to the tumor on OS. Thirty-nine patients were retrieved (Sex: 27 M, 12 F; mean age: 61.26 ± 14.95 years): 23 with hepatocellular carcinoma (HCC) and 16 with colorectal cancer (CRC) liver metastasis. Globally, patients with HCC demonstrated a significantly longer OS than those with CRC liver metastasis (22.66±19.11 vs. 10.41±8.75 months; $p=0.022$). Among patients with CRC liver metastasis, those receiving TARE and additional treatment demonstrated a longer OS than patients receiving only TARE (23.50±19.76 months vs. 8.54±5.31; $p=0.018$), there was a direct correlation between injected activity and OS ($R=0.55$, $p=0.034$) and between mean activity reaching the tumor and OS ($R=0.812$; $p=0.008$). Patients with HCC receiving TARE achieved a longer OS than those with CRC liver metastasis. Additional treatments, increasing injected activity and higher mean dose to the tumor seem beneficial for outcome, especially in patients with CRC liver metastases.

Keywords: transarterial radioembolization; hepatocellular carcinoma; liver metatastasis; microspheres; Yttrium-90

1. Introduction

Transarterial radioembolization (TARE) is a minimally invasive procedure that uses radioactive microspheres to deliver targeted radiation therapy to tumors in the liver [1]. The radiolabelling nuclide of the microspheres is Yttrium-90 (90Y) which is a beta-emitter (2.280 MeV (Emax)) with a half-life of 64.1 hours, decaying to zirconium-90, a reasonably high linear energy transfer (LET) and an approximate emission range of 5 mm [2]. 90Y-loaded microspheres are injected into the hepatic artery, the main blood vessel that supplies blood to the liver. This allows the microspheres to be delivered directly to the tumor, with little exposure to surrounding healthy tissues. This is because β

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radiation has a short penetration range, meaning that it only travels a short distance before it is absorbed by tissue [3].

There has been a growing usage of TARE by means of ^{90}Y glass or resin microspheres in patients affected by hepatocellular carcinoma (HCC) or unresectable colorectal cancer (CRC) liver metastases in the last decade [4]. Glass microspheres offer the advantage of delivering a specific radiation dose with a reduced number of particles, which can potentially minimize embolic effects. Therefore, they are considered a more appropriate option in situations where achieving early stasis or addressing reflux is a concern, especially in cases of hepatocellular carcinoma with portal vein invasion and for radiation segmentectomy. In contrast, resin microspheres have a lower activity per particle, necessitating a higher number of particles to achieve the same radiation dose. As a result, resin microspheres are typically preferred for larger tumors and those with high arterial flow [5].

While TARE proved to be an effective first- or second-line treatment in patients with advanced HCC [6], the Resin trial demonstrated in a multicentre cohort of 498 patients that TARE is an effective second-line treatment for patients with CRC liver metastases [7]. Indeed, liver is thought to be the predominant site of metastatic dissemination for CRC in approximately 60% of people [8]. Surgical removal of CRC liver metastases has shown promising 5-year survival rates of 20-70%, making it the preferred treatment option for suitable patients. However, due to technical constraints and the severity of the disease, a significant portion (70-80%) of individuals with extensive liver metastases are unable to undergo surgery [9].

There is expanding evidence that TARE provides a longer time to progression compared to transarterial chemoembolization (TACE) in patients with HCC [8]. Similarly, in patients with CRC liver metastases, according to the results of the EPOCH trial including 428 patients, TARE reduces the risk of disease progression or death compared to chemotherapy alone [8]. Although there is mounting evidence with regards to the beneficial effect of TARE in HCC and CRC liver metastases, there are still limited medical centres with trained personnel to perform TARE.

The aim of this study was investigate the influence of additional treatments, injected activity, mean dose delivered to the tumor on OS of patients treated with ^{90}Y microspheres.

