Tumor Size and Watershed Area Correlate with Incomplete Treatment and Tumor Progression after Segmental Radioembolization for Treatment-Naive and Solitary Hepatocellular Carcinoma

Qian Yu[1], Monika Neale[2], Ethan Ungchusri[1], Natalie Rothenberger[4], Mikin Patel[1], Anjana Pillai[3], Rakesh Navuluri[1], Osman Ahmed[1], Thuong van Ha[1]

1. Interventional Radiology, University of Chicago ,Chicago, IL 2. Interventional Radiology, Cleveland Clinic, Cleveland, OH
3. Hematology, Department of Medicine, University of Chicago, Chicago, IL 4. Department of Urology, University of Washington, Seattle, WA

INTRODUCTION

- The most recent Barcelona Clinic Liver Cancer 2022 guideline recommends consideration of transarterial radioembolization (TARE) for early and very early stage hepatocellular carcinoma (HCC) measuring up to 8cm[1].
- Segmental delivery of yttrium-90 (Y90) microspheres further increased the safety profile of this technique. The concentrated radiation dose provides durable radiology response, complete pathologic necrosis, and bridge to surgery and transplant[2,3].
- TARE can be as effective as ablation and even surgery in treatment of HCC[4-6].
- Incomplete radiologic response requires additional locoregional or systemic treatment yet may preclude patients from being listed for transplant.
- The present study aimed to identify factors contributing to incomplete radiologic response and tumor progression after TARE with Y90 in treatment naïve solitary HCC.

METHODS

Patient Selection

Adult patients with treatment-naive solitary HCC underwent segmental TARE with Y90 glass microspheres between November 2015 and June 2022. Inclusion criteria:

- age ≥18 years
- diagnosis of HCC confirmed by biopsy or characteristic radiological features based on Liver Imaging Reporting and Data System[7]
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- no prior local-regional or systemic therapy for HCC
- Child-Pugh score A or B.

Exclusion criteria:

- previous hepatic locoregional therapy, resection, or liver transplant
- hepatic encephalopathy grade 2 or higher
- portal vein thrombosis involving >50% of the lumen.

Technique

All TARE treatments consisted of two visits: 1) mapping angiography with lung shunt fraction measurement, and 2) subsequent Y-90 administration. Hepatic and mesenteric angiography was accomplished via femoral approach[8]. Dosing was calculated using the medical internal radiation dose model[9]. Administration of glass Y90 microspheres (Therasphere, Boston Scientific, Marlborough, MA) was accomplished via transcatheter delivery under fluoroscopic guidance.

Data Collection

In this single-center retrospective study, patient data were collected from electronic medical records: age, sex, etiology of liver disease, HCC characteristics (size, number, location), Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, sodium MELD (Na-MELD) score, albumin-bilirubin (ALBI) score, ascites, encephalopathy, Y90 dose, radiologic response, adverse events, and survival status. Tumor segments were reported according to Couinarud-Bismuth nomenclature. Watershed area was defined as tumor location situated within two or more segments on preprocedural CT/MRI or supplied by at least two distinct segmental arteries on angiogram[11].

Follow-up

Tumor response was measured according to mRECIST criteria[10] based on MRI or contrast enhanced CT findings 1-3 months postoperatively.

METHODS CONTINUED…

Radiological Response (RR)

RR were characterized into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and the best RR was reported. Incomplete treatment was defined as recurrence of target tumor per Society of Interventional Radiology guideline or residual tumor requiring repeated treatment[12].
Progression free survival (PFS) was calculated from treatment to detection of recurrent tumor or residual tumor requiring treatment. Nontarget tumor hepatic PFS was defined as the time from treatment to de novo nontarget hepatic lesion occurrence. Extrahepatic PFS was calculated from time of treatment to extrahepatic tumor development. Overall survival (OS) was defined from treatment to death or last clinical follow-up. Patients bridged to surgery/transplant were censored at the time of surgery. Data on percent of pathologic necrosis were collected for patients who received transplant and resection. For incompletely treated tumors, second line therapy and outcomes were reviewed. For those who subsequently received transarterial evaluation, angiographic findings were reviewed to identify tumor arterial supply, which was compared with initial TARE angiographic findings.

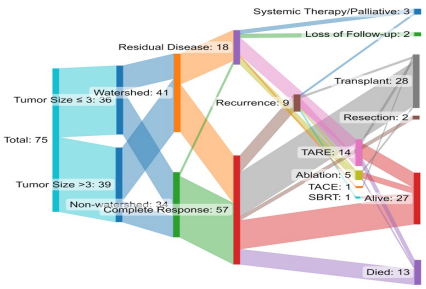
Statistical analysis

Descriptive statistics were used to summarize patient demographics and treatment parameters. Patients with complete and incomplete response were compared using t-test and chi-square/fisher exact tests. Logistic regression analysis was used to identify factors of incomplete response. Statistically significant predictors on univariable analysis were subjected to multivariable analysis. Survival analysis was performed using the Kaplan-Meier method and logrank test. Cox proportional hazard ratio regression analysis was used to identify the association between factors (tumor size and watershed area) and PFS. Subgroup analysis was performed based on tumor size and watershed area. P values <0.05 were considered statistically significant.

