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TRANSARTERIAL RADIOEMBOLIZATION OF RARE SECONDARY LIVER MALIGNANCIES USING GLASS MICROSPHERES

Doctoral dissertation

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List of Abbreviations

^{99m}Tc-MAA	^{99m}Technetium-labelled macro-aggregated albumin
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BSA	Body Surface Area
BTACE	Balloon-assiseted Transarterial Chemoembolisation
Bq	Becquerel
CA15-3	Cancer Antigen 15-3
CBCT	Cone-beam Computed Tomography
CCC	Cholangiocellular Carcinoma
CR	Complete Response
CRLM	Colorectal Liver Metastasis
CRPC	Castration Resistant Prostate Cancer
CT	Computed Tomography
CTACE	Conventional Transarterial Chemoembolisation
CTCAE	Common Terminology of Complications and Adverse Events
CUP	Carcinoma of Unknown Primary
DEB-TACE	Drug-eluting Bead Transarterial Chemoembolization
DNA	Deoxyribonucleic Acid

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ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
FNH	Focal Nodular Hyperplasia
Gy	Gray
HAIC	Hepatic Arterial Infusion Chemotherapy
HCC	Hepatocellular carcinoma
Her-2	Human Epidermal Growth Factor Receptor 2
Ho166	^{166}Holmium
HPFS	Hepatic Progression-free Survival
ICCC	Intrahepatic Cholangiocellular Carcinoma
IMDC	International Metastatic RCC Database Consortium
INR	International Normalized Ratio
IO	Interventional Oncology
IVC	Inferior vena cava
IQR	Interquartile Range
LPFS	Liver Progression-free Survival
LSF	Lung Shunt Fraction
LVD	Liver Venous Deprivation
MCC	Moffitt Cancer Center
MCRPC	Metastatic Castration Resistant Prostate Cancer
MIRD	Medical Internal Radiation Dose
MRCC	Metastatic Renal Cell Carcinoma
mRECIST	Modified Response Evaluation Criteria in Solid Tumors

MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
NET	Neuroendocrine Tumor
OS	Overall Survival
PD	Progressive Disease
PR	Partial Response
PR+	Progesterone receptor positive breast cancer
PFS	Progression-free Survival
PVE	Portal Vein Embolization
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RILD	Radioembolization Induced Liver Disease
RFA	Radiofrequency Ablation
SD	Stable Disease
SIRT	Selective Internal Radiation Therapy
SPECT	Single-photon Emission Computed Tomography
T/N	Tumor-normal Ratio
TACE	Transarterial Chemoembolization
TAE	Transarterial Embolization
TARE	Transarterial Radioembolization
TTP	Time to Progression
US	Ultrasound
VEGF	Vascular Endothelial Growth Factor

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Y90	^{90}Yttrium

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1 Introduction

Liver plays an important role in history and in our body as well. Even ancient Greeks mentioned the liver for its regenerative capability: when Zeus punished Prometheus on the mountain of Caucasus, an eagle fed from his liver each day, but it regenerated overnight [1]. This myth highlights the very precise observations made by the ancient Greeks, all this without any deep knowledge of the structure and function of the liver that we know nowadays. Many thousand years later, the liver still holds unanswered questions that are worth investigation.

1.1 Liver tumors

With the development of new imaging tools like ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI), accidental finding of liver lesions hitting new highs. While many benign lesions are also detected, like hemangiomas, focal nodular hyperplasias (FNHs), and cysts, the management of malignant lesions can be challenging. Despite the sophisticated imaging tools and diagnostic algorithms, carcinoma of unknown primary (CUP) is among the 10 most frequent cancers worldwide, constituting 3-5% of all human malignancies [2].

Liver malignancy is the most common cause of cancer-related death, especially in men from the developing countries. In numbers, this takes about 781631 cases of death, of which 548400 are men. This means more than 10% of all cancer-related mortality in men [3]. Liver is a common site for primary and secondary malignancies as well, however, secondary malignancies are far more common than primary ones.

1.1.1 Primary liver tumors

Malignant and benign lesions are both common in the liver. To keep this dissertation focused, benign lesions and primary liver malignancies are not discussed here.

1.1.2 Secondary liver tumors

The liver is a common site for metastatic disease. There are two hypotheses explaining the high frequency of liver involvement. The first is a mechanical or hemodynamic hypothesis, based on the double blood supply of the liver, causing entrapment of the circulating tumor cells in the liver. The second is the “seed-and-soil" hypothesis that

applies to malignancies that are aiming selectively the liver, like uveal melanoma (chromosome 3 loss) and triple positive breast cancer (due to ER and PR receptor positivity) [4].

The most common primary tumor of liver metastatic disease is colorectal cancer [4]. Regardless of the primary tumor, the presence of liver metastases poses a significant challenge to the health care system, as vast majority of the secondary liver tumors are unresectable.

1.1.2.1 Liver metastases of renal cell carcinoma

Renal cell carcinoma (RCC) has an incidence of 4.4 per 100 000 people globally [5]. Seventeen percent of patients with RCC have metastatic disease (mRCC) at the time of the initial diagnosis [6]. Among all metastatic sites, the liver is the fourth most common, following the lungs, bones, and lymph nodes. The liver is involved in 20.3% of mRCC patients [7]. Liver metastases carry a poor prognosis with a reported cancer-specific survival maximum of 10.6 months in RCC patients [8].

1.1.2.2 Liver metastases of castrate-resistant metastatic prostate carcinoma

Prostate cancer is the most common solid organ malignancy in men [9]. Metastatic castration-resistant prostate cancer (mCRPC) is an advanced form that progresses despite systemic androgen blockade. The most common metastatic sites for mCRPC are bone (75%–90%), lymph nodes (11.4%), liver (8%), and lung (16%) [10,11]. Liver metastases in patients with mCRPC carry a poor prognosis, with the median overall survival reported to be between 6 and 13.5 months [12–14]. The therapeutic options include systemic, radiation, and intra-arterial therapies for unresectable disease.

1.1.2.3 Liver metastases of breast cancer

Breast cancer is the most common cancer in women, affecting 1 of every 8 women in a lifetime [15]. Patients with localized disease have an excellent prognosis, with a 5-year survival exceeding 99% [16]. Unfortunately, despite advances in adjuvant therapies, breast cancer metastases will develop in 20% to 50% of patients, with bone, liver, and lungs being the most common sites [17–19]. Autopsy reports show liver metastasis in 60% of patients with breast cancer [20]. Patients with metastatic breast cancer have a poor prognosis, with a 5-year survival of only 20% to 25% [16].

1.2 Treatment of liver tumors

The possible treatment options for malignant disease in the liver is heavily dependent on the histological type of the tumor, the tumor burden and the presence of extrahepatic disease. Curative intent therapies, like surgical resection or thermal ablation, are possible mostly in primary cancer or some selected secondary tumors with very limited tumor burden [21–23]. If curative intent therapies are out, further locoregional and systemic options are available. Selected patients may highly benefit from intraarterially delivered therapies like transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) [24,25]. Recent developments on molecular diagnosis made targeted and immune-based therapies into the first-line systemic treatment for various malignancies [26]. Lastly, traditional chemotherapeutic agents and best supportive care are also an option in metastatic disease.

1.2.1 Curative treatments

1.2.1.1 Surgical resection

Although only colorectal liver metastases (CRLMs) and neuroendocrine tumor (NET) metastases were well studied, the available data shows that surgical resection remains the gold-standard curative treatment in the few eligible cases [22].

Although liver resection can prolong survival in liver metastatic RCC, 95% of patients are not surgical candidates due to multi-segmental liver metastases or significant comorbidities [27]. Ishihara et al [28] studied the significance of metastasectomy in the postcytokine therapy era of mRCC, and found that metastasectomy – either complete or incomplete – prolongs survival, and should play an important role in the management of mRCC.

Available treatment options for patients with breast cancer with liver metastases are limited. Surgical resection of liver metastases has not been widely adopted because only 10% to 20% of patients are surgical candidates due to the presence of multisegmental liver disease at the time of diagnosis and due to the high recurrence rate of up to 67% after resection [29–31]. However, R0 resected patients showing improved survival rates based on recent studies [32–34].

1.2.1.2 Percutaneous ablation

Image-guided ablation is the first choice after the patient is deemed to be unresectable. Multiple ablation modalities are available and used in daily practice. Radiofrequency ablation (RFA) is using uni- or multipolar electrodes to generate heat around the active tip of the needle using friction of the free ions (i.e., water). Microwave ablation (MWA) generates an electromagnetic field around the active part of the antenna in a frequency between 0.9 and 2.450 GHz. In the high frequency electromagnetic field, the polar water molecules are continuously realigning what will lead to significant heat. Cryoablation uses multiple cycles of freeze and heat, the developing ice crystals will cause defects on the cell membrane, and microcirculatory failure developing due to thrombosis in the capillary vessels [35–42].

The cornerstone of all percutaneous ablation technique is the adequate covering of the tumor and a safety margin around it [43,44]. Initially, conventional CT-/US-guidance was used, but recurrence rate was significantly higher compared to resection, and covering lesions larger than 3 cm was very unreliable. Recently, with the availability of stereotactic navigation systems, more and larger lesions can be treated in the liver, and long-term results are comparable to surgery [45–47].

Available data on the percutaneous ablation of liver-metastatic mRCC, mCRPC and breast cancer is very limited. Ishihara et al [28] included 3 patients in the liver-resection group who underwent radiofrequency ablation. Findakly et al [48] performed MWA on a patient with mCRPC, in combination with systemic poly (ADP-ribose) polymerase-1 inhibitor. 18 months after the MWT, the patient demonstrated a complete response of the liver lesion. Hino et al [49] presented a case in which RFA was used to manage a solitary liver metastasis from prostate cancer, however, the patient developed recurrence and multiple liver metastases despite repeated RFA treatments.

1.2.2 Palliative locoregional treatments of liver tumors

If curative therapies are not possible due to the widespread disease, wide range of palliative therapies are available. In case of liver-involvement, especially in liver-dominant disease, IR has many tools to disease control. The below described therapies are widely used in primary malignancies (mostly HCC) and some secondary malignancies (mostly CRLMs), however, their efficacy may differ based on the origin of the primary

tumor. Available data on rare secondary liver malignancies is very limited and will be discussed below for each treatment modality.

