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Retrospective Study

Disease control and failure patterns of unresectable hepatocellular carcinoma following transarterial radioembolization with yttrium-90 microspheres and with/without sorafenib

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Abstract

BACKGROUND

Impressive survival outcome of our previous study in unresectable hepatocellular carcinoma (HCC) patients undergoing yttrium-90 glass microspheres transarterial radioembolization (TARE) with/without sorafenib according to individuals' disease burden, *i.e.*, intrahepatic tumor load (IHT) and adverse disease features (ADFs) might partly be confounded by other treatments and underlying hepatic

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function. Therefore, a dedicated study focusing on treatment response and assessment of failure patterns might be a way to improve treatment outcome in addition to patient selection based on the disease burden.

AIM

To assess the tumor response, disease control and patterns of disease progression following TARE with/without sorafenib in unresectable HCC patients.

METHODS

This retrospective study was conducted in successful TARE procedures with available pre- and post-treatment imaging studies ($n = 169$). Three treatment subgroups were (1) TARE only (*TARE_alone*) for IHT $\leq 50\%$ without ADFs, *i.e.*, macrovascular invasion, extrahepatic disease (EHD) and infiltrative/ill-defined HCC ($n = 63$); (2) TARE with sorafenib (*TARE_sorafenib*) for IHT $> 50\%$ and/or presence of ADFs ($n = 81$); and (3) TARE only for patients who could not receive sorafenib due to contraindication or intolerance (*TARE_no_sorafenib*) ($n = 25$). Objective response rate (ORR; consisted of complete response (CR) and partial response (PR)), disease control rate (DCR; consisted of CR, PR and stable disease) and failure patterns of treated, intrahepatic and extrahepatic sites were assessed using the modified response evaluation criteria in solid tumors. Time to progression (TTP) was calculated from TARE to the first radiologic progression at any site using Kaplan-Meier method. Identification of prognostic factors for TTP using the univariate Kaplan-Meier method and multivariate Cox proportional hazard model were performed in major population subgroups, *TARE_alone* and *TARE_sorafenib*.

RESULTS

The median radiologic follow-up time was 4.4 mo (range 0.5-48.8). In treated area, ORR was highest in *TARE_sorafenib* (53.1%), followed by *TARE_alone* (41.3%) and *TARE_no_sorafenib* (16%). In intrahepatic area, DCR remained highest in *TARE_sorafenib* (84%), followed by *TARE_alone* (79.4%) and *TARE_no_sorafenib* (44%). The overall DCR was highest in *TARE_alone* (79.4%), followed by *TARE_sorafenib* (71.6%) and *TARE_no_sorafenib* (40%). Dominant failure patterns were intrahepatic for both *TARE_alone* (44.5%) and *TARE_sorafenib* (38.4%). Extrahepatic progression was more common in *TARE_sorafenib* (32%) and *TARE_no_sorafenib* (40%) than in *TARE_alone* (12.7%). TTP was longest in *TARE_alone* (8.6 mo; 95%CI: 3.4-13.8), followed by *TARE_sorafenib* (5.1 mo; 95%CI: 4.0-6.2) and *TARE_no_sorafenib* (2.7 mo; 95%CI: 2.2-3.1). Pre-existing EHD (HR: 0.37, 95%CI: 0.24-0.56, $P < 0.001$) was a sole prognostic factor for TTP in *TARE_sorafenib* with no prognostic factor for TTP in *TARE_alone*.

CONCLUSION

TARE with/without sorafenib according to individuals' disease burden provided DCR approximately 70% with intrahepatic progression as dominant failure pattern. Extrahepatic progression was more common in procedures with initially high disease burden.

Key Words: Radioembolization; Selective internal radiotherapy; Tumor response; Pattern of progression; Time to progression; Sorafenib

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Core Tip: Hepatocellular carcinoma (HCC) patients treated with yttrium-90 transarterial radioembolization (TARE) alone for intrahepatic tumor load $\leq 50\%$ and TARE with sorafenib for intrahepatic tumor load $> 50\%$ and/or present macrovascular invasion, extrahepatic disease or infiltrative HCC yielded acceptable disease control rates of 79.4% and 71.6%, respectively. Between these 2 subgroups, incidence of intrahepatic progression was comparable (about 40%) but extrahepatic progression was much less common with TARE alone (12.7% vs 32%). Strategies that improve intrahepatic control for liver-only disease (dosimetry-based TARE) and extrahepatic control for

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metastatic disease (additional systemic therapy) could improve TARE outcome for unresectable HCC patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major health problems worldwide. It is the 6th most common malignancy with over 900000 new cases and 830000 deaths per year and the 3rd leading cause of cancer deaths[1]. HCC has a high mortality rate due to the fact that the majority of patients are diagnosed at an advanced stage of disease beyond the curative surgical options. This group of patients, sometimes called unresectable HCC patients, generally have two standard treatment options; local therapies, trans-arterial chemoembolization (TACE) and/or ablation, or systemic therapy[2-5].

Trans-arterial radioembolization (TARE) with yttrium-90 (Y-90) microspheres is an alternative local therapy option for unresectable HCC patients[2,5,6]. Currently, TARE is not an established treatment in most HCC treatment guidelines outside the United State. Consequently, each institution has its own algorithm for selecting TARE candidates. As a result, there exists marked variations in reported treatment outcome for TARE, depending on disease characteristics of enrolled patients[7-10].

