



Intrahepatic cholangiocarcinoma: a dose threshold evaluation in those undergoing transarterial radioembolization

Shamar Young^{1^}, Pooya Torkian², Siobhan Flanagan², Donna D'Souza², Tina Sanghvi³, Jafar Golzarian²

¹Division of Interventional Radiology, Department of Medical Imaging, University of Arizona, Tucson, AZ, USA; ²Division of Interventional Radiology, Department of Radiology, University of Minnesota, Minneapolis MN, USA; ³Department of Radiology, Arizona Veterans Administration Hospital, Tucson, AZ, USA

Contributions: (I) Conception and design: S Young; (II) Administrative support: P Torkian; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: S Young, T Sanghvi, P Torkian; (V) Data analysis and interpretation: S Young; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shamar Young, MD. Department of Medical Imaging, University of Arizona, 1501 N Campbell Ave, Tucson, AZ 85724, USA. Email: shamar@arizona.edu.

Background: Intrahepatic cholangiocarcinoma (ICC) is a rare primary hepatic malignancy. One of the treatment strategies which has shown some promise is transarterial radioembolization (TARE). However, data on dose thresholds, arguably the most important aspect of the procedure itself, is still limited. The study aims to evaluate the relationship between dose to tumor and radiologic response in intrahepatic cholangiocarcinoma patients undergoing transarterial radioembolization.

Methods: Twenty-patients who underwent treatment for 26 tumors were retrospectively reviewed. Radiologic response at 3-month was evaluated and post yttrium-90 bremsstrahlung single photon emission computerized tomography computed tomography was evaluated to determine tumor dose. Other factors such as particle load and activity per particle were evaluated.

Results: The mean tumor dose for those with progressive disease or stable disease, partial response, and complete response (CR) by European Association for the Study of Liver (EASL) criteria for the glass cohort was 294±0, 465.4±292.4 and 951.8±666.5 Gy respectively (P=0.039). A receiver operating characteristic (ROC) curve analysis of tumor dose demonstrated an area under the curve (AUC) of 0.738 (P=0.038) with Youden-index analysis demonstrated a cutoff point of >541.7 Gy (sensitivity: 55.56%; specificity: 92.86%) for the glass cohort. Significantly longer survival was noted in those who achieved a CR [HR: 4.79 (95% CI: 1.41–16.25)] and those treated with glass as compared to resin [HR: 5.02 (95% CI: 1.23–20.55), P=0.025]. Of the 17 treatments in 13 patients which were done concomitantly with chemotherapy 7/17 (41.2%) required a delay in chemotherapy, however all patients reinitiated chemotherapy after a delay.

Conclusions: There appears to be a relationship between tumor dose and radiologic response, with this study suggesting a target of ≥541.7 Gy being warranted in patients receiving treatment with glass microspheres.

Keywords: Intrahepatic cholangiocarcinoma; dosimetry; transarterial radioembolization

Submitted Mar 11, 2023. Accepted for publication Aug 07, 2023. Published online Sep 22, 2023.

doi: 10.21037/jgo-23-210

View this article at: <https://dx.doi.org/10.21037/jgo-23-210>

[^] ORCID: 0000-0003-4839-9885.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare primary hepatic malignancy, however its incidence has been increasing in Western countries (1-3). While chemotherapy is the gold standard treatment for non-resectable ICC patients, the results of chemotherapy alone are less than desirable (4). This has led to the investigation of other treatment algorithms for this patient cohort. Most of these treatment algorithms have investigated the addition of locoregional therapies to systemic chemotherapy given the systemic nature of the disease (5-8).

One of the treatment strategies which has shown some promise is transarterial radioembolization (TARE) (5-17). However, data on dose thresholds, arguably the most important aspect of the procedure itself, is still limited (18-21). Furthermore, the majority of dose threshold studies are macroaggregated albumin (MAA) based (18-20). Utilizing MAA distribution to determine realized dose to tumor is fraught with error and thus these studies are limited (21). Understanding dose response thresholds is of particular importance as a recent production of prospective data suggesting the combination of TARE with chemotherapy is safe and may be efficacious (8). Given the promise of the technique and the known importance of dose to response as a general concept, further evaluation of dose

response curves is needed.

Finally, other important factors such as particle load and specific activity per particle have to the authors knowledge not been investigated in relationship to treatment outcomes and ICC. The two commercially available yttrium-90 products differ significantly in specific activity and particle load, with resin (SIR-Spheres, Sirtex medical, Woburn) having relatively low specific activity and associated high particle load and glass (Therasphere, Boston Scientific, Marlborough, MA) having relatively high specific activity and low particle load. Furthermore, even within the two products there can be significant variation in these parameters with resin offering flex dosing, allowing for variation in specific activity to some degree and glass particles being created on Sunday's allowing users to reduce the specific activity by delivering later in the two-week time span.

Therefore, the aim of this retrospective single center study was to evaluate the dose response relationship of TARE in patients with ICC to evaluate the hypothesis that a relationship between dose and response does exist. We present this article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-210/rc>).