1.2.2.1 Intraarterial therapies

Intraarterial treatments are performed by interventional radiologists. The procedure takes place in an angio suite, where image guidance (fluoroscopy, DSA, optionally US, CBCT or even full-featured CT) is available. Access to the arteries is gained using the Seldinger technique [50]. Most used puncture point for interventional oncology (IO) procedures are common femoral, brachial or radial arteries. After placing sheet in the artery, the feeding vessels of the liver are catheterized under image guidance, using fine tools like catheters, guidewires. Notably, the arterial supply of the liver may come with many variations, that can prolong procedures or lead to inadequate treatment. The most common variations were categorized by Michels based on inspections during dissections [51].

After proper catheterization of the liver, various materials can be injected intraarterially. The goal of these treatments to cause lethal damage to the tumor cells – either via ischemia, anticancer effect of drugs or beta radiation – without harming the normal parenchyma significantly. The rationale of intraarterial therapies based on the double blood supply of the liver: while the normal parenchyma is fed by 80-85% of the portal vein and only 15-20% of hepatic arteries, malignant lesions almost exclusively fed by the hepatic artery. Thus, the hepatic artery is an optimal path to deliver anticancer treatment and block blood supply. Although intraarterial therapies are mostly studied in primary liver cancer and CRLM's, growing evidence is available for non-colorectal secondary cancer [52].

1.2.2.1.1 Hepatic Arterial Infusion Chemotherapy (HAIC)

During a HAIC procedure, a temporary catheter is placed in the proper hepatic artery and various chemotherapeutic agents can be administered locally through an intra-arterial pump. The chemotherapeutic agent varies based on the type of the primary tumor. Combination with systemic treatments is also possible. One cycle of treatment can take a few days, and multiple cycles may be needed. Embolic agents are not used for this procedure. Most of the studies on HAIC were done on patients with CRLMs, advanced

HCC or metastatic melanoma, however, study protocols vary a lot, what makes comparison and interpretation challenging for HAIC.

Hsiao JH et al [53] published a retrospective series of HAIC on patients with liver-predominant metastatic disease from breast cancer. Of the 42 patients included, 28 were responders and the responder group had a significantly longer overall survival (OS) compared to non-responders. The median OS for all patients was 19.3 months.

There is no data available so far with RCC or mCRPC liver metastases treated with HAIC.

1.2.2.1.2 Transarterial (bland) embolization (TAE)

TAE is a well-established technique to treat primary and secondary malignancies of the liver. The most studied malignant tumors treated with TAE are HCC and liver metastases from neuroendocrine tumors, however, theorically any hypervascular lesion in the liver may respond well to TAE. Some studies demonstrated that despite the embolization result in cell death and necrosis, the ischemia may also induce neoangiogenesis via proangiogenetic factors and may also provide a mechanism for resisting apoptosis [54,55].

Various materials can be used during TAE procedures. Iodinized-oil (Lipiodol, Guerbet LLC) is a liquid embolic agent made from poppy seeds, that can be taken up by healthy hepatocytes, but struck in the vessels that are feeding the tumors. Iodinized-oil is also frequently used for TACE procedures (see below). Solid particles are also effectively blocking blood flow: gelatin sponge, polyvinyl-alcohol particles, and microspheres of various materials are used in the liver and other organs as well.

Despite its wide use in daily practice, no comprehensive data is available for liver metastasis of RCC, mCRPC, or breast cancer.

1.2.2.1.3 Transarterial chemoembolization (TACE)

In contrast to TAE, that solely relies on the ischemic effect, TACE uses tree synergistic effect to increase therapeutic efficacy: 1) direct ischemia caused by the embolic agent and endothelium injury caused by the chemotherapeutic agent; 2) locally high concentration of the chemotherapeutic agent, achieving a prolonged anti-tumor effect; 3) minimized systemic effect due to the embolization, that avoids the wash-out from the tumor.

Different devices are available to perform a TACE treatment. Traditionally, the chemotherapeutic agent was mixed with iodized oil (Lipiodol, Guerbet Inc), and optionally polyvinyl particles were also added to prevent washout and complete the embolization. This variation is called cTACE (conventional TACE), that is the gold-standard treatment for intermediate stage HCC. Recently, loadable microspheres are also available, what is usually called DEB-TACE (drug-eluting bead TACE) [56]. During a DEB-TACE, chemotherapeutic agent is mixed with the microspheres that take up some of the drug, and the loaded spheres will be injected into the liver. While DEB-TACE was very promising, there is no proven superiority in terms of OS or progression-free survival (PFS) [57]. Gelatin sponge mixed with chemotherapeutic agent was also used previously for TACE procedures [58].

TACE is now also available with degradable microspheres that are loaded with drug (DEM-TACE). Initial studies reported improved tumor response rate and favorable safety profile compared to cTACE [59–61].

The chemotherapeutic agent used in TACE procedure may differ based on the histology of the tumor. Doxorubicin, epirubicin, idarubicin is commonly used for HCC, irinotecan for CRLM. For breast cancer liver metastases, various agents are reported, in some cases even combined with intra-arterial injection of non-embolizing chemotherapeutic agents: doxorubicin-TACE after 5-fluorouracil and cisplatin injection [62], doxorubicin DEB-TACE [63], gemcitabine TACE with starch microspheres and Lipiodol [64], mitomycin-C or mitomycin-C plus gemcitabine TACE [65]. As breast cancer is usually a systemic disease, local treatment is rational only in heavily liver-dominant cases.

1.2.2.1.4 Transarterial radioembolization (TARE)

During TARE or selective internal radiation therapy (SIRT) procedures microspheres loaded with beta-emitting material are delivered to the liver trans-arterially, that will cause damage to the surrounding cells. In contrast to external radiation, higher tumor dose can be achieved that will result in a better response of the treated lesion. As the malignant lesions exclusively fed by the hepatic artery, while normal liver parenchyma got most of the blood from portal vein, the transarterial approach is reasonable to maximize the exposure to the tumor and limit the toxicity of the liver. Due to often seen variational

anatomy and possible extrahepatic feeders to the tumors, proper angiographic planning is needed to fully cover the disease.

Currently three products are available for TARE in the European market, that utilizes two different isotopes: Yttrium-90 (Y90) labeled glass and resin microspheres and Holmium-166 (Ho166) labeled poly-L-lactides microspheres. There are slight differences between these products, especially the size of the microspheres, number of spheres needed (thus potential embolic effect) and specific activity per sphere. The properties of the spheres are detailed in **Table 1**.

Table 1: Comparison of products available for TARE in Europe (as of 2023). Y90: ^{90}Yttrium; µm: micrometer; Bq: Becquerel; h: hour; MeV: mega-electron-volt; KeV: kilo-electron-volt; Tc-99m-MAA: ^{99m}Technetium-labelled macro-aggregated albumin

	Y90 resin	**Y90 glass**	**Ho-166-poli-L-lactate-acid**
Product name	SIR-Spheres	TheraSpheres	QuiremSpheres
Manufacturer	Sirtex Medical	Boston Scientific	Quirem Medical
Sphere size	20-60 µm	20-30 µm	30 µm (15-60 µm)
Specific activity	50 Bq/sphere	1250-2500 Bq/sphere	200-400 Bq/sphere
Relative embolization effect	High	Low	Mid
Radionuclid (halflife)	Yttrium-90 (64,1 h)	Yttrium-90 (64,1 h)	Holmium-166 (26,8 h)
Energy of beta emission (E_{max})	2,28 MeV	2,28 MeV	1,85 MeV
Gamma emission	-	-	81 KeV (6,7%)
Planning	Tc-99m-MAA	Tc-99m-MAA	Ho-166 QuiremScout
Contrast medium during treatment	Yes	No	Yes
Paramagnetic	No	No	Yes

Before injecting therapeutic activity of the isotope-labelled microspheres into the liver, a simulation is needed to ensure safe treatment. As Y90 is a purely beta-emitting isotope, it cannot be used for simulation. Therefore, 99m-Technetium-labelled macroaggregated albumin (99m-Tc-MAA) is injected. Because Ho166 also has a gamma-spectrum, the same spheres can be used for simulation. After injecting the 99m-Tc-MAA or low amount of Ho166 labelled spheres, planar and/or SPECT images will be captured. The following parameters need to be checked for a safe treatment:

- Lung shunt fraction (LSF): some amount of the spheres of albumin is getting through the capillary system and will end up in the lung. Normally, this value is

<10%. If the mean absorbed dose of the lungs exceeds 20-30 Gray (Gy) (per treatment, or 50 Gy overall), the risk of radiation pneumonitis is high, and dose reduction may be inevitable [66].

- Extrahepatic deposition: the migration of the spheres into other organs can cause serious adverse events. Therefore, proper angiographic planning is needed, and event SPECT/CT can be used to detect any extrahepatic deposition of the isotope. Main endangered organs are the stomach, pancreas, and duodenum.

- Intrahepatic distribution, tumor-to-normal ratio (T/N): this parameter helps to find the ratio of how much activity will end up in the tumor, and how much in the normal liver parenchyma. Hypervascular tumors (HCC, iCCC, mRCC, NET, etc.) come with a high T/N, while hypovascular tumors (CRLMs, breast cancer liver metastases, etc.) have lower T/N value. The measured T/N may also be affected by the catheter position. Using a multicompartment model for dose planning can allow more aggressive dosing, that will result in higher tumor-absorbed dose, thus in a better tumor response.

TARE can be performed in various settings, depending on the tumor load of the liver. In the early studies patients with bilobar metastatic disease were treated covering the whole liver in a single session. This approach led to limited tumor response and high toxicity; therefore, single session whole liver treatments are not widely used anymore. For bilobar disease, sequential lobar treatments proved to be a safer solution, with at least 3 to 7 weeks between the treatments [67]. If the tumor burden is limited to a single lobe – which is more often seen in primary liver cancer like HCC or iCCC, unilobar treatment is reasonable. Unilobar treatment can be performed with standard dosing, however, recent development proved that the untreated lobe of the liver can show significant hypertrophy [68–70]. The effect is similar to other procedures that aims contralateral hypertrophy, like Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS), portal vein embolization (PVE) or liver venous deprivation (LVD), however, radiation lobectomy also provides tumor control in the treated lobe, without increasing the risk of progression in the future liver remnant. A further selective treatment is called radiation segmentectomy [71–73]. In this setting, the therapeutic activity of isotope is injected into intrahepatic arteries that feed only one or two segments of the liver, including the

malignant lesion. Delivering relatively high activity into small volumes will result in a high absorbed dose, that will lead to very extensive necrosis in the treated area. The mean absorbed dose was initially targeted to 190 Gy, however, recent studies recommend 400 Gy or even higher mean dose for better results [71,74,75]. This high-dose, “ablative” approach elevates TARE to the “potentially curative” treatments.