At our institution, we offer TARE as monotherapy to patients with intrahepatic tumor (IHT) involvement less than or equal to 50% of total liver parenchyma (IHT ≤ 50%). Patients with IHT greater than 50% (IHT > 50%) or with advanced disease features (ADFs), defined as macrovascular invasion (MVI), extrahepatic disease (EHD) and infiltrative/ill-defined HCC, are candidates for TARE with systemic therapy which historically first line was sorafenib[11].

The clinical outcomes in terms of overall survival (OS) and progression-free survival (PFS) following TARE at our institution has been previously reported[12]. We reported median OS and PFS durations of 21.6 mo (95%CI: 6.1-37.1) and 9.1 mo (95%CI: 5.2-13.0), respectively, for HCC patients with IHT ≤ 50% treated with TARE only; while those for HCC patients treated with TARE in combination with sorafenib were 12.4 mo (95%CI: 9.1-15.6) and 5.1 mo (95%CI: 2.6-7.5), respectively. Better OS for HCC patients treated with TARE in combination with sorafenib was associated with patients with lower disease burden [IHT ≤ 50%, hazard ratios (HR) = 0.39, *P* = 0.004 and alpha-fetoprotein (AFP) < 400, HR = 0.5, *P* = 0.027]. Unilobar involvement (HR = 0.43, *P* = 0.029) correlated with better PFS in HCC patients with IHT ≤ 50% treated with TARE only. However, the OS and PFS survival outcomes reported was affected by several treatment combinations and not solely due to the effect of TARE itself. The objective of this study was to quantify and characterize the benefits of TARE as a local therapy. More specifically, we investigated the objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and, in the case of progression, the pattern and location of disease progression, for HCC patients treated at our institution with TARE, either as monotherapy or in combination with sorafenib.

MATERIALS AND METHODS

Patient selection

This institutional review board approved retrospective study was conducted in unresectable HCC patients who received TARE with Y-90 glass microspheres at The University of Texas MD Anderson Cancer Center (Houston, TX, United States) from November 16, 2010, to October 1, 2018. Inclusion criteria were successful TARE

procedures with available pre-treatment imaging study within 1 mo before TARE and at least one post-treatment imaging study within 2 mo after TARE ($n = 176$). In case of multiple follow-ups, all of imaging studies were done with the same imaging technique, *i.e.*, all contrast-enhanced computed tomography (CT) or all magnetic resonance imaging (MRI). Exclusion criteria were TARE procedures with restrictions on imaging interpretation and/or comparison, *i.e.*, non-contrast enhanced studies ($n = 5$), poor quality imaging study ($n = 1$) and hypo-vascular HCC ($n = 1$). A total of 169 procedures from 151 patients were finally included for analysis in this study.

Pretreatment evaluation

Pretreatment clinical histories and laboratory tests, including AFP and liver function tests were reviewed retrospectively in procedure-based fashion. Staging of disease and performance status were assessed by the Barcelona Clinic Liver Cancer (BCLC) staging system and Eastern Cooperative Oncology Group (ECOG) performance status, respectively[3,13]. Contrast-enhanced CT or MRI was used to evaluate cirrhosis, infiltrative tumor, MVI, EHD (consisted of lymph node and distant metastasis), number of tumors, lobar involvement and IHT.

Treatment

The technetium-99m macro aggregated albumin (Tc-99m MAA) pre-treatment scan was done to assess vascular anatomies and simulate Y-90 microspheres distribution in all procedures. TARE was usually performed within 1 mo after the Tc-99m MAA pre-treatment evaluation. Administration of Y-90 glass microspheres and sorafenib followed the manufacturer's instructions for use and per the direction of the treating oncologist[14,15]. Dose of sorafenib was adjusted on the basis of patients' tolerability and was reduced or withdrawn due to toxicity. Other treatments *e.g.*, TACE, chemotherapy, immunotherapy, *etc.* were given at the time of progression at the discretion of the treating oncologist.

Treatment strategies were classified into 3 subgroups according to patients' disease burden as assessed by IHT ($\leq 50\%$ *vs* $> 50\%$) and ADFs (absence *vs* presence) and patients' general conditions as considered by ECOG and underlying conditions at time of procedures: (1) *TARE_alone* was referred to TARE as a sole treatment in patients with IHT $\leq 50\%$ and absence of ADFs; (2) *TARE_sorafenib* was a combination of TARE and sorafenib in patients with IHT $> 50\%$ and/or presence of ADFs; and (3) *TARE_no_sorafenib* was TARE only treatment in patients who could not receive *TARE_sorafenib* due to contraindication or intolerance. All combined treatments were given concurrently or within a 1-month interval.

Post-treatment evaluation

Contrast-enhanced CT or MRI was obtained, usually within 2 mo after TARE and every 2-3 mo thereafter. All imaging studies were reinterpreted by a team, consisting of 4 interventional radiologists and 2 nuclear medicine physicians with diagnostic radiology training. All equivocal findings were determined by a consensus of 2 or more members in a team. The modified response evaluation criteria in solid tumors (mRECIST) was applied for response assessment[16].

Evaluation were performed in both intrahepatic and extrahepatic areas. Intrahepatic area was composed of treated area, referred to target lesions according to mRECIST and untreated area, referred to intrahepatic area outside treated area. Extrahepatic area was elsewhere outside the liver. Radiologic assessment was performed until initiation of new systemic treatment, last radiological follow-up, or patient's death, whichever came first. If patients received additional treatment for residual tumor in treated area (*e.g.*, TACE, radiofrequency ablation (RFA), surgical resection *etc.*), response assessment was not performed after these treatments.

