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Research Article

Yttrium-90 Radioembolization Therapy for Combined Hepatocellular and Cholangiocarcinoma

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Keywords
Hepatocellular carcinoma · Cholangiocarcinoma · Mixed hepatocellular-cholangiocarcinoma · Propensity score matching · Transarterial radioembolization

Abstract
Purpose: To report outcomes of transarterial radioembolization (TARE) using glass microspheres for the treatment of mixed hepatocellular-cholangiocarcinoma (HCC-CC) in a propensity-matched study. ***Material and Methods:*** Between 2013 and 2019, 10 consecutive patients with histologically confirmed HCC-CC received TARE of a targeted territory using glass microspheres as a primary initial treatment. Baseline demographics in addition to tumor distribution, Child Pugh score, and BCLC were recorded. Tumor response was assessed according to modified RECIST criteria. The HCC-CC cohort was matched to the HCC cohort, and objective response and survival analysis was performed. ***Results:*** In the HCC-CC cohort, patients had a 70% objective response rate (ORR), and in the HCC cohort, patients had a 90% ORR after matching (p = 0.54). The median overall survival (OS) for HCC patients was 12.3 months (95% CI: 6.0–17.4 months) in the matched population, and for HCC-CC patients, the median OS was 15.2 months (95% CI: 2.7–20.2 months) (p = 0.98). The median progression-free survival (PFS) for HCC patients was 11.6 months (95% CI: 2.53–19.3 months) in the matched population, and for HCC-CC patients, the median PFS was 15.2 months (95% CI: 2.7–20.2 months) (p = 0.94). The median transplant-free survival (TFS) for HCC patients was 12.3 months (95% CI: 6.0–17.4 months) in the matched population, and for HCC-CC patients, the median TFS was 15.2 months (95% CI: 2.7–20.2 months) (p = 0.98). ***Conclusions:*** While outcomes of combined HCC-CC are poor and optimal treatment remains undefined, TARE appears to represent an effective locoregional treatment with survival outcomes similar to that of HCC treated by TARE.

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Introduction

Cholangiocarcinoma (CC) and hepatocellular carcinoma (HCC) are the 2 most common forms of primary liver tumors [1]. While HCC can be diagnosed strictly from imaging, CC requires histological analysis for diagnosis. Combined HCC-CC is seen in about 0.4–14.2% of patients with primary liver tumors and is distinguished by having histological characteristics of both HCC and CC [2]. The mainstay treatment for HCC-CC is tumor resection although the overall prognosis is poor. Specifically, the median overall survival time for patients receiving resection is 18–22 months compared to 6–12 months in unresectable cases. The median time to recurrence for this aggressive tumor is 5.4 months with a 5-year survival rate after resection of 30% [2, 3].

In nonresectable or recurrent cases of HCC-CC, nonsurgical approaches to treatment have commonly been used. Some of these locoregional therapies (LRT) include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and ablative approaches. While there is an overall lack of studies looking at the safety and efficacy of LRT for HCC-CC, recent literature has suggested that LRT for HCC-CC is not as safe compared to HCC [4]. This study was however limited by a small sample size with heterogeneity in the treatments utilized. TARE is a safe and effective method of treatment for HCC with favorable survival and objective response. Furthermore, it is an effective means to bridge liver cancer patients to transplant and therefore is widely used in nonresectable HCC [5]. It is less clear whether TARE can also be used to effectively manage patients with nonresectable HCC-CC. The purpose of this study was to therefore assess the efficacy of TARE as a primary treatment strategy for the treatment of nonresectable HCC-CC compared to HCC by using propensity score matching.

Materials and Methods

Patient Selection

Institutional board review approval was obtained for this single-institution retrospective study. Informed consent was not required due to the retrospective review of medical records during this study. Between March 2013 and April 2019, a total of 133 patients (94 males and 39 females, mean age 64, range 52–86) underwent radioembolization treatment for HCC or HCC-CC at an urban tertiary care academic center with an active liver transplantation program. HCC was diagnosed from contrast imaging studies based on AASLD guidelines [6]. HCC-CC was diagnosed based on histopathological studies performed by a pathologist with specialization in liver disease. The cohorts' baseline characteristics are listed in Table 1. Data were handled in compliance with the Health Insurance Portability and Accountability Act. Retrospective clinical, radiological, and oncologic data were recorded.