There are different models available to calculate the required dose for a treatment [76,77]. To provide a quick overview, empiric, body surface area (BSA), medical internal radiation dose (MIRD) and partition dosimetry models are descibed below. It is important to understand, that therapeutic isotopes can be ordered by activity (Becquerel - Bq), the physiological effect depend on the absorbed dose (Gy), therefor we need models to predict the required activity for an effective treatment. Initially, empiric model was used that solely relied on the size of the liver and percentage of tumor involvement of the liver. Unfortunately, dose prediction by the empiric model was very inaccurate, resulting in high rate of adverse events. BSA model was widely used due to its simplicity and better safety compared to the empiric model. BSA model assumes that the size of the liver correlates with the BSA. This eliminates the lengthy volumetric calculations required for empiric model. The MIRD model was developed in the 1960’s and 1970’s that considers the energy and half-life of the isotope and volume of the treated mass. Despite its benefits, MIRD is still a single-compartment model assuming homogeneous distribution in the target tissue, therefor it has several limitations. In 1996 Ho et al [78] described the partition model, to overcome MIRD model’s limitations: tumor, non-tumor and lung compartments were implemented into the MIRD equation. Partition model was the first model considering T/N ratio, however, still assuming homogeneous distribution in the target volumes. More recently, personalized dosimetry was introduced that is capable to deal with inhomogeneous distribution and maximize treatment efficacy while also improving safety [79].

The response after the TARE procedure is dose-dependent: higher mean tumor dose will result in better response [80–83]. However, when dealing with high doses to normal liver parenchyma, future liver remnant (untreated, healthy parts of the liver) needs to be considered similarly to major surgical hepatectomy. Cautious evaluation of future liver remnant is important [84]. The use of Ho166 spheres opens the possibility of same time liver function evaluation and TARE planning [85,86].

TARE comes with limited side effects or adverse events [87]. The complications can be grouped into hepatic, biliary, pulmonary and gastrointestinal complications. Among hepatic complications, radioembolization induced liver disease (RILD) may happen in 1-3 months after the treatment, when damage to normal parenchyma is extensive. Symptoms include newly developed ascites, hepatic encephalopathy, changes in liver-related laboratory tests. Biliary complications may happen in patients with previous biliary procedures (eg sphincterectomy or hepaticojejunostomy), or if the treated lesion placed very centrally in the liver. Radioembolization induced cholecystitis was also described, however, practice varies widely how centers dealing with the cystic artery [88]. Pulmonary complications are rare nowadays, as planning with 99m-Tc-MAA is mandatory and sophisticated tools are available for dose planning. Previously, pulmonary fibrosis was noted in up to 6.3% of cases, especially in large volume and/or large activity treatments, and in patients with LSF > 13% [89]. Gastrointestinal complications may happen due to non-target embolization to the small bowel or to the pancreas. The risk of non-target embolization can be significantly reduced with the use of CBCT during planning. Non-target embolization may also happen due to reflux next to the catheter to a more proximal vessel, especially with resin microspheres that has the highest embolization potential among the available products.

Previously only few case reports or case series were available about TARE in RCC [90–92]. TARE in mCRPC is even more underreported. Despite liver metastases are common in mCRPC, they developed in late stage of the disease. The only available data is a single case report by Bunck et al [93], without any long term follow-up. TARE in breast cancer is way more studied, as liver metastases are common in this disease. Despite the common involvement of the liver, liver-directed therapies are usually limited and questionable, as breast cancer is deemed to be a “systemic disease”. Recently, a systematic review, a meta-analysis of TARE and a meta-analysis of all intra-arterial therapies were published, however, majority of TARE studies included were done using resin microspheres [94–96]. The only studies that included patients treated with glass microspheres were published by Bangash et al in 2007 and Gordon et al in 2014, but overleap in patient cohorts may present [97,98]. Our working group at Moffitt Cancer Center (MCC) also evaluated the safety and efficacy of Y90 TARE with glass microspheres in patients with liver-metastatic pancreatic cancer [99].

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2 Objectives

Because TARE with glass microspheres in rare secondary liver tumors is not well studied, the main objective of the current work is to demonstrate the safety and efficacy of TARE in three secondary liver malignancies:

(1) Safety of TARE with Y90-labeled glass microspheres in patients with liver-dominant metastatic renal cell carcinoma.

(2) Safety of TARE with Y90-labeled glass microspheres in patients with liver-dominant castrate-resistant prostate cancer.

(3) Safety of TARE with Y90-labeled glass microspheres in patients with liver-dominant chemorefractory breast cancer.

(4) Efficacy of TARE with Y90-labeled glass microspheres in patients with liver-dominant metastatic renal cell carcinoma.

(5) Efficacy of TARE with Y90-labeled glass microspheres in patients with liver-dominant castrate-resistant prostate cancer.

(6) Efficacy of TARE with Y90-labeled glass microspheres in patients with liver-dominant chemorefractory breast cancer.

3 Methods

All three studies were approved by the Institutional Review Board. All patients were presented and discussed at a multidisciplinary tumor board including medical oncology, surgical oncology, radiation oncology, and interventional radiology. Liver-dominant disease was defined when the liver involvement was likely the survival-limiting factor for the patient. Generally, TARE candidates were required to fit into Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and having satisfactory liver, and kidney function (total serum bilirubin ≤2 mg/dL, serum creatinine ≤2 mg/dL, and international normalized ratio and platelet count correctable to ≤1.5 and ≥50,000/mL).

3.1 TARE procedure

The treatment included a planning angiogram whereby the tumor-feeding vessels and anatomical variants were identified, and target treatment liver volumes were measured. Vessels feeding non-target organs were embolized using coils, if needed. The planning angiogram also included the injection of technetium-99m–labeled macro-aggregated albumin (99m-Tc-MAA) into the hepatic arteries to calculate the lung-shunt fraction. Technetium isotope activity in the liver and lungs was measured by gamma camera immediately after the planning angiogram. The MIRDmodel was used for dose calculation in all cases. TARE was performed one to three weeks after the planning angiogram using glass microspheres labeled with Yttrium-90 (Y90) isotope (TheraSphere; Boston Scientific, Marlborough, MA, USA). In patients with bilobar disease, the left and right lobes were treated separately, approximately four to seven weeks apart.

3.2 Liver-dominant metastatic RCC

Medical records of 38 consecutive patients with liver-dominant mRCC, who were treated with TARE at MCC between July 2010 and September 2019, were reviewed. TARE was offered for patients with liver-dominant disease who progressed on systemic therapy or refused systemic therapy. Of the 38 patients reviewed, two were excluded from further analysis: one patient did not have liver-specific follow-up, and one patient was lost to follow-up one month after the treatment. [100]

Twenty-seven men and 9 women were included in this study with median age of 67 years (interquartile range [IQR]: 57, 71). Most patients had a performance status of ECOG 0 (23 patients) or 1 (12 patients) and only one patient had a performance status of ECOG 2. Twenty-six patients (72.2%) had extrahepatic metastases at the time of the first TARE treatment; the most common sites were the lymph nodes, lungs, and bones. The demographic data and disease characteristics are summarized in **Table 2**. Twenty patients received systemic chemotherapy before TARE and 28 received after TARE (**Table 3**). There were only four patients who did not receive any systemic therapy before or after TARE, all of whom had liver-only disease. [100]

Follow-up imaging (either contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging) was performed every three months after TARE. Because RCC liver metastases are highly hypervascular, imaging data were evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [101]. Imaging data of one patient was evaluated using RECIST 1.1 due to lack of contrast-enhanced follow-up imaging. Model for End-stage Liver Disease (MELD) scores were calculated to asses post-embolization liver toxicity [102,103]. Biochemical and clinical toxicity was assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The difference between baseline and the three-month post-TARE MELD score was investigated using the Wilcoxon test. The probabilities of overall survival (OS) were estimated using the Kaplan-Meier method. The median overall survival (OS) was calculated from the initial RCC diagnosis, from the diagnosis of liver metastasis, and from the first TARE treatment up to death or last follow-up. Liver progression-free survival (LPFS) was also calculated using the Kaplan-Meier method from the first TARE procedure until radiographic progression or death. Univariate and multivariate Cox proportional hazards regression analyses were conducted to investigate the predictors of OS. The multivariate Cox proportional hazards regression analysis included response (complete/partial response versus stable/progressive disease), extrahepatic metastasis status, tumor distribution (solitary vs multiple hepatic sites), receipt of systemic therapy before TARE, lung shunt, albumin, alanine-aminotransferase, MELD score at baseline, and time from liver metastasis diagnosis to TARE. Statistical analyses were conducted using the MedCalc Software (MedCalc Software Ltd, Ostend, Belgium). [100]

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Table 2. Demographic characteristics of patients with liver-dominant mRCC. ECOG: Eastern Cooperative Oncology Group. IMDC: International Metastatic RCC Database Consortium. TARE: Transarterial Radioembolization. IVC: Inferior vena cava. Table from Bibok et al, 2021 *[100]*

	n	%
Age		
<70	23	36.1
≥70	13	63.9
Gender		
Male	27	75.0
Female	9	25.0
ECOG		
0	23	63.9
1	12	33.3
2	1	2.8
Tumor histology		
Clear cell	30	83.3
Papillary cell	5	13.9
Chromophobe cell	1	2.8
IMDC risk group		
Poor	2	5.6
Intermediate	27	75.0
Favorable	7	19.4
Tumor distribution		
Unilobar	14	38.9
Bilobar	22	61.1
Number of tumors		
Solitary	7	19.4
Multiple	29	80.6
Extrahepatic disease		
Yes	26	72.2
Lymph node	12	33.3
Lung	11	30.6
Bone	7	19.4
Pancreas	4	11.1
Adrenal gland	2	5.6
IVC	3	8.3
Peritoneum	2	5.6
Local recidive	3	8.3
Other	6	16.7
None	10	27.8
Nephrectomy		
No	2	5.6
Radical nephrectomy	32	88.8
Partial nephrectomy	2	5.6
Systemic therapy before TARE		
None	16	44.4
Yes	20	55.6
Systemic therapy after TARE		
None	8	22.2
Yes	28	77.8
Liver-directed therapy before TARE		
None	29	80.6
Thermoablation	2	5.6
Radiation	5	13.9
Liver-directed therapy after TARE		
None	33	91.7
Bland embolization	2	5.6
Radiation	1	2.8