Treatment response and failure patterns

Treatment response was referred to the best radiologic response at any time point during the evaluation period. Responses were categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) following the mRECIST. ORR was a sum of CR and PR. DCR was a sum of CR, PR and SD. These responses were reported according to the assessed areas which were (1) Treated area; (2) Intrahepatic area, composed of treated and untreated areas; and (3) Overall, composed of intrahepatic and extrahepatic areas.

In case of progression, failure patterns were evaluated. The failure patterns in patients that progressed were classified into 3 categories according to the site of first progression: (1) Treated area; (2) Untreated area; and (3) Extrahepatic area. The first

instance of progression in treated area at any time during the follow-up period was classified into 5 categorized: (1) Development of new HCC; (2) Recurrence/increased enhancement of previously treated HCC; (3) Development of new MVI; (4) Progressive MVI; and (5) Mixed patterns. Progression in untreated area was defined as appearance of new lesion or progression of pre-existing untreated lesion.

Estimation of TTP was performed for: (1) Treated area; (2) Untreated area; and (3) Overall. TTP was defined as the time from TARE to the first unequivocal radiologic progression at pre-specified sites (treated and untreated areas) or at any site (overall). Deaths or loss follow-up were censored at time of last follow-up without radiologic evidence of progression. Analysis on prognostic factors for TTP of overall disease was performed only in major population subgroups, *TARE_alone* and *TARE_sorafenib*.

Statistical analysis

Baseline characteristics, response rate and patterns of disease progression were analyzed by using descriptive statistics. TTP and its 95% confidence interval (95%CI) were estimated by using Kaplan-Meier method and comparison between subgroups were done with log-rank test. The univariate analysis was performed using Kaplan-Meier method. The HR were calculated by using a Cox proportional hazard regression. Factors in the univariate analysis with $P < 0.1$ were further analyzed in a multivariate analysis using Cox proportional hazard model. In the multivariate analysis, statistically significant P value was set at 0.05. All statistical analyses were conducted using IBM SPSS Statistics software for Windows, version 21.0 (Armonk, NY: IBM Corp.).

RESULTS

Baseline patient characteristics

The median age at time of diagnosis was 66 years (range 17-85) with most patients being male (76.2%). In our study cohort, 80/151 (53%) patients received TARE as their first treatment, 46/151 (30.5%) patients received local treatments prior to TARE, and 25/151 (16.6%) patients received systemic treatments prior to TARE. Local treatments included surgical resection, trans-arterial embolization, TACE, TARE with Y-90 resin microspheres, RFA, and microwave ablation; while systemic treatment included targeted therapy, immunotherapy, and chemotherapy. Most patients (133/151, 88.1%) received single TARE treatments only, with 16/151 (10.6%) and 2/151 (1.3%) patients receiving two and three separate TARE procedures, respectively.

Patient and tumor characteristics at time of TARE

Patient and tumor characteristics at time of TARE procedure ($n = 169$) stratified by treatments are shown on [Table 1](#); the two most common treatments were *TARE_alone* (37.3%) and *TARE_sorafenib* (47.9%). Majority of patients had ECOG status either 0 (48.5%) or 1 (48.5%). While the *TARE_alone* subgroup had similar proportions of BCLC B and C (41.3% vs 49.2%), the remaining subgroups predominantly consisted of BCLC C patients (> 80%). Most patients were Child-Pugh A (92.9%) and presented with cirrhosis (69.2%) and multiple tumors (83.4%). While the *TARE_alone* subgroup had similar proportions of unilobar and bilobar disease (52.4% vs 47.6%), the remaining subgroups predominantly consisted of ($\approx 70\%$) patients with bilobar disease.

TARE characteristics

TARE characteristic stratified by treatment are displayed on [Table 2](#). *TARE_alone* procedures had the lowest median lung shunt fraction (4.6%), median lung dose (4.7 Gy) and median administered activity (1.7 GBq). In all subgroups, lobar treatment was the most common TARE approach (39.1%), followed by whole liver treatment (27.8%).

Best radiologic response

The median radiologic follow-up time was 4.4 mo (range 0.5-48.8). The best radiologic mRECIST response categorized by treatment are shown on [Table 3](#). In the treated area, *TARE_sorafenib* subgroup had the highest ORR (53.1%), DCR (87.7%), and CR rate (11.1%), with *TARE_alone* subgroup having slightly lower ORR (41.3%) but similar DCR (85.7%). In the treated and intrahepatic areas, the two dominant response categories for *TARE_alone* and *TARE_sorafenib* were PR and SD, accounting for over 70% of all responses; the two dominant response categories for *TARE_no_sorafenib* were SD and PD, accounting for over 80%. The two highest overall DCRs were

Table 1 Patient and tumor characteristics at time of transarterial radioembolization procedures