TARE Protocol

TheraSphere® (Boston Scientific; Marlborough, MA, USA) glass microspheres conjugated with radioactive Y-90 particles were used for all radioembolization procedures as the primary treatment strategy for both HCC and HCC-CC patients. Dose calculations for both treatments were made after technetium-99 macroaggregated albumin (MAA) mapping procedures were done to delineate tumor vascular distribution, identify and embolize potential nontarget enterohepatic vessels, and calculate hepatopulmonary shunt fractions. Y-90 administration was performed by one of four interventional radiologists with greater than 5 years of experience with radioembolization. Dosimetry using the medical internal radiation dose model for lobar and segmental treatments was calculated between 120 and 200 Gy, respectively, for all treatments. All doses were delivered the subsequent Tuesday through Friday from the date of calibration. As per protocol, all treatments were calculated to deliver <30 Gy to the lungs per single treatment and <50 Gy cumulatively.

Measuring of Tumor Response

Imaging was performed on each patient at 3 and 6 months after treatment. Tumor response was graded as either complete (CR), partial (PR), stable (SR), or progression (PGR) based on contrast enhancement in follow-up imaging following the American Association for the Study of Liver Diseases and *Journal of the*

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Table 1. Summary of baseline characteristics of HCC and HCC-CC patients receiving radioembolization before and after matching

	Before matching		*p* value	After matching	
	HCC (*n* = 123)	HCC-CC (*n* = 10)		HCC-CC (*n* = 10)	HCC (*n* = 10)
Age	66.5	64.5		64.5	66.8
Gender					
M	72.30%	50.00%	0.169	50.00%	40.00%
F	27.60%	50.00%		50.00%	60.00%
ECOG					
0	34.40%	30%	0.882	30%	30%
1	63.20%	70%		70%	70%
2	2.40%	0%		0%	0%
3	0%	0%		0%	0%
CPS					
A	71.50%	100%	0.046	100%	100%
B	27.60%	0%		0%	0%
C	0.80%	0%		0%	0%
BCLC					
A	67.40%	80%	0.59	80%	70%
B	26.80%	20%		20%	30%
C	5.80%	0%		0%	0%

National Cancer Institute (AASLD-JNCI) guidelines for evaluating liver tumor response using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) assessment tool [7]. Objective response was characterized as either partial or complete response on imaging.

Evaluation of Measured Outcomes

The 3 main outcomes measured were overall survival (OS), progression-free survival (PFS), and transplant-free survival (TFS). OS was characterized as the time from treatment to time of death. Patients were followed until their death or last clinical encounter. PFS was characterized as the time from treatment to either the last clinical encounter, death, or disease progression on imaging. Lastly, TFS was characterized as the time from initial treatment to last clinical encounter, death, or orthotopic liver transplantation. The conclusion of the study was August 2019.

Statistical Analysis

The purpose of statistical analysis in this study was to simulate a randomized study for patients receiving TARE for either HCC or HCC-CC with similar baseline characteristics. The baseline characteristics considered were gender, age, BCLC, ECOG, and CPS. These findings are summarized in Table 1. Each of these baseline characteristics was evaluated for statistical significance using either Kruskal-Wallis or Fisher tests. Using these baseline characteristics, patients with HCC-CC were matched to patients with HCC using propensity score matching. Each patient with HCC-CC was matched to a patient with HCC using the nearest neighbor approach [8]. The characteristics of the matched population are summarized in Table 1. OS, PFS, and TFS were evaluated before and after matching using the Kaplan-Meier analysis. Survival data between HCC or HCC-CC patients were analyzed after matching using the Cox proportional hazard model. Objective response was compared for statistical significance using Fisher tests. All statistical analysis was performed using RStudio 3.6.1 (RStudio Inc., Vienna, Austria).

Results

Baseline Characteristics

The only baseline characteristic that differed in the prematch cohort was CPS ($p = 0.046$) from Fisher testing. The other *p* values are summarized in Table 1. Concomitant therapies in addition to TARE therapy are listed in Table 2 for the matched HCC and HCC-CC cohorts.