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Table 3. Pre- and post-treatment systemic therapies in liver-dominant mRCC. Table from Bibok et al, 2021 *[100]*

	n	%
Pre-treatment systemic therapies		
Sunitinib	11	30.6
Interleukin-2	7	19.4
Pazopanib	5	13.9
Temsirolimus	3	8.3
Nivolumab	3	8.3
Cabozantinib	3	8.3
Axitinib	3	8.3
Everolimus	2	5.6
Sorafenib	2	5.6
Bevacizumab	2	5.6
Erlotinib	1	2.8
5-fluoroacil	1	2.8
none	16	44.4
Post-treatment systemic therapies		
Sorafenib	6	16.7
Cabozantinib	6	16.7
Everolimus	5	13.9
Pazopanib	5	13.9
Bevacizumab	4	11.1
Axitinib	3	8.3
Sunitinib	2	5.6
Interleukin-2	1	2.8
Temsirolimus	1	2.8
Pembrolizumab	1	2.8
Levatinib	1	2.8
none	8	22.2

3.3 Liver-dominant castrate-resistant metastatic prostate carcinoma

All TAREs between January 2012 and May 2019 at MCC were retrospectively reviewed to identify patients with liver-dominant mCRPC. Of the nine identified patients two did not receive treatment after the planning procedure due to elevated liver enzymes and limited performance status. Those two patients were therefore excluded from further analysis. Finally, analysis was performed on the 7 patients who successfully underwent TARE with glass Y-90 microspheres [104].

Median age at the time of the first treatment was 69 years (range: 62-84). Five patients were treated within 3 months diagnosis of liver metastases, whereas 2 patients had progressive liver disease while on systemic therapy before TARE. In 2 patients, liver was the only metastatic site; 5 patients had synchronous bone metastases of which 1 had simultaneous thoracic lymph node metastases. Detailed patient characteristics and treatment data are displayed in **Table 4**. All patients received multiple lines (median: 5; range 2-6) of systemic therapy including androgen deprivation therapy (ADT) (**Table 4**). [104]

Baseline and clinical follow up was performed per standard institutional clinical pathways. Laboratory data and imaging results were collected at baseline, 3-month follow-up, and every 3-6 months until death, if possible. Imaging follow-up was performed either with contrast-enhanced computed tomography or magnetic resonance imaging. Imaging data were retrospectively reviewed by the authors in a consensus fashion using Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 to evaluate for disease progression. [105] Median overall survival (OS), liver progression-free survival (LPFS) and time to progression (TTP) were calculated using Kaplan-Meier method. TTP included disease progression in any organ. Radioembolization-related adverse events (AE) were collected via retrospective chart review and categorized using Common Terminology Criteria for Adverse Events (CTCAE) version 5 and included changes in functional status and lab abnormalities. AEs were attributed to TARE if they occurred within 30 days of the treatment. [104]

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Table 4: Demographic characteristics and treatment data of patients with liver-dominant mCRPC. TARE: Transarterial radioembolization. ECOG: Easter Cooperative Oncology Group, GNRH: Gonadotropin-releasing hormone. Table from Bibok et al, 2022 *[104]*

#	Age (years)	ECOG	Gleason score	Liver involvement	Number of liver lesions	Largest lesion (cm)	Extra-hepatic disease	Systemic treatment before TARE	Systemic treatment after TARE	TARE session	Dose (Gy)	Activity (GBq)
1	84	0	3+4	Multifocal, bilobar	3	2.4	Bone	enzalutamide	leuprorelin	2	113, 110.6	2.26, 0.6
2	72	0	5+5	Multifocal, unilobar	2	5.8	Bone	abiraterone, enzalutamide, leuprorelin, zoledronic acid	enzalutamide, docetaxel	1	109.8	2.65
3	69	0	6	Multifocal, bilobar	5	1.6	None	leuprorelin, bicalutamide, abiraterone, enzalutamide, docetaxel	degarelix, docetaxel, abiraterone	3	122.2, 110.4, 97.5	2.95, 0.59, 2.35
4	69	0	4+4	Multifocal, bilobar	3	6.0	Bone	bicalutamide, flutamide, hydrocortisone, ketaconazole, abiraterone, prednisolone	docetaxel	2	124.1, 143.3	0.95, 1.12
5	64	0	4+5	Multifocal, bilobar	5	5.8	None	leuprorelin, bicalutamide, cabazitaxel with bicalutamide and GnRH-agonist	leuprorelin, abiraterone, enzalutamide, cabazitaxel, docetaxel,	3	123.1+132.5, 80.2, 93.7+119.1	2.83+1.75, 0.59, 0.59+2.18
6	62	0	4+5	Solitary	1	6.4	Lymph node, bone	docetaxel, leuprorelin, zoledronic acid, abiraterone	docetaxel, denosumab	1	128	4.32
7	74	2	4+4	Solitary	1	22.2	Bone	bicalutamide, leuprorelin; docetaxel and carboplatin	cyclophosphamide	1	122.6	13.36

3.4 Liver-dominant chemorefractory breast cancer

Review of MCC's electronic medical records and imaging system identified 31 eligible female patients with breast cancer with chemorefractory hepatic metastases who underwent TARE using glass microspheres (TheraSphere; Boston Scientific, Marlborough, MA) between May 2010 and August 2019. All patients had hepatic tumor progression after systemic chemotherapy. Seventeen patients received 1 prior line chemotherapy, 12 patients got 2 lines of chemotherapy, 1 patient received 3 lines, and 1 patient received 9 lines of chemotherapy. Patients were selected for TARE by a multidisciplinary tumor board. Criteria for receiving TARE treatment included liver-dominant metastases that progressed on at least 1 line of chemotherapy. [106]

Patient demographics are summarized in **Table 5**. The study included 31 females with a mean age of 59.6 ± 13.2 years. Bilobar disease was present in 22 patients and the receptor status for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2) was positive in 25, 21, and 5 cases, respectively. Three triple-negative and 4 triple-positive patients were included in the current study. Extrahepatic metastases were present in 21 patients, and 13 of them had metastases in bones only besides the liver. Five patients received other liver-directed treatments before TARE, which included surgical resection in 2 patients and external radiation therapy in 3 patients. Eight patients underwent other liver directed treatments after the TARE, which included bland embolization in 2 patients, repeated TARE in 2 patients, TACE in 2 patients, and percutaneous ablation in 2 patients. The median follow-up period between the first TARE and the date of last visit/death was 12 months (range, 2-44 months). [106]

Statistical analysis was performed with IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY). Data are presented as mean ± standard deviation. The probabilities of actuarial OS and HPFS were calculated by the Kaplan-Meier method with the last date of contact or death used for censoring. The log-rank test was used to evaluate the effect of clinical factors and patient characteristics on disease outcome. A P value of .05 was taken as significant. [106]

Table 5. Demographic characteristics of patients with liver-dominant chemorefractory breast cancer. Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; Her-2 = human epidermal growth factor receptor 2; PR = progesterone receptor; TARE = transarterial radioembolization. Table from Barakat et al, 2022 [106]

	n	%
Age in years (mean ± standard deviation)		
65.5 ± 11.2		
Sex		
Male	0	0
Female	31	100
ECOG		
0	10	32.3
1	18	58.1
2	2	6.5
3	1	3.2
Distribution of hepatic metastases		
Unilobar	9	29
Bilobar	22	71
Genetic markers		
ER+	25	80.6
PR+	21	67.7
Her-2+	5	16.1
Extrahepatic metastasis		
No	10	32.3
Yes	21	67.7
Bone only	12	38.7
Extraosseous § bone	9	29.0
Previous chemotherapy		
Yes	31	100
No	0	0
Previous liver-directed therapy		
Yes	5	16.1
No	26	83.9
Liver-directed therapy after TARE		
Yes	8	25.8
No	23	74.2

4 Results

4.1 Results of patients with liver-dominant metastatic RCC

TARE was performed 38.6 months (median, IQR: 14.4, 81.9) after the initial RCC diagnosis and 8.1 months (median, IQR: 3.5, 20) after diagnosis of the liver metastases. Median OS was 72.6 months from RCC diagnosis (95% confidence interval, CI: 52.4-364.1), 36.5 months from liver metastasis diagnosis (95% CI: 26.4-49.8) and 19.3 months (95% CI: 10.1-43.5) from the first TARE treatment (**Figure 1**). At the time of the data analysis eight patients were still alive. [100]

4.1.1 Clinical and radiological response

Median OS from TARE was 32.9 months (95% CI: 0.0-93.7, n=7) of patients in the favorable International Metastatic RCC Database Consortium (IMDC) risk group and 19.3 months (95% CI: 11.25-27.35, n=27) of patients in the intermediate risk group. Only two patients were in the poor risk group, therefore, median OS was not calculated. [100]

The best radiographic liver-response was complete response (CR) in 21 patients (58.3%), partial response (PR) in 11 patients (30.6%) and stable disease (SD) in two patients (5.6%). Two patients (5.6%) had liver progression (PD) despite the TARE treatment (**Figure 2**). Best radiographic liver-response was evaluated at the 3 or 6 months follow-up for all patients. Hepatic progression was observed in 28 patients (77.8%) during the study period. Median liver progression free survival was 9.5 months (95% CI: 8.0-17.7). [100]

Multivariate analysis of OS showed a significant survival benefit for patients achieving objective response (HR: 156.3, P=0.0002), having higher albumin level (HR: 0.08, P=0.003), and lower lung shunt ratio (HR: 1.2, P=0.03). Detailed results of the univariate and multivariate analysis can be found in **Table 6**.