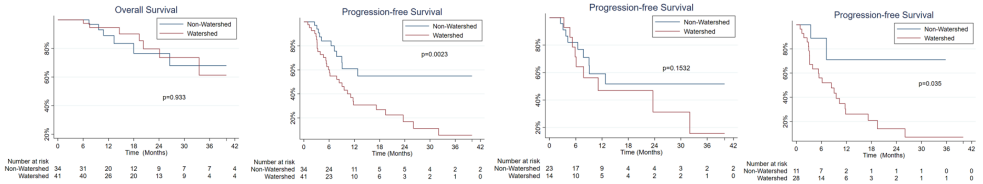
RESULTS

Baseline Characteristics

The mean age of 75 participants was 68.5 ±8.0 years with 25/75 (33.3%) being female. HCV (34.7%), NASH (24.0%), and EtOH (14.7%) were the most common etiologies of liver disease. The mean CTP, MELD score, and ALBI grade were 5.5 ± 1.2, 10.1 ± 4.3, and 1.6 ± 0.6, respectively. The mean dominant tumor size was 3.8 ± 2.2 cm. Tumor location by hepatic segments was listed in Table 1, with 41/75 (54.7%) located in the watershed zone. The mean dominant target dose was 222.6 ± 123.9 Gy with a mean lung-shunt fraction of 4.0 ± 3.9. The mean follow-up was 31.4 ± 24.4 months



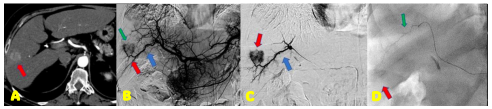
- Complete response was observed in 48 patients (64.0%). Eighteen patients (24.0%) had residual disease and target tumor recurrence occurred in 9 (12.0%).
- Logistic regression analysis suggested that both tumor size (p=0.015) and watershed zone were associated with incomplete response (p=0.011).
- A larger proportion of patients with complete response were bridged to resection/transplant (52.1% vs 22.2%, p=0.015).
- A total of 16/27 patients (59.3%) with incomplete response underwent catheter-directed angiography. Alternative vascular supply to the tumor was noted in nine (56.3%) patients.
- An alternative vessel was selected for embolization in 10/16 (62.5%) cases, which was not identified during index TARE mapping and treatment. CR, PR, and SD were achieved in 11 (72.3%), 3 (20.0%), 1 patients (6.7%), respectively.
- Among the 11 patients who did not undergo transarterial interventions, three were lost to follow-up and two were transitioned to palliative care. Among the remaining six patients, one patient was treated with stereotactic body radiation therapy and five patients underwent percutaneous ablation CR was achieved in all six patients who received second-line therapy (100%).



DISCUSSION

TARE has evolved from a palliative role for advanced stage HCC to a selective delivery method for early and very early-stage HCC with curative intent[1,13]. While previous research focused on identifying the threshold of absorbed dose required to achieve CPN and objective response[14-16], the present study suggests that tumor size and location also play significant roles in treatment effectiveness,

Despite results from the present study emphasizing the importance of preoperative planning, prospectively identifying alternative blood supply can be challenging. Not all feeders can be identified, especially if they involve the microvasculature beyond the scope of CT or cone beam CT visualization. Additionally, in cases where the tumor is being supplied by two branches of a single vessel, there is no consensus regarding whether two separate doses infused separately in two branches or a higher dose to the common vessel should be administered.



70 year old female with 3.1 cm segment 6/7 tumor (red arrow) on pre-interventional magnetic resonance imaging (A). Intraoperative angiogram shows tumor supply from both segment 6 branch (blue arrow) and a small parasitized segment 8 branch (green arrow). Figures C) and D) Superselective angiography through segment 6 branch and segment 8 branch, from which split dose was administered

By including larger tumors, the present study showed that tumor size was an independent factor for incomplete treatment. These findings align with recent data from the United Network for Organ Sharing database, which reported a correlation between tumor size and complete pathologic necrosis after locoregional therapy[26].

Larger tumors are often associated with high histologic grade and microvascular invasion. They are also more likely to straddle two vascular territories, receiving multiple arterial blood supplies[27], which in turn may contribute to heterogenous uptake. Further, it is plausible that in cases of larger tumors, increased pressure through the capillary bed increase back flow arterial pressure on the tumoral side, creating an environment that is not conducive for penetration of particles, affording protection for micro-areas of tumors, which can then continue to proliferate.

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