Parameters	All procedures (n = 169)	TARE_alone (n = 63)	TARE_sorafenib (n = 81)	TARE_no_sorafenib (n = 25)
ECOG				
0	82 (48.5)	32 (50.8)	40 (49.4)	10 (40)
1	82 (48.5)	28 (44.4)	40 (49.4)	14 (56)
2	4 (2.4)	2 (3.2)	1 (1.2)	1 (4)
3	1 (0.6)	1 (1.6)	0	0
BCLC				
A	5 (3)	5 (7.9)	0	0
B	45 (26.6)	26 (41.3)	16 (19.8)	3 (12)
C	118 (69.8)	31 (49.2)	65 (80.2)	22 (88)
D	1 (0.6)	1 (1.6)	0	0
Child-pugh class				
A	157 (92.9)	57 (90.5)	78 (96.3)	22 (88.0)
B	12 (7.1)	6 (9.5)	3 (3.7)	3 (12.0)
AFP ¹				
< 400 ng/mL	118 (70.2)	54 (85.7)	52 (64.2)	12 (50)
≥ 400 ng/mL	50 (29.8)	9 (14.3)	29 (35.8)	12 (50)
Cirrhosis				
Absence	52 (30.8)	15 (23.8)	29 (35.8)	8 (32)
Presence	117 (69.2)	48 (76.2)	52 (64.2)	17 (68)
Infiltrative tumor				
Absence	133 (78.7)	63 (100)	58 (71.6)	12 (48)
Presence	36 (21.3)	0	23 (28.4)	13 (52)
Vascular invasion ²				
Absence	131 (78)	63 (100)	56 (70)	12 (48)
Presence	37 (22)	0	24 (30)	13 (52)
Extrahepatic disease				
Absence	137 (81.1)	63 (100)	60 (74.1)	14 (56)
Presence	32 (18.9)	0	21 (25.9)	11 (44)
Number of tumors				
Single	28 (16.6)	12 (19)	9 (11.1)	7 (28)
Multiple	141 (83.4)	51 (81)	72 (88.9)	18 (72)
Lobar involvement				
Unilobar	63 (37.3)	33 (52.4)	22 (27.2)	8 (32)
Bilobar	106 (62.7)	30 (47.6)	59 (72.8)	17 (68)
Intrahepatic tumor				
≤ 50%	116 (68.6)	63 (100)	37 (45.7)	16 (64)
> 50%	53 (31.4)	0	44 (54.3)	9 (36)
TARE procedures				
1	151 (89.3)	56 (88.9)	71 (87.7)	24 (96)
2	16 (9.5)	7 (11.1)	8 (9.9)	1 (4)
3	2 (1.2)	0	2 (2.5)	0

¹Unavailable AFP in one *TARE_no_sorafenib* patient.²Unavailable vascular invasion in one *TARE_sorafenib* patient.

Values represent number of procedures (%). TARE: Transarterial radioembolization; ECOG: Eastern cooperative oncology group; BCLC: Barcelona clinic liver cancer; AFP: Alpha-fetoprotein.

Table 2 Characteristics of transarterial radioembolization procedures

	All procedures (n = 169)	TARE_alone (n = 63)	TARE_sorafenib (n = 81)	TARE_no_sorafenib (n = 25)
LSF, %	6.0 (0.8-30.4)	4.6 (1.0-26.4)	6.1 (0.8-30.4)	6.3 (2.0-13.6)
Lung mean dose, Gy ¹	8.2 (0.3-29.7)	4.7 (0.3-29.2)	10.1 (0.5-29.7)	11.2 (2.0-29.2)
Mean dose to treated liver volume, Gy ¹	110 (80-135)	110 (80-135)	110 (80-135)	110 (80-135)
Interval between Tc-99m MAA and TARE, d ¹	20 (0-125)	21 (0-125 ²)	17 (0-44)	21 (10-34)
Administered activity, GBq	2.5 (0.3-8.1)	1.7 (0.3-6.3)	2.9 (0.6-8.1)	2.7 (0.8-5.9)
TARE approach, n (%)				
Whole liver ³	47 (27.8)	16 (25)	25 (31)	6 (24)
Lobar + segment	22 (13)	4 (6)	15 (18)	3 (12)
Lobar	66 (39.1)	23 (37)	30 (37)	13 (52)
Multiple segments	23 (13.6)	13 (21)	7 (9)	3 (12)
Single segment	11 (6.5)	7 (11)	4 (5)	0

¹Mean absorbed doses values for each treatment session.²The outlier interval of 125 d was from a single patient whose initial treatment plan was a whole liver treatment with sequential lobar infusion three weeks apart. His subsequent left lobar treatment was delayed for months because of his medical conditions. Administered activity of left lobar approach was calculated using the original Tc-99m MAA plan and re-evaluation CT scan performed prior to left lobar treatment.³Consisted of single infusion (n = 19), separate infusion (n = 24) and sequential infusion (n = 4).

Values represent median (range) unless otherwise stated. TARE: Transarterial radioembolization; Tc-99m MAA: The technetium-99m macro aggregated albumin.

observed in *TARE_alone* (79.4%) followed by *TARE_sorafenib* (71.6%) subgroups.

Overall failure patterns

Table 4 shows the overall failure patterns categorized by treatment. Disease progression were observed in 65.7% of all procedures. The lowest and highest rates of progression were noted in *TARE_alone* (57.1%) and *TARE_no_sorafenib* (72%) subgroups, respectively. The most common site of first disease progression was intrahepatic area for both *TARE_alone* (44.5%) and *TARE_sorafenib* procedures (38.4%). Extrahepatic progression (including both extrahepatic only and intrahepatic with extrahepatic) contributed to more than 30% cases in *TARE_sorafenib* (32%) and *TARE_no_sorafenib* (40%) subgroups, much higher than *TARE_alone* (12.7%) subgroup.

Intrahepatic failure patterns

Of total 169 procedures, intrahepatic progression was observed in 100 procedures (59.2%) with 75 procedures being progression in treated area (44.4%). **Table 5** stratifies intrahepatic failure patterns of disease progression when intrahepatic progression was observed by treatment subgroups (n = 100). The progression rates in treated area of *TARE_alone* (67.6%) subgroup was lower than that of *TARE_sorafenib* (81.6%) and *TARE_no_sorafenib* (70.6%) subgroups. The two most common cause of disease progression in treated area across all subgroups were the development of new HCC (34%), followed by the recurrence/increased enhancement of previously treated HCC (20%). The progression rate of untreated area was highest (32.4%) and lowest (18.4%) in *TARE_alone* and *TARE_sorafenib* subgroup, respectively.