4.1.2 Safety

The 30-day mortality rate was 0%. Mild (CTCAE grade 1-2) clinical toxicities were reported by 22 patients: fatigue (n=17), nausea (n=5), abdominal pain (n=4), and decreased appetite (n=2). Two patients presented with grade 3 biliary strictures 3 and 8 months after TARE, which were not related to tumor progression and were attributed to the TARE treatment. [100]

There were 58 events of CTCAE grade 1-2 biochemical toxicities in 27 patients; 8 events of decreased albumin, 7 events of elevated creatinine, 3 events of elevated INR, 2 events of elevated bilirubin, 17 events of elevated ALP, 13 events of elevated AST and 8 events of elevated ALT. MELD score did not significantly changed from the baseline (median: 8; 95% CI 7-9.3 vs median: 8, 95% CI 6-9.3; P=0.148). [100]

Two patients died before the 3-month follow-up; none of these deaths were related to the TARE treatment; 1 patient died of sepsis-induced multi-organ failure 46 days after TARE and the other patient died of rapid tumor progression and renal failure at 51 days after TARE. [100]

Table 6. Predictors of overall survival following TARE. CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; TARE: Transarterial radioembolization; ALT: Alanine-aminotransferase; * Based on the Kaplan Meier analysis. Table from Bibok et al, 2021 *[100]*

Variables	Univariate Analysis			Multivariate Analysis	
	Median survival (months)*	**Hazard Ratio (95% CI)**	**P value**	**Hazard Ratio (95% CI)**	**P value**
Extrahepatic metastasis					
No	32.9	1.00	0.196	1.00	0.43
Yes	16.6	1.77 (0.74-4.26)		1.56 (0.50, 4.83)	
Tumor distribution					
Solitary	56.9	1.00	0.1798	1.0	0.69
Multiple	17.1	1.97 (0.72, 5.36)		0.76 (0.19, 2.94)	
Best imaging response					
CR or PR	22.80	1.00	0.0004	1.00	0.0002
SD or PD	1.70	64.22 (6.4, 643.46)		156.29 (11.39, 2144.70)	
Systemic treatment before TARE					
No	32.9	1.00	0.165	1.00	0.70
Yes	12.4	1.72 (0.79, 3.71)		0.81 (0.29, 2.29)	
Time from liver metastasis diagnosis to TARE (days)		1.00 (1.00, 1.002)	0.04	1.00 (0.99, 1.00)	0.20
Lung shunt (%)		1.18 (1.03, 1.35)	0.01	1.19 (1.01-1.39)	0.03
Albumin (g/dL)		0.23 (0.07, 0.68)	0.008	0.08 (0.02, 0.36)	0.0008
ALT (U/L)		1.01 (0.99, 1.04)	0.16	1.02 (0.99, 1.04)	0.08
MELD		1.06 (0.96, 1.18)	0.18	1.14 (0.97, 1.33)	0.09

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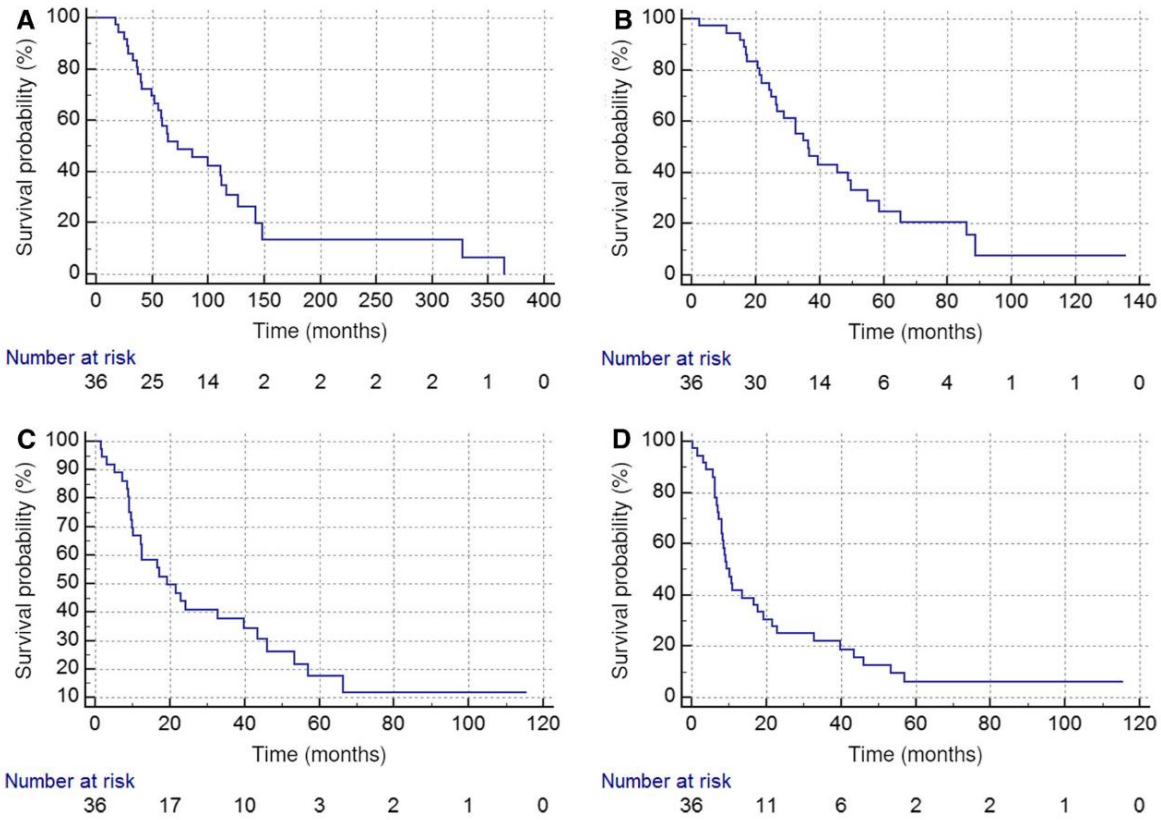

Figure 1: (A) Overall survival (OS) from diagnosis of renal cell carcinoma (RCC) of 36 patients who underwent TARE procedure. Kaplan–Meier method revealed that the median OS from RCC diagnosis was 72.6 months (95% CI: 52.4–364.1). (B) OS from diagnosis of liver metastasis from RCC of 36 patients who underwent TARE procedure. Kaplan–Meier method revealed that the median OS from liver metastasis diagnosis was 36.5 months (95% CI: 26.4–49.8). C) OS from TARE treatment of 36 patients with liver-dominant metastatic RCC. Kaplan–Meier method revealed that the median OS from TARE was 19.3 months (95% CI: 10.1–43.5). D) Liver progression-free survival (LPFS) from TARE treatment of 36 patients with liver-dominant metastatic RCC. Kaplan–Meier method revealed that the median LPFS from TARE was 9.5 months (95% CI: 8.0–17.7). TARE: Transarterial radioembolization. Figure from Bibok et al, 2021 *[100]*

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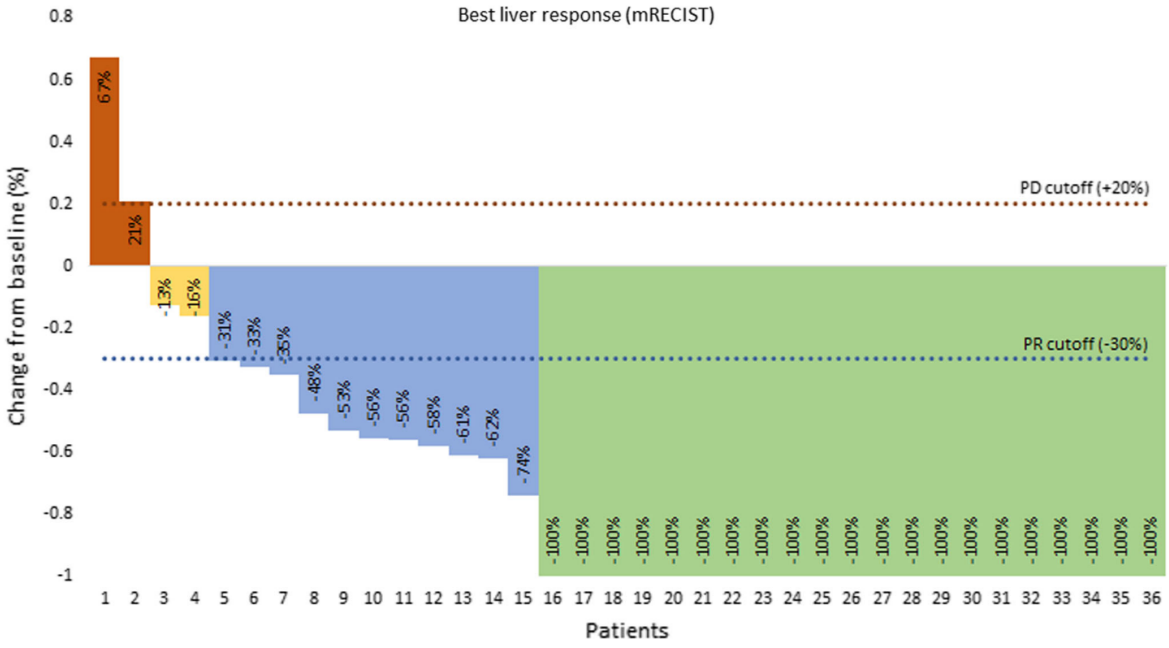

Figure 2: *Best liver response for each patient. mRECIST: Modified response evaluation criteria for solid tumors; PD: Progressive disease; PR: Partial response.* Figure from Bibok et al, 2021 *[100]*

4.2 Results of patients with liver-dominant castrate-resistant metastatic prostate carcinoma

Median time from prostate cancer and liver metastases diagnosis to TARE was 79.5 months (range: 15.3-253.1) and 1.8 months (range: 0.8-59.1), respectively. One patient, who received lobar TARE underwent subsequent stereotactic radiation therapy for new solitary metastasis. Median delivered radiation activity per procedure was 2.35 GBq (range 0.59 – 13.36) and median target tissue absorbed dose per procedure was 122.2 Gy (range: 80.2-255.6). Treatments were lobar (n=11), segmental (n=1) or mixed lobar and segmental (n=1) TARE. [104]