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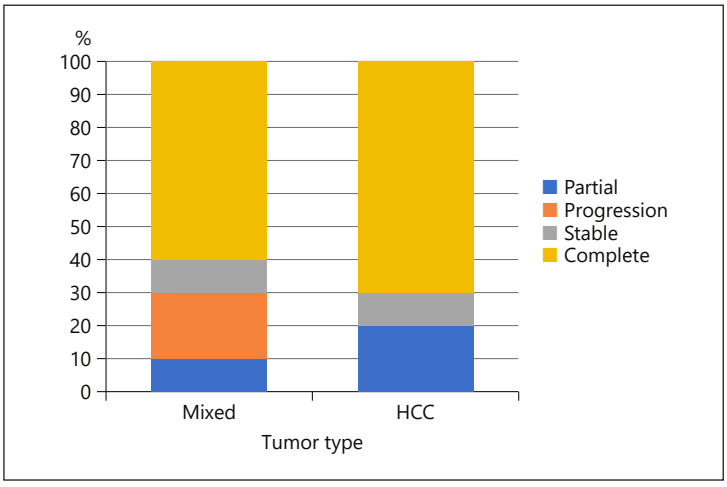

Fig. 1. A graphical representation of mRECIST imaging response of HCC versus HCC-CC patients after matching. Response is classified as either partial, complete, stable, or progression. This is represented as a percent. Yellow signifies complete response, orange signifies progression on imaging, gray signifies stable response, and blue signifies complete response on imaging based on mRECIST imaging criteria.

Table 2. Concomitant therapy for HCC and HCC-CC patients

Concomitant therapy	HCC only patients (n = 10), %	HCC-CC patients (n = 10), %
Sorafenib	30	0
Irinotecan and fluorouracil	0	10
Pembrolizumab	0	10
Gemcitabine and cisplatin	0	70
No other therapy	70	10

Imaging Response

In the HCC-CC cohort, patients had 20% PGR, 10% SR, 10% PR, and 60% CR with a 70% objective response rate (ORR). In the HCC cohort, patients had a 26.8% PGR, 15.4% SR, 24.4% PR, and 33.4% CR with a 57.8% ORR before matching. After matching, HCC patients had 0% PGR, 10% SR, 20% PR, and 70% CR with a 90% ORR. This is summarized in Figure 1. After matching, statistical significance of response was evaluated using the Fisher test. There was no statistically significant difference in objective response after matching with $p = 0.54$.

Overall Survival

Before matching, the median OS in HCC was 23.2 months (95% CI: 18.4–25.3 months). After matching, the median OS for HCC patients was 12.3 months (95% CI: 6.0–17.4 months). For HCC-CC patients, before and after matching, the median OS was 15.2 months (95% CI: 2.7–20.2 months). The Kaplan-Meier survival curves are shown in Figure 2. After matching, the Cox proportional hazard model was applied and showed a HR of 0.98 ($p = 0.98$).

Progression-Free Survival

Before matching, the median PFS in HCC was 9.1 months (95% CI: 7.6–12.3 months). After matching, the median PFS for HCC patients was 11.6 months (95% CI: 2.53–19.3 months). For HCC-CC patients, before and after matching, the median PFS was 16.6 months (95% CI: 2.7–25.2 months). The Kaplan-Meier survival curves are shown in Figure 2. After matching, the Cox proportional hazard model was applied and showed a HR of 1.05 and $p = 0.94$.