TTP

Median overall TTP of all procedures was 4.9 mo (95%CI: 3.9-5.9). TTP of treated area,

Table 3 Summary of the best radiologic response (modified response evaluation criteria in solid tumors) following transarterial radioembolization

	All procedures (n = 169)	TARE_alone (n = 63)	TARE_sorafenib (n = 81)	TARE_no_sorafenib (n = 25)
Treated area				
CR	12 (7.1)	2 (3.2)	9 (11.1)	1 (4)
PR	61 (36.1)	24 (38.1)	34 (42)	3 (12)
SD	66 (39.1)	28 (44.4)	28 (34.6)	10 (40)
PD	30 (17.8)	9 (14.3)	10 (12.3)	11 (44)
OR	73 (43.2)	26 (41.3)	43 (53.1)	4 (16)
DC	139 (82.2)	54 (85.7)	71 (87.7)	14 (56)
Intrahepatic area				
CR	12 (7.1)	2 (3.2)	9 (11.1)	1 (4)
PR	58 (34.3)	22 (34.9)	33 (40.7)	3 (12)
SD	59 (34.9)	26 (41.3)	26 (32.1)	7 (28)
PD	40 (23.7)	13 (20.6)	13 (16)	14 (56)
OR	70 (41.4)	24 (38.1)	42 (51.9)	4 (16)
DC	129 (76.3)	50 (79.4)	68 (84)	11 (44)
Overall				
CR	10 (5.9)	2 (3.2)	7 (8.6)	1 (4)
PR	52 (30.8)	22 (34.9)	28 (34.6)	2 (8)
SD	56 (33.1)	26 (41.3)	23 (28.4)	7 (28)
PD	51 (30.2)	13 (20.6)	23 (28.4)	15 (60)
OR	62 (36.7)	24 (38.1)	35 (43.2)	3 (12)
DC	107 (69.8)	50 (79.4)	58 (71.6)	10 (40)

Values represent number of procedures (%). Objective response consisted of complete response (CR) and partial response (PR). Disease control consisted of CR, PR and stable disease. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; OR: Objective response; DC: Disease control; TARE: Transarterial radioembolization.

untreated area and overall stratified by treatment subgroups are provided in Table 6. Amongst the 3 subgroups, median overall TTP for TARE_alone was highest at 8.6 mo followed by TARE_sorafenib at 5.1 mo and TARE_no_sorafenib at 2.7 mo.

Prognostic factors of TTP

The result of univariate and multivariate analysis of TTP of TARE_alone and TARE_sorafenib are provided in Table 7. None of the variables explored were found to be statistically significant prognostic factors for TTP in TARE_alone subgroup. Both child-pugh class and lobar involvement with $P < 0.1$, in both univariate and multivariate analysis, could be considered marginally significant factors. For TARE_sorafenib subgroups, univariate analysis showed ECOG, EHD, and IHT to be statistically significant prognostic factors for TTP, that compressed to a single factor of EHD in multivariate analysis with a $P < 0.001$ (Table 8).

Lobar involvement marginally stratified TTP duration (unilobar 11.0 mo; 95%CI: 5.0-17.0 vs bilobar 5.6 mo; 95%CI: 2.4-8.8, $P = 0.058$) for TARE_alone patients. Statistically significant differences in TTP duration of TARE_sorafenib procedures were noted when stratified by EHD (absent 7.5 mo; 95%CI: 4.9-10.0 vs present 2.8 mo; 95%CI: 2.6-3.1, $P < 0.001$) and IHT ($\leq 50\%$ 7.7 mo; 95%CI: 5.1-10.3 vs $> 50\%$ 5.1 mo; 95%CI: 4.0-6.2, $P = 0.024$).

Table 4 Site of first progression in all cases of progression

	All procedures (n = 169)	TARE_alone (n = 63)	TARE_sorafenib (n = 81)	TARE_no_sorafenib (n = 25)
No progression	58 (34.3)	27 (42.9)	24 (29.6)	7 (28)
Progression	111 (65.7)	36 (57.1)	57 (70.4)	18 (72)
Intrahepatic only	67 (39.6)	28 (44.5)	31 (38.4)	8 (32)
Treated area only	36 (21.3)	16 (25.4)	17 (21)	3 (12)
Untreated area only	20 (11.8)	10 (15.9)	6 (7.4)	4 (16)
Both treated and untreated areas	11 (6.5)	2 (3.2)	8 (9.9)	1 (4)
Extrahepatic only	17 (10.1)	3 (4.8)	13 (16)	1 (4)
Intra- and extrahepatic	27 (16)	5 (7.9)	13 (16)	9 (36)

Values represent number of procedures (%). TARE: Transarterial radioembolization.

Table 5 First pattern of intrahepatic progression in cases with intrahepatic progression

	All procedures (n = 100)	TARE_alone (n = 34)	TARE_sorafenib (n = 49)	TARE_no_sorafenib (n = 17)
Progression in treated area	75 (75)	23 (67.6)	40 (81.6)	12 (70.6)
New HCC	34 (34)	12 (35.3)	19 (38.8)	3 (17.6)
Recurrence/increased enhancement of previously treated HCC	20 (20)	5 (14.7)	9 (26.5)	6 (35.3)
With new MVI	8 (8)	2 (5.9)	6 (12.2)	0
With progressive MVI	3 (3)	0	3 (6.1)	0
With mixed patterns ¹	10 (10)	4 (11.8)	3 (6.1)	3 (17.6)
Progression in untreated area	25 (25)	11 (32.4)	9 (18.4)	5 (29.4)

¹New HCC with one or more other patterns (n = 11) and new MVI with increased enhancement of previously treated HCC (n = 1). Values represent number of procedures (%). TARE: Transarterial radioembolization; HCC: Hepatocellular carcinoma; MVI: Macrovascular invasion.