4.2.1 Clinical and radiological response

Partial response was achieved in 4 patients and three patients had stable disease (**Figure 3-4**). Median OS was 27.2 (range: 2.3-34.8; mean: 19.9; 95% CI 9.3 to 30.5), 32.1 (range: 4.1-86.4; mean: 32.8; 95% CI 12.6 to 53), and 108.1 (range: 17.6-257.3; mean: 118; 95% CI 57.1 to 179) months from TARE, diagnosis of liver metastases, and initial cancer diagnosis, respectively. Median LPFS was 7.3 (range: 2.3-19.2; mean: 7.86; 95% CI 3.56 to 12.2) months. Median TTP was 4.2 months (range: 2.3-19.2; mean: 7.26; 95% CI 2.75 to 11.8). 30-day mortality rate was 0%. [104]

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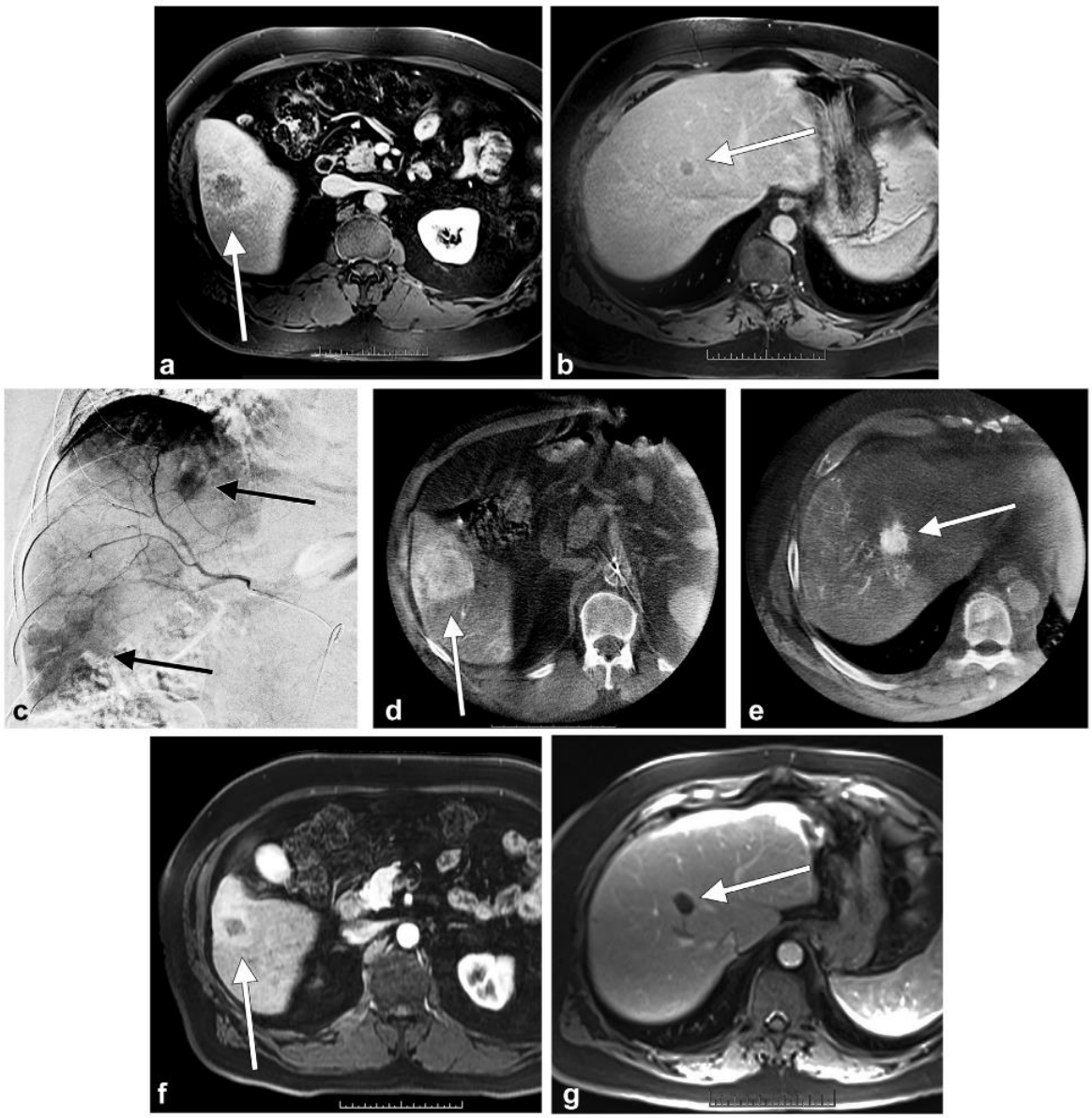

Figure 3: Treatment response after the transarterial radioembolization of representative right lobe metastases from prostate cancer (patient 5). (a) A pretreatment, contrast-enhanced, T1-weighted magnetic resonance (MR) image demonstrated a large, enhancing tumor in segments 5/6 (arrow). (b) An additional, small, enhancing tumor was identified in segment 8 (arrow). (c) Digital subtraction angiography of the right hepatic artery (with breathing motion artifact) confirmed the presence of hypervascular tumors (arrows). (d) Cone-beam computed tomography confirmed the complete perfusion of the hypervascular segment 5/6 tumor (arrow) and (e) the segment 7/8 tumor (tumor), both of which had increased in size since diagnostic MR imaging. (f, g) Follow-up MR imaging 6 months after transarterial radioembolization showed a decrease in the size of both the

tumors and the resolution of tumoral hypervascularity. Figure from Bibok et al, 2022. [104]

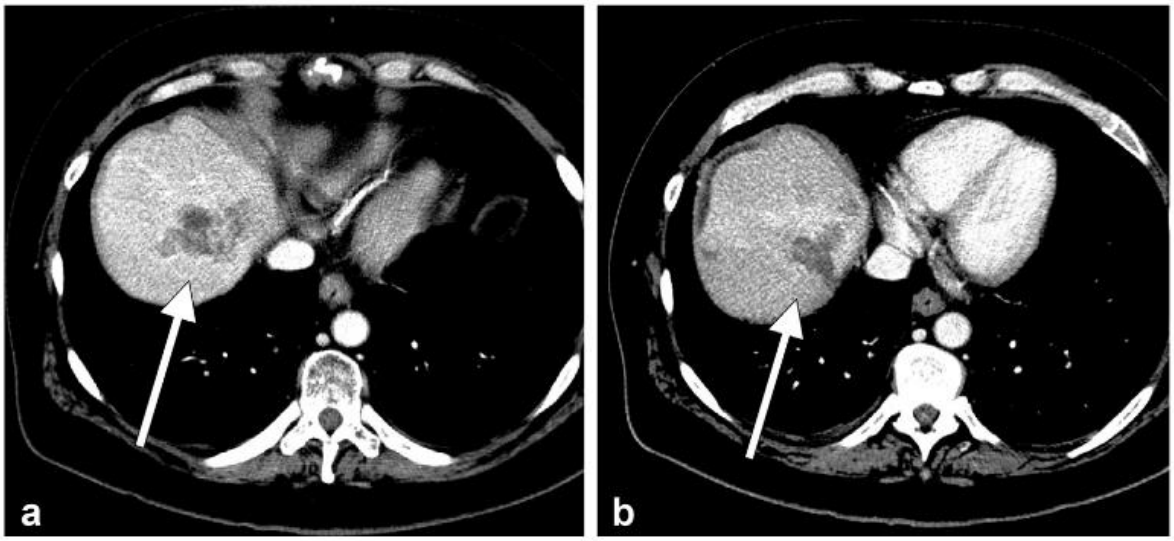

Figure 4: Treatment response after the transarterial radioembolization of a metastasis in the dome involving segments 7 and 8 (patient 6). (a) Pretreatment, contrast-enhanced computed tomography demonstrated heterogeneous enhancement, with central hypodensity. Procedural angiography confirmed isoenhancement/hypoenhancement of the mass relative to the liver parenchyma (not shown because of poor image quality and artifact). (b) Follow-up, contrast-enhanced computed tomography 3 months after transarterial radioembolization demonstrated partial response, despite baseline hypovascularity. Figure from Bibok et al, 2022. [104]

4.2.2 Safety

Three patients were asymptomatic after treatment, and 4 patients reported CTCAE grade 1-2 effects (abdominal pain n=2, back pain n=2, fatigue n=1) that required no interventions. 3 patients had CTCAE grade 1-2 biochemical toxicity at 3-month follow-up (elevated values of international normalized ratio [INR] n=2, alkaline phosphatase [ALP] n=1, aspartate aminotransferase [AST] n=2, alanine aminotrasferase [ALT] n=1). MELD score at the 3-month follow-up showed no significant differences (P=0.204) (**Table 7**). [104]

Table 7. Survival, treatment response, and adverse events. TARE: Transarterial radioembolization. LPFS: Liver progression-free survival; mRECIST: modified Response Evaluation Criteria for Solid Tumors; PR: Partial Response; CR: Complete Response; SD: Stable disease. INR: International Normalized Ratio; ALP: alkaline-phosphatase; AST: aspartate transaminase; ALT: alanine aminotransferase. Table from Bibok et al, 2022 [104]

Age (years)	Survival from TARE (months)	LPFS (months)	Best liver response (mRECIST)	Adverse events	
				Clinical	Biochemical
84	4.2	4.2	PR	None	Elevated INR, ALP, AST
72	28.7	7.3	PR	None	None
69	27.2	19.2	CR	Back pain	Elevated AST, ALT
69	34.8	3.1	PR	Back pain	None
64	33.5	10.4	CR	Fatigue, abdominal pain	None
62	2.3	2.3	PR	None	N/A
74	8.5	8.5	SD	Abdominal pain	Elevated INR