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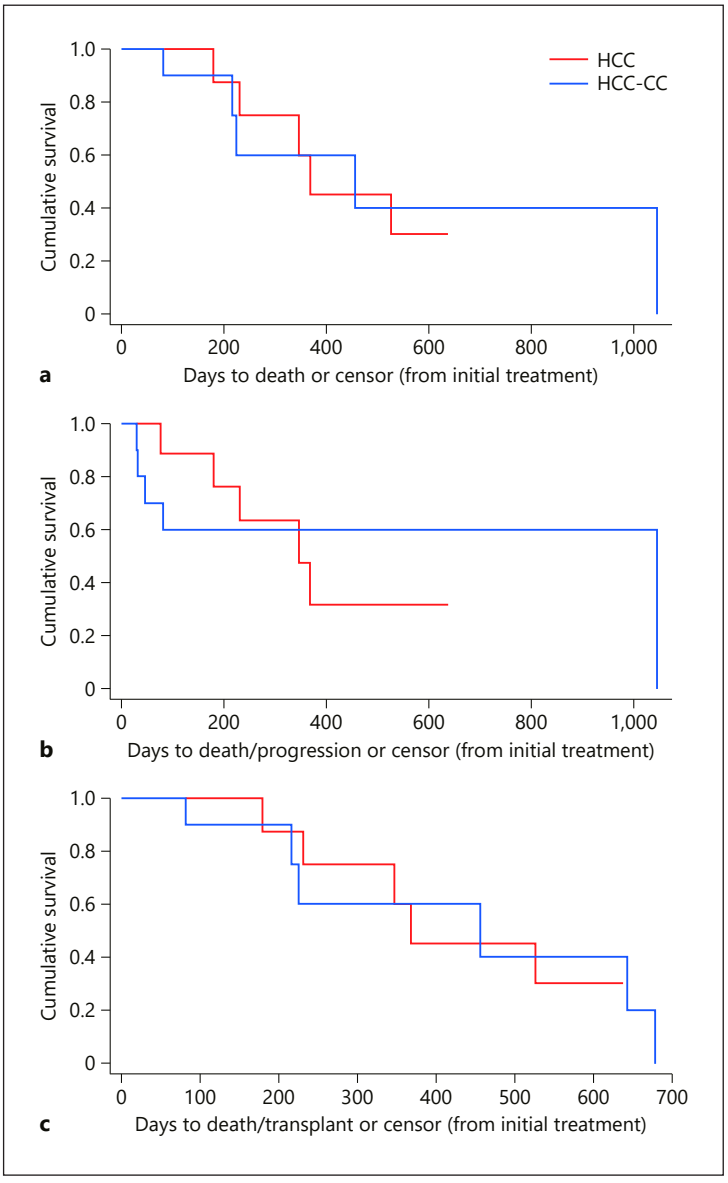

Fig. 2. A Kaplan-Meier survival curve for OS, PFS, and TFS in both HCC and HCC-CC patients after matching. The *X*-axis represents days till sensor or an event (death, progression, or transplant). The *Y*-axis represents the cumulative proportion of surviving proportion. Red signifies the HCC population receiving TARE while blue signifies the mixed population. OS, overall survival; PFS, progression-free survival; TFS, transplant-free survival.

Transplant-Free Survival

Before matching, the median TFS in HCC was 13.7 months (95% CI: 2.73–21.4 months). After matching, the median TFS for HCC patients was 12.3 months (95% CI: 6.0–17.4 months). For HCC-CC patients, before and after matching, the median TFS was 15.2 months (95% CI: 2.73–21.4 months). The Kaplan-Meier survival curves are shown in Figure 2. After matching, the Cox proportional hazard model was applied and showed a HR of 0.98 and $p = 0.98$.

Discussion

The potential for TARE as a primary treatment for unresectable HCC-CC was reported by Fowler et al. [9] in a retrospective study that investigated the survival outcomes of HCC-CC patients undergoing TACE or TARE. In the study, TARE demonstrated an overall ORR of 50%

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(*n* = 6) compared to 20% with TACE (*n* = 6) [9]. The median PFS was 8.3 months and OS was 16.0 months. Similarly, the potential for LRT as an initial treatment for HCC-CC was reported by Huang et al. [4]. In this study, the authors performed a retrospective propensity-matched study evaluating the efficacy of multiple methods of LRT including TACE, TARE, and RF ablation in patients with HCC and HCC-CC. Their results showed a decreased PFS in patients with HCC-CC, with a median PFS of 2.4 months in patients with HCC-CC and a median PFS of 7.4 months in patients with HCC [4]. Specifically, no statistically significant differences in objective response were observed between the 2 cohorts, suggesting the utility in LRT for disease control in HCC-CC similar to HCC. The propensity score matching allowed for similar baseline characteristics between patients as well as a pseudo-randomized study; however, due to the heterogeneity of treatments, it was difficult to delineate the specific benefit of any one locoregional therapy.