DISCUSSION

TARE has been an increasing treatment option for unresectable HCC patients[2,5,6]. Treatment outcomes of TARE in the literatures varied considerably, depending on several factors such as the characteristics and stage of enrolled patients, and the experience and preferences of investigators with TARE[7-10,17-20]. In this study, we reported disease control and objective response with TARE for unresectable HCC per our institutional treatment algorithm which may include combination treatment with sorafenib based on two unique features: disease burden assessment by IHT and presence of ADFs. Pertinent findings in our study included development of new HCC tumors as a major intrahepatic failure pattern, disease progression in treated area and extrahepatic area as the most common overall disease failure patterns in *TARE_alone* and *TARE_sorafenib* procedures, respectively.

Our finding that 70% of treated lesions could achieve PR or SD was consistent with the previous studies[9,21]. Interestingly, the *TARE_sorafenib* subgroup provided the highest response rate (ORR 53.1% and CR 11.1%) followed by the *TARE_alone* subgroup (ORR 41.3% and CR 3.2%) which consisted of patients without ADFs or lower IHT. When comparing between subgroups with similar disease burden, DCR of *TARE_sorafenib* was much higher than *TARE_no_sorafenib* (87.7% vs 56%). Furthermore, median TTP duration of treated area for *TARE_sorafenib* was much longer than *TARE_no_sorafenib* (7.5 vs 3.6 mo). Acknowledging that antiangiogenic effect of sorafenib could promote oxygenation to the core of tumor and thereby increase tumor sensitivity to radiation[19,22,23], we postulated that better disease control observed for *TARE_sorafenib* might be attributed to the beneficial effect of sorafenib.

Table 6 Time to progression

	All procedures (n = 169)	TARE_alone (n = 63)	TARE_sorafenib (n = 81)	TARE_no_sorafenib (n = 25)
Treated area				
Censored patients	87	39	37	11
TTP, mo	7.8 (6.4-9.3)	12.3 (10.4-14.1)	7.5 (6.2-8.8)	3.6 (0.8-6.4)
Untreated area				
Censored patients	119	47	59	13
TTP, mo	12.8 (4.3-21.3)	22.9 (10.2-35.7)	11.9 (8.0-15.8)	3.6 (2.1-5.1)
Overall				
Censored patients	58	27	24	7
TTP, mo	4.9 (3.9-5.9)	8.6 (3.4-13.8)	5.1 (4.0-6.2)	2.7 (2.2-3.1)

TTP values represent median (95%CI) in months. TTP: Time to progression; TARE: Transarterial radioembolization.

It is noteworthy that in subgroups without sorafenib, *TARE_alone* and *TARE_no_sorafenib*, decrease of DCRs of treated area and intrahepatic area were 6.3 percentage points (from 85.7% to 79.4%) and 12 percentage points (from 56% to 44%), respectively. In the meantime, decrease of DCR of *TARE_sorafenib* was only 3.7 percentage points (from 87.7% to 84%). Given that intrahepatic area consisted of treated and untreated areas, disease progression in untreated area should make DCR of intrahepatic area lower than DCR of treated area. Thus, a less prominent change of DCR of *TARE_sorafenib* subgroup, compared to others might suggest that addition of sorafenib to TARE could reduce disease progression in untreated area and thereby provided a better intrahepatic control.

The most common intrahepatic failure patterns according to several studies, including this work was the development of new HCC, both in treated or untreated areas[9,21,24]. This might be explained by the hypothesis that newly detected HCC during follow-up might be pre-existing undetectable microscopic HCC. These lesions have generally less developed arterial blood supply compared to the macroscopic ones, and therefore, they do not achieve the tumoricidal dose from TARE. These small tumors might subsequently progress giving the impression of new HCC following TARE[21,24,25].

Regarding the patterns of disease progression, *TARE_alone* which had lowest disease burden was the only subgroup that the most common site of first disease progression was treated area ($n = 16/36$, 44.4%). Additionally, disease progression of *TARE_alone* were mostly limited in intrahepatic area ($n = 28/36$, 77.8%). Therefore, aggressive TARE based on advanced and personalized dosimetry with radiation dose to tumor exceeding tumoricidal threshold, around 200 Gy as claimed by several studies, might increase response of treated area[26,27]. We acknowledge that tumor specific dose estimates may further stratify tumor response status, but the retrospective calculation of tumor doses are beyond the scope of this work. Furthermore, cone-beam CT (CBCT) has been proven to demonstrate additional tumors overlooked by angiography and Tc-99m MAA scan[28]. Consequently, incorporating CBCT to treatment planning might be another way to improve intrahepatic control with TARE.

Rates of first disease progression in extrahepatic area of *TARE_sorafenib* (32%) and *TARE_no_sorafenib* (40%) subgroups were obviously higher than that of *TARE_alone* subgroup (12.7%). We hypothesized that this might be a result of higher baseline disease burden of these subgroups compared with *TARE_alone* (IHT > 50% and/or ADFs vs IHT ≤ 50% without ADFs). *TARE_alone* was also the only cohort without EHD whereas *TARE_sorafenib* and *TARE_no_sorafenib* had EHD in 25.9% and 44.4% cases, respectively. Considering *TARE_sorafenib* subgroup as an example, given that overall disease control was a consequence of both intrahepatic and extrahepatic control, a decrease of DCR, from 84% of intrahepatic area to 71.6% of overall could contemplate that extrahepatic progression occurred in a considerable number of *TARE_sorafenib* procedures (12.4%). Hence, enhancement of extrahepatic control by introducing a more potent systemic therapy might be a key of more effective treatment in this group of patients.