4.3 Results of patients with liver-dominant chemorefractory breast cancer

4.3.1 Cilincal and radiological response

At the time of data analysis 8 patients were still alive and 23 were deceased. The median OS from the date of TARE was 13 months (95% confidence interval [CI], 9.1-16.9 months) (**Figure 5A**). The 1-, 2-, and 3-year survival probability was 60.1%, 36.7%, and 24.5%, respectively. The median hepatic progression-free survival (HPFS) was 7 months (95% CI, 6.1-7.9 months) (**Figure 5B**). Median OS for patients with ER+ tumors was significantly higher compared with ER- patients (14 vs 9 months, P = .028) (**Figure 6A**). Patients with PR+ tumors had longer median OS compared with patients with PR tumors, but the difference was not statistically significant (14 vs 9 months, P = .24) (**Figure 6B**). The Her-2 status of the tumor had no effect on survival; however, only 5 patients had Her-2 positive tumors (**Table 8**). Patients with unilobar disease had a longer OS of 30 months compared with 12 months in patients with bilobar disease; however, the difference was not statistically significant (P = .28) (**Table 8**). There was no significant difference in median OS of patients without or with extrahepatic metastases (14 vs 12 months, P = .22) (**Figure 7A**). However, patients with bone-only extrahepatic disease had longer median OS than patients having other extrahepatic metastases (23 vs 8 months, P = .02) (**Figure 7B**). There was no significant correlation between median OS and baseline ECOG performance status (P = .09), albumin-bilirubin score (P = .9), and MELD score (P = .12) (**Table 8**). There was no difference in median OS when comparing patients who had decreased cancer antigen 15-3 (CA15-3) after TARE to patients who had increased CA15-3 after TARE (**Table 8**). Patients who received liver-directed therapy after TARE had significantly longer median OS then patients who did not receive any liver-directed therapy after TARE (30 vs 12 months, P = .049) (**Table 8**). [106]

Baseline and follow-up contrast-enhanced cross-sectional imaging were available for 30 patients (96.7%). The radiographic responses at 3 months were evaluated by RECIST criteria [105], which showed complete response in 1 patient (3.3%), partial response in 13 patients (43.3%), stable disease in 7 patients (23.3%), and progressive disease in 9 patients (30%) with objective response rate (complete and partial response) of 46.6% and disease control rate (complete and partial response plus stable disease) of 70%. There was

no difference in median OS between patients who had objective response after TARE and patients who did not (**Table 8**).

4.3.2 Safety

After TARE, the 30-day mortality rate was 0%. Grade 3 clinical toxicity was noted in 3 patients (9.4%), necessitating hospitalization for pain (2 patients), and newly developed ascites required paracentesis in 1 patient. Laboratory values at the 3-month follow-up were available in 29 of the 31 patients: 1 patient died 2 months after the first treatment and another patient's follow-up was done at an outside institution and laboratory data were not available. Mild (grade 1-2) biochemical toxicities were noted in 24 patients. Alkaline phosphatase was elevated in 18 patients, albumin level was below normal in 7 patients, and bilirubin level was elevated in 1 patient at 3-month follow-up. No grade 3 or higher biochemical toxicities were detected. The MELD score at 3 months was not significantly different compared with baseline (6.84 ± 1.68 vs 6.96 ± 1.61, P=.45). [106]

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Table 8. Univariate analysis between variables and overall survival. Abbreviations: CI = confidence interval; ECOG = Eastern Coopera-tive Oncology Group; ER = estrogen receptor; Her-2 = human epidermal growth factor receptor 2; PR = progesterone receptor; RECIST = Response Table from Barakat et al, 2022 [106]

Variables (n)	**Median survival (months)**	**95% CI**	**P value**
Age			
<60 years (15)	10	6, 14	.3
>60 years (16)	23	7, 37	
ECOG			
0 and 1 (28)	13	9, 37	.22
2 and 3 (3)	4	4, 35	
Distribution of hepatic metastases			
Unilobar (9)	30	4, 43	.28
Bilobar (22)	12	7, 23	
ER status			
ER+ (25)	14	8, 37	.028
ER- (5)	9	2, 13	
PR status			
PR+ (21)	14	8, 37	.23
PR- (9)	9	2, 43	
Her-2 status			
Her-+ (5)	14	9, 43	.7
Her-2- (24)	12	7, 37	
Extrahepatic metastases			
No (10)	14	4, 44	.22
Yes (21)	12	7, 30	
Extrahepatic extraosseous metastases			
No (12)	23	7, 37	.02
Yes (9)	8	3, 12	
Previous liver-directed therapy			
Yes (5)	12	7, 37	.8
No (26)	23	7, 30	
Liver-directed therapy after TARE			
Yes (8)	12	7, 14	.05
No (23)	30	4, 44	
Radiographic (RECIST) objective response			
Yes (14)	12	7, 43	.8
No (16)	13	6, 30	

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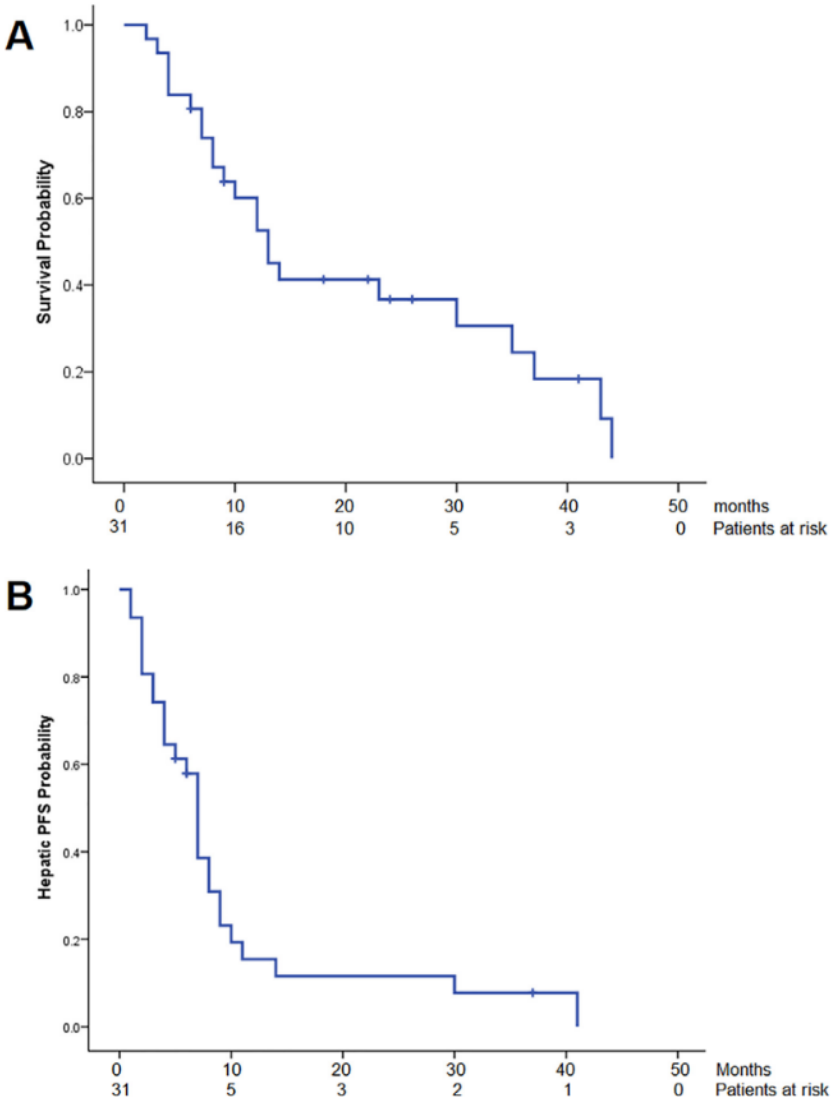

Figure 5: Overall survival (OS) and hepatic progression-free survival from radioembolization treatment. (A) Median OS from the radioembolization treatment was 13 months (95% confidence interval [CI], 9.1-16.9 months). (B) Hepatic progression-free survival from the radioembolization treatment was 7 months (95% CI, 6.1-7.9 months). Figure from Barakat et al, 2022. [106]

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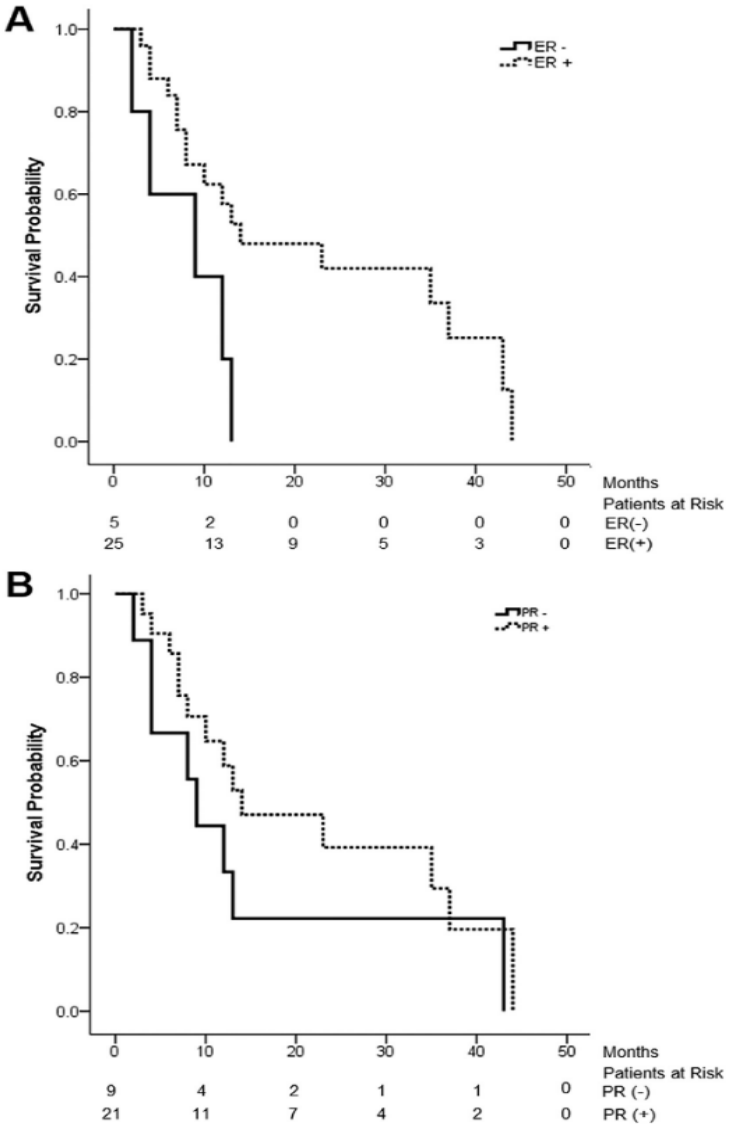