The present study attempted to overcome some of these aforementioned limitations by attempting to look specifically at TARE as a primary treatment for HCC-CC with a propensity-matched HCC cohort. It demonstrated no statistically significant difference in objective response between HCC-CC versus HCC patients (70 vs. 90%, $p = 0.54$). Further, all three of the performed survival analyses demonstrated no differences between patients receiving TARE for either HCC or HCC-CC in the matched cohorts. These findings dispute previously stated literature that states poorer survival outcomes for LRT in patients with HCC-CC as it found that TARE provided similar objective response, PFS, and OS when matched with HCC [4]. As TARE is an established method of treatment for HCC, our findings suggest it may be used for primary treatment of HCC-CC with similar survival outcomes.

This study is limited by many factors, namely, by its retrospective, single-center design. In addition, there were only 10 patients with HCC-CC due to the rarity of pathology. With this small sample size, it is difficult to provide general recommendations for the HCC-CC population or draw definitive conclusions. Nonetheless, the results of this study provide limited evidence regarding the safety and efficacy of TARE for HCC-CC patients. A multi-institutional study in the future may potentially provide a more robust HCC-CC population as well as diversity in treatment approaches that can allow adequately powered analyses. Furthermore, since this was a retrospective study with propensity score matching, there were limitations in how the matched cohort was acquired. This study considered BCLC, CPS, ECOG status, age, and gender for matching purposes; however other factors can also be considered such as concomitant therapies patients may have received. Although our goal was to study TARE as a primary form of tumor treatment, subsequent concomitant therapies may have impacted the OS outcomes in patients and should be evaluated in future studies.

In conclusion, this study presents evidence regarding safety and efficacy of TARE for patients with HCC-CC. Objective response and survival outcomes are similar between patients receiving TARE for HCC or HCC-CC and therefore may be considered an acceptable method for LRT in this select population.

Statement of Ethics

For this type of study, formal consent was not required. All ethical standards were upheld. Institutional board review approval was obtained for this single-institution retrospective study. Informed consent was obtained from every individual included in this study. Consent for publication was obtained prior to submission. IRB Reference No. 16889. The data were completely anonymized/de-identified.

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Conflict of Interest Statement

Osman Ahmed reports consulting role with Cook Medical®, Argon Medical®, and Cardiva Medical®.

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Author Contributions

Mr. Badar was responsible for preparing the manuscript and performing the statistical analysis. Dr. Ahmed, Dr. Zangan. Dr. Van Ha, and Dr. Navuluri are interventional radiologists responsible for performing the radioembolization procedures. Dr. Pillai is the transplant hepatologist working with Dr. Baker, the transplant surgeon to provide patients for this study.

References

1 West J, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971–2001. Br J Cancer. 2006;94(11):1751–8.
2 Stavraka C, Rush H, Ross P. Combined hepatocellular cholangiocarcinoma (cHCC-CC): an update of genetics, molecular biology, and therapeutic interventions. J Hepatocell Carcinoma. 2018;6:11–21.
3 Lee JH, Chung GE, Yu SJ, Hwang SY, Kim JS, Kim HY, et al. Long-term prognosis of combined hepatocellular and cholangiocarcinoma after curative resection comparison with hepatocellular carcinoma and cholangiocarcinoma. J Clin Gastroenterol. 2011;45(1):69–75.
4 Huang YH, Park BV, Chen YF, Gaba RC, Guzman G, Lokken RP. Locoregional therapy of hepatocellular-cholangiocarcinoma versus hepatocellular carcinoma: a propensity score-matched study. J Vasc Interv Radiol. 2019;30(9):1317–24.
5 Kallini JR, Gabr A, Salem R, Lewandowski RJ. Transarterial radioembolization with yttrium-90 for the treatment of hepatocellular carcinoma. Adv Ther. 2016;33(5):699–714.
6 Arslanoglu A, Seyal AR, Sodagari F, Sahin A, Miller FH, Salem R, et al. Current guidelines for the diagnosis and management of hepatocellular carcinoma: a comparative review. AJR Am J Roentgenol. 2016;207(5):W88–98.
7 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52–60.
8 Randolph J, Falbe K, Manuel A, Balloun J. A step-by-step guide to propensity score matching in R. Pract Assess Res Eval. 2014;19:7.
9 Fowler K, Saad NE, Brunt E, Doyle MB, Amin M, Vachharajani N, et al. Biphenotypic primary liver carcinomas: assessing outcomes of hepatic directed therapy. Ann Surg Oncol. 2015;22(13):4130–7.