Table 7 Univariate analysis of time to progression using Kaplan-Meier method

Prognostic factors	TARE_alone (n = 63)				TARE_sorafenib (n = 81)			
	n ¹	c ¹	HR (95%CI)	P value	n ¹	c ¹	HR (95%CI)	P value
ECOG ²								
0	32	13	0.57 (0.27-1.19)	0.131	40	8	1.96 (1.11-3.45)	0.018
1	28	13			40	16		
BCLC stage ³								
B	26	9	0.62 (0.30-1.28)	0.193	16	5	1.02 (0.53-1.99)	0.947
C	31	14			65	19		
Child-pugh class								
A	57	24	0.35 (0.10-1.22)	0.083	78	23	0.75 (0.18-3.13)	0.694
B	6	3			3	1		
AFP								
< 400 ng/mL	54	22	0.73 (0.25-2.10)	0.556	52	15	0.78 (0.45-1.35)	0.378
≥ 400 ng/mL	9	5			29	9		
Cirrhosis								
Absence	15	6	1.08 (0.51-2.32)	0.835	29	7	1.39 (0.82-2.38)	0.222
Presence	48	21			52	17		
Number of tumors								
Single	12	6	0.71 (0.29-1.73)	0.449	9	5	0.59 (0.21-1.65)	0.308
Multiple	51	21			72	19		
Lobar involvement								
Unilobar	33	16	0.52 (0.27-1.04)	0.058	22	7	0.95 (0.52-1.74)	0.870
Bilobar	30	11			59	17		
Infiltrative tumor ⁴								
Absence					58	15	1.14 (0.62-2.09)	0.673
Presence					23	9		
MVI ⁴								
Absence					56	12	1.76 (0.92-3.35)	0.081
Presence					24	11		
EHD ⁴								
Absence					60	23	0.37 (0.21-0.65)	< 0.001
Presence					21	1		
IHT ⁴								
≤ 50%					37	15	0.54 (0.32-0.93)	0.024
> 50%					44	9		

¹Total patients (n) and censored patients (c).

²ECOG 2 (n = 2 TARE_alone, n = 1 TARE_sorafenib) and ECOG 3 (n = 1 TARE_alone, n = 0 TARE_sorafenib) excluded.

³BCLC A (n = 5 TARE_alone, n = 0 TARE_sorafenib) and BCLC D (n = 1 TARE_alone, n = 0 TARE_sorafenib) excluded.

⁴Absent in all TARE_alone procedures according to institutional treatment algorithm.

Hazard ratios (HR) with Cox proportional hazard regression and P value with log-rank test. TARE: Transarterial radioembolization; ECOG: Eastern cooperative oncology group; BCLC: Barcelona clinic liver cancer; AFP: Alpha-fetoprotein; MVI: Macrovascular invasion; EHD: Extrahepatic disease; IHT: Intrahepatic tumor.

Table 8 Multivariate analysis of time to progression using Cox proportional hazard model

Population	Prognostic factors	<i>n</i> ¹	<i>c</i> ¹	HR (95%CI)	<i>P</i> value
<i>TARE_alone</i> (<i>n</i> = 63)	Child-pugh class				
	A	57	24	0.32 (0.09-1.10)	0.073
	B	6	3		
	Lobar involvement				
	Unilobar	33	16	0.51 (0.26-1.00)	0.051
<i>TARE_sorafenib</i> (<i>n</i> = 81)	Bilobar	30	11		
	ECOG ²				
	0	40	8	0.85 (0.59-1.22)	0.370
	1	40	16		
	MVI				
	Absence	56	12	1.15 (0.74-1.80)	0.532
	Presence	24	11		
	EHD				
	Absence	60	23	0.37 (0.24-0.56)	< 0.001
	Presence	21	1		
	IHT				
	≤ 50%	37	15	0.72 (0.49-1.06)	0.096
	> 50%	44	9		

¹Total patients (*n*) and censored patients (*c*).

²ECOG 2 (*n* = 1) and ECOG 3 (*n* = 0) excluded.

TARE: Transarterial radioembolization; ECOG: Eastern cooperative oncology group; MVI: Macrovascular invasion; EHD: Extrahepatic disease; IHT: Intrahepatic tumor.

In a prospective study on efficacy of TARE in unresectable HCC patients with IHT ≤ 50%, variables affecting TTP were tumor diameter (> 6 cm *vs* ≤ 6 cm., HR 3.65; 95%CI: 1.39-9.59, *P* = 0.0087) and treatment response according to European Association for the study of the liver (PD *vs* CR + PR + SD, HR 22.48; 95%CI: 4.53-111.61, *P* = 0.0001) [7]. Nevertheless, there was no prognostic factor of TTP for *TARE_alone* subgroup in our study. We presumed that our institutional selection criteria for *TARE_alone*, IHT ≤ 50% and absence of EHD, MVI and infiltrative/ill-defined HCC probably made this group of patients had relatively low disease burden. *TARE_alone* was rather effective for all, therefore, minor differences in baseline characteristics might not affect the duration of TTP.