Figure 6: The effect of hormone receptor status on overall survival (OS) after radioembolization treatment. (A) Median OS of patients with estrogen receptor positive (ER+) versus negative (ER-) status (14 vs 9 months; P = .028). (B) Median OS of patients with progesterone receptor positive (PR+) versus negative (PR-) status (14 vs 9 months; P = .23). Figure from Baraket et al, 2022. [106]

DOI:10.14753/SE.2025.3124

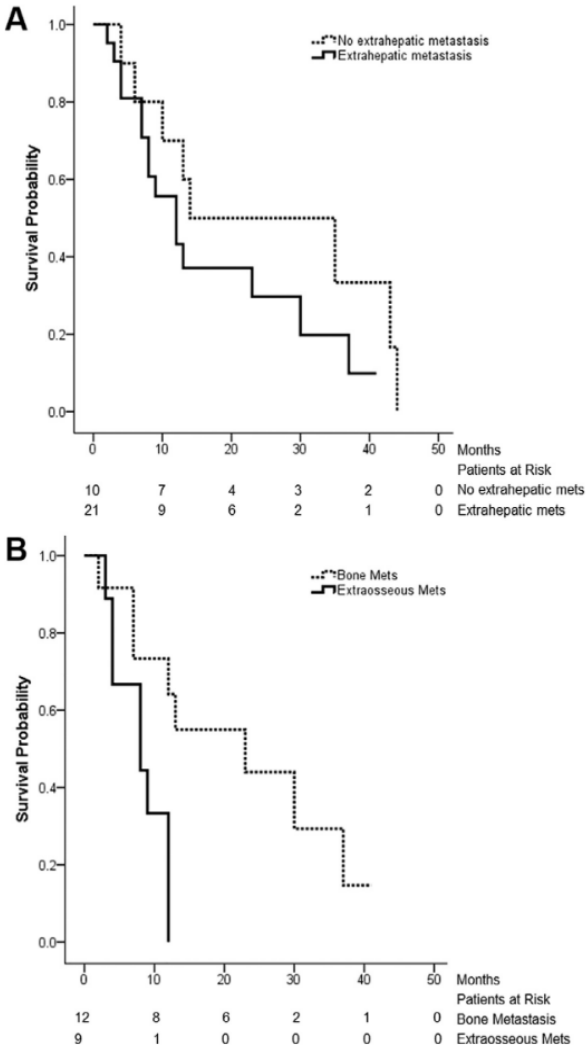

Figure 7: The effect of extrahepatic metastatic disease on overall survival (OS). (A) Median OS of patients without and with extrahepatic metastasis (14 vs 12 months; P = .22). (B) Median OS of patients with bone-only extrahepatic metastasis and patients with extrahepatic extraosseous metastasis (23 vs 9 months; P = .02). Figure from Barakat et al, 2022. [106]

5 Discussion

In this thesis we provided initial data on TARE of three rare secondary liver malignancies. Based on our results, TARE seems to be a safe treatment option with an acceptable rate of AE's, thus efficacious compared to the survival data reported by the literature.

Safety is the utmost priority for a new treatment modality. Although TARE is widely used since the early 2000's, most of the data that is currently available is about HCCs and CRLMs. The 30-day mortality was 0% in all three studies [100,104,106]. Mild, CTCAE grade 1-2 AEs were rather common, with fatigue, abdominal pain or nausea being the most reported. The most complication was grade 3 biliary strictures in two patients. Biliary stricture is a known possible late complication after TARE, especially after whole lobar treatments, that was the most common treatment form in our study population. The complication rate in our studies are in line with the complications reported in the literature for other liver malignancies [71,87].

Despite the wide availability of modern diagnostic tools, like US, CT, and MRI, only a small minority of liver metastatic RCC, CRPC, and breast cancer patients are candidates for curative therapies, i.e., resection or ablation [8,12,13,19,27,29,107]. Moreover, the presence of liver metastases significantly worsens the expected OS [7,14,18]. Intraarterial therapies may be a valuable addition in the management of this patient population.

The presented results suggest that TARE may improve survival in the examined patient groups. The reported median OS of 19.3, 27.2 and 13 months for mRCC, mCRPC and liver-dominant breast cancer is well over the expected survival in similar disease, reported in the literature [8,12–14,16].

Careful patient selection is crucial in TARE. Previously, TARE was studied mostly in primary liver malignancies and in CRLMs [108–112]. Unfortunately, many of these large prospective trials failed to reach the primary endpoint [113,114]. The reason for the failure may include wide inclusion criteria (i.e. presence of extrahepatic disease in CRML), non-personalized dosimetry and inclusion of centers with limited experience with TARE. The studies included in this dissertation were also inclusive, allowing extrahepatic lesions. The importance of liver-only disease may vary based on the primary tumor. In the RCC trial [100], the patients were sorted into risk groups according to the

IMDC scores. In the favorable subgroup, the median OS was significantly higher compared to the intermediate risk group (32.9 vs 19.3 months). In the mCRPC trial [104], all but one patient had extrahepatic disease, therefore no subgroup analysis was possible. Among patients treated for chemotherapy-refractory breast cancer metastases, extrahepatic involvement alone did not mean any difference in median OS (14 vs 12 months, P=0.22), however, patients with extraosseal metastases (22 vs 9 months, P=0.02) and ER- tumors (14 vs 9 months, P=0.028) had worse prognosis compared to liver and bone limited disease and ER+ tumors [106]. These differences highlight the need for personalized treatment decisions, that consider the primary tumor, extrahepatic involvement, and further characteristics of the tumor, like the ER status in breast cancer. Similarly, patients undergoing TARE for CRLM from left vs right side primary colon cancer proven to have different prognosis [115,116].

Given the salvage setting for TARE in our studies, systemic therapies were widely used before and after the procedures. However, using multiple lines of systemic treatment further complicates the assessment of response and prediction of best timing of TARE during the disease. Some of the new targeted therapies are blocking the development of new vessels via the VEGF receptor [26]. While this approach proved to be effective in large clinical trials, it may alter the delivery of the arterial injected therapeutic isotopes. Continuous development of systemic drugs may also affect the outcomes.

During surgery or thermal ablation using high temperatures the affected part of the liver got completely removed or isolated from the circulation, leaving not much to the immune system but healing. In contrast, after a TARE procedure, the cell death will be prompted by dual chain breaks on the DNA, and even the circulation remains intact. This fact provides new opportunities to the immune system to detect and kill cancerous cells that were not even covered by the TARE treatment. This is the so-called “abscopal effect” [117]. Unfortunately, the exact mechanism is not known yet. The immune response may be further strengthened with the combination of TARE and novel immunotherapeutic agents; however, more data is needed on this field to build robust evidence [118].

It is important to highlight the limitations of the presented results. First, all three studies are retrospective analysis of the available data, and control group was not available for comparison. Despite being one of the largest series for each, the number of included

patients was low. As the processed conditions are relatively rare, a long time frame was analyzed to increase the number of patients. During this period systemic treatments and other therapies also improved, that may influence our results. For response evaluation both RECIST and mRECIST were used. While the former is widely accepted, has many limitations especially when applied on after locoregional treatments, the latter is only validated for use in response evaluation for HCC. Most importantly, the delivered dose for all patients treated in these series was calculated using the standard dosimetry approach, that is nowadays almost completely replaced by the personalized dosimetry. With personalized dosimetry, results may be further improved, especially in patients with limited tumor burden.

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6 Conclusions

Based on our findings we can conclude that TARE with Y90-labeled glass microspheres is:

(1) Safe in patients with liver-dominant metastatic renal cell carcinoma.

(2) Seems to be safe in patients with liver-dominant castrate-resistant prostate cancer.

(3) Safe in patients with liver-dominant chemorefractory breast cancer.

Most frequently reported mild adverse events were fatigue, abdominal pain or nausea, and few occasions of biliary complications were also noted.

We can also conclude, that TARE with Y90-labeled glass microspheres is:

(4) Efficacious in patients with liver-dominant metastatic renal cell carcinoma.

(5) Efficacious in patients with liver-dominant castrate-resistant prostate cancer.

(6) Efficacious in patients with liver-dominant chemorefractory breast cancer.

As the observed overall survival in our cohorts were above the expected survival based on the literature and imaging follow-up demonstrated durable response to the treatment, however, optimal patient selection for TARE in the studied secondary malignancies needs further research.

Due to the rarity of liver-dominant diseases in these neoplasms, future studies should be based on large, international registries to gather more data.

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7 Summary

In present work we investigated the safety and efficacy of transarterial radioembolization (TARE) using glass microspheres in three types of rare secondary liver malignancies (liver-dominant metastatic renal cell carcinoma, liver-dominant castrate-resistant metastatic prostate carcinoma, liver-dominant disease from chemorefractory breast cancer). Despite TARE is widely used for hepatocellular carcinoma and liver-dominant metastatic colorectal cancer, the available data about other malignancies is very limited. All the studies were initiated in a tertiary cancer center in the USA, based on a chart review of the previous decade's TARE treatments. These malignancies pose a challenge to the clinicians due to the limited available treatment options. TARE was used in a salvage setting, after multiple lines of systemic treatments. Survival data, clinical and radiological response, laboratory parameters were collected and analyzed during the chart review. TARE was found to be safe, with 0% 30-day mortality, and mostly mild (CTCAE grade 1-2) clinical and laboratory adverse events. The median OS was 19.3, 27.2 and 13 months for metastatic renal cell carcinoma, metastatic castrate-resistant prostate carcinoma and liver-dominant chemorefractory breast cancer, respectively. Due to the retrospective nature of the study, control group was not available for comparison, but our data exceeds the results reported in the literature for similar patient groups. Finally, we discussed the importance of patient selection for TARE, and the potential improvements using combination therapies and personalized dosimetry. In conclusion, TARE seems to be safe and efficacious in the examined secondary liver-dominant diseases.

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9 Bibliography of the candidate's publications

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9.2 Unrelated publications of the author

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