2. Materials and Methods

Patients

The database of our centre was interrogated to retrieve patients who had undergone TARE with ^{90}Y glass or resin microspheres. The eligibility criteria for enrolment to the study were: age ≥ 18 years, histologically proven or imaging-based diagnosis of unresectable HCC or CRC liver metastasis; life expectancy > 6 months; preserved liver function with Child–Pugh Class A or B; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; bilirubin < 2.0 mg/dL, albumin > 2.0 g/dL; availability of pre-treatment hepatic angioscintigraphy with 99mTc-macroaggregated albumin (MAA); a post-radioembolization ^{90}Y PET/CT scan carried out within 12 hours from TARE; information on additional treatment beyond TARE and a minimum follow-up of 24 months. Patient with CRC liver metastases had undergone surgical removal of the primary tumor.

Main exclusion criteria included previous radiotherapy to the liver, ascites, unresolved toxicity from first-line therapy, extra-hepatic metastases, or contraindications to angiography. The following patient information were also retrieved from the hospital database: sex; age; administered activity and mean dose to the tumor at of ^{90}Y-loaded microspheres; date of cancer-specific death.

Ethical approval for conducting the study was waived by the local Ethics Committee in view of the retrospective nature of the study (n.1007, 31st May 2023).

Pre-Treatment Imaging

Before TARE, all patients underwent at our centre an angiography of the hepatic vasculature for treatment planning and a liver angioscintigraphy with ^{99m}Tc-MAA (fixed dose: 185 MBq) to evaluate the percentage of injected activity shunted to the lungs and foresee the distribution of the ^{90}Y-TARE

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spheres. These procedures were performed in a fully equipped Innova angiography suite (General Electric Healthcare, Milwaukee, WI).

The 99mTc-MAA scan was acquired on a dual-head gamma camera (Infinia; General Electric Healthcare, Milwaukee, WI, USA) using a high-resolution, low-energy collimator. Whole-body anterior and posterior projections of the superior abdominal regions were obtained using 120-second planar pictures, with the energy window set at 140 ± 10 keV. Ninety-nine step-and-shoot mode projections were recorded in 360 degrees (10 s per step) for the SPECT/CT using a 256 × 256 matrix. Each ^{99m}Tc-MAA scan was reviewed jointly by two board certified nuclear medicine physicians, both with >5 years of experience on a XELERIS-1.123 GE workstation (GE medical systems, Milwaukee, USA). The CT and ^{99m}Tc-MAA SPECT/CT scans were analysed and compared jointly by an interventional radiologist and a nuclear medicine physician to evaluate the uptake of 9mTc MAA within the tumor area (CT-MAA agreement) and classified as positive or negative for presence of shunts to the lungs. In the case of no evidence of hepato-pulmonary shunts, patients were submitted to ^{90}Y-TARE within 21 days from the ^{99m}Tc-MAA scan.

^{90}Y-TARE Procedure

Pre-procedural exams to complete staging included baseline imaging studies: liver sonography, clinical and laboratory examination, contrast-enhanced CT (ce-CT), and [^{18}F]FDG PET/CT. After selective catheterization of the right/left hepatic artery to assess the vascular, tumor anatomy and blood-flow, the patient was administered with either ^{90}Y- resin spheres (SIR-Spheres; Sirtex Medical, Sydney, Australia) or ^{90}Y-glass microspheres (Therasphere; Boston Scientific, USA). The choice of the radiopharmaceutical between ^{90}Y- resin spheres and 90Y-glass microspheres was made based on a multidisciplinary discussion among the nuclear medicine physician, the interventional radiologist and the physicist.

The prescribed 90Y activity was determined on the basis of a dosimetric estimation on a commercial software as the patient-specific activity. Administered activity and mean dose to the tumor were calculated in order to achieve a desirable minimal dose of 120 Gy.