EHD at time of procedure (absence *vs* presence; HR 0.37; 95%CI: 0.24-0.56, *P* < 0.001) was a sole prognostic factor of TTP for *TARE_sorafenib*. A quarter of *TARE_sorafenib* procedures also had EHD before treatment (25.9%) and 32% of progression of *TARE_sorafenib* subgroup was extrahepatic area first. All of these findings supported a significance of pre-existing EHD on disease control. Taking all of these findings together, *TARE_sorafenib* for patient with pre-existing EHD might be inadequate. More aggressive treatment such as TARE with other novel agents should be considered for future clinical trial.

In this study, we demonstrated a correlation between disease burden, given treatment and disease control. Moreover, we successfully identified some unique failure patterns which could guide possible ways to provide a better disease control. To the best of our knowledge, the current study was one of very few studies addressing this kind of issues. Our outcome measurements, TTP and tumor response were both direct parameters reflecting efficacy of treatment[8,29]. Additionally, treatment response of all procedures were re-assessed by using the mRECIST. Anti-tumor effects of TARE and sorafenib might not result in tumor shrinkage but they could produce tumor necrosis[30,31]. As a result, assessment on the basis of enhancement like mRECIST was more appropriate to our study than size-based

evaluation of response evaluation criteria in solid tumors.

Several limitations of our study related to natures of retrospective study. First, we acknowledged that mixed imaging techniques for evaluation of treatment response (CT $n = 102$, 60.4% and MRI $n = 67$, 39.6%) might produce some heterogeneities in diagnostic performance. Second, median radiologic follow-up duration was only 4.4 mo. This period was rather short because many patients that were referred for TARE at our institution had only 1 imaging follow-up study at our institution. Furthermore, all of 3 post-treatment imaging studies done within the first month after TARE showed rapid disease progression, either in treated area (*TARE_sorafenib* $n = 1$) or extrahepatic area (*TARE_no_sorafenib* $n = 2$). Lastly, number of patients in *TARE_no_sorafenib* subgroup was too limited to be statistically meaningful.

In the present study, we found that disease progression in *TARE_alone* subgroup usually limited to intrahepatic area and majority of progression originated in treated area. Therefore, either local or systemic treatment which promotes disease control at treated area might lead to better overall disease control. In contrast, disease progression in *TARE_sorafenib* subgroup tends to be extrahepatic and pre-existing EHD could worsen disease control. Study on using of TARE in combination with novel systemic therapy that is more potent than sorafenib might be required to improve treatment outcome.

CONCLUSION

TARE_alone for procedures with IHT $\leq 50\%$ and absence of ADFs and *TARE_sorafenib* for procedures with IHT $> 50\%$ and/or presence of ADFs could provide acceptable disease control of approximately 70% in unresectable HCC patients. Intrahepatic progression was the most common failure pattern in both subgroups but extrahepatic progression was far more common in *TARE_sorafenib*. Strategies that improve intrahepatic control for liver-only disease (dosimetry-based TARE) and extrahepatic control for metastatic disease (additional systemic therapy) could improve TARE outcome for HCC patients.

ARTICLE HIGHLIGHTS

Research background

Survival outcome of unresectable hepatocellular carcinoma (HCC) patients post yttrium-90 (Y-90) glass microspheres transarterial radioembolization (TARE) with/without sorafenib according to individual's disease burden might partly be confounded by subsequent treatments. Therefore, a study on tumor response might better represent effectiveness of TARE with/without sorafenib.

Research motivation

Disease control and failure patterns following TARE with/without sorafenib might suggest how to intensify treatment to improve treatment outcome.

Research objectives

This study describes the disease control and failure patterns of unresectable HCC patients who underwent Y-90 microspheres TARE with/without sorafenib according to individuals' disease burden, *i.e.*, intrahepatic tumor (IHT) and adverse disease features (ADFs), consisting of macrovascular invasion, extrahepatic disease (EHD) and infiltrative/ill-defined HCC.

Research methods

Y-90 microspheres TARE procedures with available pre and post-treatment imaging studies ($n = 169$) were retrospectively reviewed and categorized into 3 subgroups on the basis of treatment given and individuals' disease conditions: (1) *TARE_alone*, referred to TARE only for IHT $\leq 50\%$ without ADFs ($n = 63$); (2) *TARE_sorafenib*, referred to TARE with sorafenib for IHT $> 50\%$ and/or presence of ADFs ($n = 81$); and (3) *TARE_no_sorafenib*, referred to TARE only for patients with contraindication to sorafenib or side effect intolerance ($n = 25$). Disease control rate (DCR; consisted of complete response, partial response and stable disease) and failure patterns of treated, intrahepatic and extrahepatic sites were assessed using mRECIST.

Research results

The key findings were that *TARE_alone* for procedures with IHT $\leq 50\%$ and absence of ADFs and *TARE_sorafenib* for procedures with IHT $> 50\%$ and/or presence of ADFs could provide comparable DCR (79% *vs* 72%) with similar incidence of intrahepatic progression (44.5% *vs* 38.5%). However, extrahepatic progression was much more common in *TARE_sorafenib* procedures (13% *vs* 32%).

Research conclusions

DCR of *TARE_alone* and *TARE_sorafenib* procedures were similar (about 70%). Intrahepatic progression was dominant failure pattern for both (about 40%) but extrahepatic progression was far more common in *TARE_sorafenib* procedures.

Research perspectives

On the basis of findings in the present study, we suggested further investigations on additional treatment to enhance disease control. Disease progression in *TARE_alone* subgroup usually originated in treated area and mostly limited to intrahepatic area. Thus, local or systemic treatment which potentiates disease control at treated lesion might result in better overall disease control. In *TARE_sorafenib* subgroup, extrahepatic progression was common and pre-existing EHD could worsen disease control. Study on novel systemic therapy that is more potent than sorafenib might be required to improve treatment outcome in this group of patients.

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