Transarterial Radioembolization of Rare Secondary Liver Malignancies Using Glass Microspheres

Ph.D. thesis

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1. Introduction

The liver is a common site for metastatic disease from various primary tumors. Regardless of the primary tumor, the presence of liver metastases carries a bad prognosis and poses a significant challenge to the health care system, as vast majority of the secondary liver tumors are unresectable. Interventional radiology can offer multiple treatment modalities for primary and secondary liver cancer. Radioembolization is one of the most interesting treatment option, that can be utilized in secondary liver cancer. Instead of ischemia or locally high concentration of chemotherapeutic agent, radioembolization destroys cells with beta-emitting microspheres. Despite radioembolization is widely used for hepatocellular carcinoma and liver-dominant metastatic colorectal cancer, the available data about other malignancies is very limited.

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).

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 Medical Internal Radiation Dose (MIRD) model was used for dose calculation in all cases. TARE was performed one to three weeks after the planning angiogram using glass microspheres labelled with Yttrium-90 (Y90) isotope (TheraSphere; Boston Scientific, Marlborough, MA). In patients with bilobar disease, the left and right lobes were treated separately, approximately four to seven weeks apart.

3.1. Liver-dominant metastatic renal cell carcinoma

Medical records of 38 consecutive patients with liver-dominant mRCC, who were treated with TARE at Moffitt Cancer Center 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. 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. Twenty patients received systemic chemotherapy before TARE and 28 received after TARE. There were only four patients who did not receive any systemic therapy before or after TARE, all of whom had liver-only disease.

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). 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. 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).

3.2. Liver-dominant castrate-resistant metastatic prostate carcinoma

All TAREs between January 2012 and May 2019 at Moffitt Cancer Center 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.

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. All patients received multiple lines (median: 5; range 2-6) of systemic therapy including androgen deprivation therapy (ADT).

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. 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.

3.3 Liver-dominant chemorefractory breast cancer

Review of Moffitt Cancer Center'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 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.

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).

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.

4. Results

4.1 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. At the time of the data analysis eight patients were still alive.

4.1.1. Clinical and radiological responses

Median OS from TARE was 32.9 months (95% CI: 0.0-93.7, n=7) of patients in the favorable 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.

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. 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).

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).

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.

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).
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.

4.2 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.

4.2.1. Clinical and radiological responses

Partial response was achieved in 4 patients and three patients had stable disease (Fig 1-2). 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%.

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).

4.3 Liver-dominant castrate-resistant metastatic prostate carcinoma

4.3.1. Clinical and radiological responses

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], 9.116.9 months). 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) (Fig 1B). Median OS for patients with ER+ tumors was significantly higher compared with ER- patients (14 vs 9 months, P = .028). 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). The Her-2 status of the tumor had no effect on survival; however, only 5 patients had Her-2 positive tumors. 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). There was no significant difference in median OS of patients without or with extrahepatic metastases (14 vs 12 months, P = .22). However, patients with bone-only extrahepatic disease had longer median OS than patients having other extrahepatic metastases (23 vs 8 months, P = .02). 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). 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. 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).

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, 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.

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).

5. 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.

6. Bibliography of the candidate's publications

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