Post-Treatment Imaging

After ^{90}Y-TARE procedure, all subjects underwent a ^{90}Y-PET/CT scan within 4-12 hours to assess the microsphere distribution pattern. The PET/CT scan was carried out using a PET/CT scanner (GE Discovery STE, GE Healthcare). The first procedure was a CT scan (140 kVp, 30-300 mA, 3.75-mm slice thickness). After that, an OSEM algorithm was integrated to reconstruct the PET image (15 min per bed position).

The ^{99m}Tc-MAA SPECT/CT and ^{90}Y PECT/CT scans were compared to evaluate the overlap of the distribution between MAA particles and microspheres.

Statistics

OS of each patient was retrieved based on the time interccured from the date of TARE and the date of death at the last available follow-up. OS of the different groups of patients, based on pathology (HCC patients vs. patients with CRC liver metastases) and additional treatment (patients receiving only TARE and patients receiving TARE and additional treatments) were compared ($p<0.05$). A bivariate correlation ($p<0.05$) was used to investigate the association between injected activity and OS, and between mean dose delivered to the tumor and OS. Statistics were performed using MedCalc 11.3.8.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

From a total of 150 patients who had undergone TARE, 39 patients with complete datasets (liver angioscintigraphy, post-radioembolization ^{90}Y PET/CT scan and clinical information listed in the eligibility criteria) were retrieved (Sex: 27 M, 12 F; mean age: 61.26 ± 14.95 years; 23 with unresectabile HCC and 16 with liver metastases from CRC).

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The median follow-up from TARE to the last available record (April 2023) was 69 months (range: 39-91 months). Mean administered activity was 2.2 ± 0.9 GBq; mean dose to the tumor was 282.68 Gy. Ten of 16 patients with liver metastases from CRC had additional treatments with Sorafenib (n=7), or Regorafenib (n=2) or both (n=1).

Patients with HCC demonstrated a significantly longer OS than those with liver metastasis from CRC (22.66±19.11 vs. 10.41±8.75 months; p=0.022).

Patients with CRC liver metastasis

Patients with liver metastases from CRC receiving additional treatment demonstrated a longer OS than patients receiving only TARE (23.50±19.76 months vs. 8.54±5.31; p=0.018). There was a direct correlation between injected activity at TARE and OS (R=0.55, p=0.034) and between mean activity reaching the tumor and OS (R=0.812; p=0.008). A representative case of a patient with CRC liver metastasis treated with TARE is shown in **Figure 1**.

Patients with HCC

Among patients with HCC, subjects receiving TARE and additional treatment (n=8) demonstrated a trend for longer OS than HCC patients receiving only TARE (n=15; 31.07±18.20 months vs. 18.20±18.66; p=0.13); in the whole group of HCC patients there was a trend towards a direct correlation between mean dose to the tumor and OS (R=0.45, p=0.118).

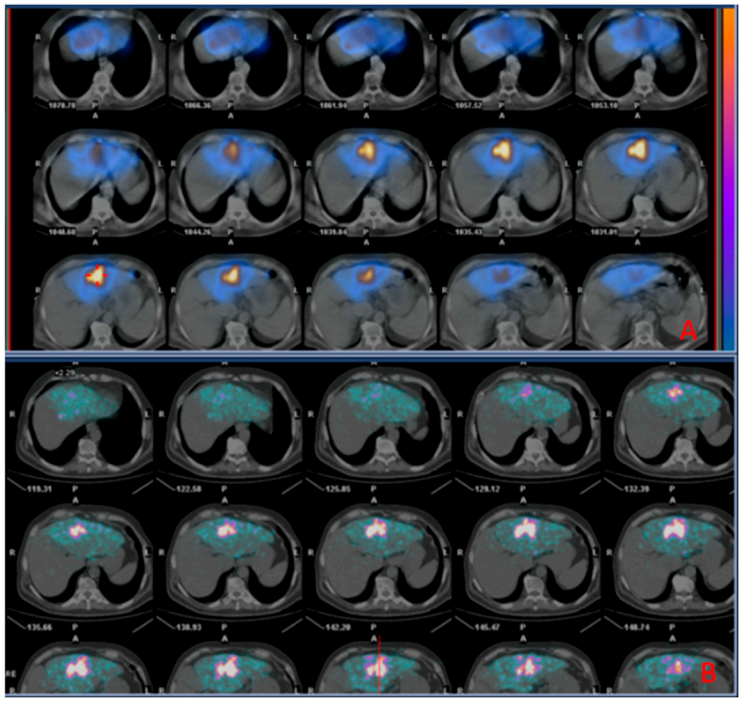

Figure 1. Images of a patient undergoing radioembolization of a hepatic metastasis from colorectal cancer. **A:** SPECT/CT images (diagnostic phase) 2h acquired after administration of ^{99m}Tc-MAA; **B:** PET/CT images (therapeutic phase) acquired 2h after administration of ^{90}Y theraspheres, showing successful distribution of ^{90}Y theraspheres matching that of ^{99m}Tc-MAA in the diagnostic phase.

4. Discussion

TARE is an effective therapy that can be used to shrink tumors before surgery or liver transplantation. It is also a bridging and downstaging therapy, meaning that it can help patients who are not yet eligible for surgery or transplantation to become eligible [10].

TARE has been traditionally used to treat advanced hepatocellular carcinoma (HCC), but recent improvements in the technique have made it effective for treating solitary HCC as well. Furthermore, it is a safe procedure when performed in the context of an expert multidisciplinary team. Alternative

embolization treatments include conventional transarterial chemoembolization (cTACE), and drug-eluting beads (DEB-TACE) [8]. TARE has significantly less complications than conventional transarterial chemoembolization (cTACE), drug-eluting beads (DEB-TACE) in patients with HCC [11].

In our center experience, patients undergoing TARE with either resin- or glass- ^{90}Y-spheres showed an OS comparable with those reported in literature (22.66±19.11 for patients with HCC and 10.41±8.75 months for patients with liver metastases from CRC). Interestingly, the effect of additional treatments resulted more beneficial in the group of patients with liver metastases from CRC (23.50±19.76 months vs. 8.54±5.31 not receiving a concomitant pharmacological treatment). In keeping with the literature, in the group of patients with liver metastases from CRC there was a correlation between injected activity and OS and between mean activity reaching the tumor and OS [12].

The efficacy of TARE as second-line treatment in chemorefractory hepatic metastases from CRC has been widely reported [4]. The additional treatments in our patient cohort included Sorafenib, Regorafenib or combination of both. Also in our study patients with CRC liver metastases presented a longer survival in presence of additional treatments.

Conversely, a significant improvement of OS and a correlation between injected activity and OS and between mean activity and OS were not proved in patients with HCC. Given the existence of a statistical trend, we suppose the lack of statistical significance may be attributed due to the limited number of the patient sample.

Person-related predictors of unfavourable outcome in patients undergoing TARE include older age (>70 years) [13,14], male sex [15], higher tumor grade, size, and stage, lack of treatment with surgery or systemic therapy, and presence of lymphatic or vascular invasion [16], Child-Pugh score (CPS: B or C vs. A), Eastern Cooperative Oncology Group Performance status (ECOG-PS: 2 or 1 vs. 0) [17,18]. Other factors that positively influence survival in patients receiving TARE are administered activity and mean dose to the tumor [19]. All these variables might have influenced the individual survival in our patient cohort, but in order to assess their real importance they would need to be tested in studies with larger patient samples.

5. Conclusions

Patients with HCC receiving TARE achieved a longer OS than those with liver metastases from colon cancer. Additional treatments and increasing injected activity and mean dose to the tumor may be beneficial for outcome, especially in patients with liver metastases from CRC.

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Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

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Conflicts of Interest: The authors declare no conflicts of interest.

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