Methods

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board (IRB) of the University of Minnesota (No. STUDY00003416). Informed consent was waived by the IRB for this retrospective study but all patients were consented for the procedure. After IRB approval all ICC patients treated with TARE between 1/1/2013–6/1/2021 (n=24) at a single-institution were reviewed. The primary endpoint was radiologic-response (RR) at 3-month. Patients without 3-month follow-up imaging (n=1) and those without single-photon-emission-computerized tomography (SPECT) computed-tomography (CT) following yttrium-90 delivery (n=3) were excluded. If patients had multiple TARE treatments of a single-lesion, which were separated by at least 3-month, each was included and analyzed separately for the primary endpoint. In total 20-patients who underwent treatment of 26-tumor were included with demographic data available in *Table 1*. No patients had extra hepatic disease at the time of treatment, 18/20 (90%) had 1 tumor, 1/20 (5%) had 3 and 1/20 (5%) had greater than 5.

Highlight box

Key findings

- Realized tumor dose may correlate with radiologic response and patients who achieve a complete radiologic response may obtain a survival benefit. When treating with glass microspheres a target dose of ≥ 541.7 Gy to the tumor may be warranted.

What is known and what is new?

- Phase 2 data has suggested that the combination of systemic therapy and transarterial radioembolization may be a viable treatment option for well selected patients with intrahepatic cholangiocarcinoma.
- This study demonstrates that there may be a correlation between tumoral dose and radiologic response, and identifies a potential target dose for patients undergoing glass microsphere yttrium-90 treatment.

What is the implication, and what should change now?

- Those treating intrahepatic cholangiocarcinoma patients with glass microspheres should consider targeting a tumoral dose of ≥ 541.7 Gy. However, further data on dose thresholds in this patient population is needed.

Table 1 Demographic data

Variable	Entire cohort	Resin only	Glass only
Age (years)	62.6±10.5	65.4±6.5	61.8±8.8
Sex			
Men	13/20, 65%	4/7, 57.1%	9/13, 69.2%
Women	7/20, 35%	3/7, 42.9%	4/13, 30.8%
Total Bilirubin (mg/dL)	0.8±0.4	0.8±0.3	0.8±0.3
Albumin (g/dL)	3.4±0.4	3.3±0.5	3.4±0.4
INR	1.1±0.2	1.2±0.3	1.1±0.1
Creatinine (mg/dL)	0.8±0.3	0.7±0.2	0.8±0.3
Platelets (10 ⁹ /L)	150.6±75.2	134.4±87	154±71.2
Lymphocytes (10 ⁹ /L)	1±0.5	0.8±0.3	1.1±0.4
Child-Pugh	6.2±1.3	6.7±1.5	6.1±1.1
Cancer Antigen 19-9 (U/mL)	127.5 (102.25)	165 (165.3)	129 (105)
Prior chemotherapy	11/20, 55%	3/7, 42.9%	8/13, 61.5%
Concomitant chemotherapy	17/26, 65.4%	6/9, 66.7%	11/17, 64.7%
Prior radiation	1/20, 5%	1/7, 14.3%	0/13, 0%
Prior TACE	1/20, 5%	1/7, 14.3%	0/13, 0%
Microsphere utilized		N/A	N/A
Resin	9/26, 34.6%		
Glass	17/26, 65.4%		
Delivery target:			
Lobar	8/26, 30.8%	5/9, 55.6%	3/17, 17.7%
2–3 segments	6/26, 23.1%	2/9, 22.2%	4/17, 23.5%
≤1 segment	12/26, 46.1%	2/9, 22.2%	10/17, 58.8%
Activity delivery (mCi)	80.5±74	22±9	111.4±74.7
Particle load	4,000,000 (6,400,350.5)	11,116,232 (8,105,586)	2,400,000 (2,000,000)
Specific activity (Bq)	658.5 (1,407.1)	76 (0)	1,389.7 (708.1)
Lung shunt percent	3.3±2.9	4.4±3.2	2.8±2.8
Perfused volume (mL)	536.8±341.8	389.1±140.9	588.9±378.5
Tumor size (cm)	5.5±2.6	5.3±1	5.5±3
Predicted T:N ratio	2.2±2.2	2.8±2.8	2±0.8
Realized T:N ratio	2.1±0.7	1.9±0.6	2.2±0.7

Data are expressed as mean ± standard deviation, median (IQR) or n, %. INR, international ratio; T:N ratio, tumor to normal ratio; TACE, transarterial chemoembolization.

Electronic-medical-records were evaluated for laboratory, imaging, and clinical factors. Furthermore, type of yttrium-90 microsphere utilized (resin or glass), activity, particle-load, and delivery points were recorded. All resin treatments utilized day of calculation doses and glass microspheres were delivered on 2 (9/17, 52.9%), 3 (1/17, 5.9%), 4 (3/17, 17.6%), and 5 (4/17, 23.5%) days after calibration respectively. Adverse events were evaluated using common terminology criteria for adverse events version 5.

RR was evaluated using the European Association for the Study of Liver (EASL) criteria and response evaluation criteria in solid tumors (RECIST) version 1.1. However, because EASL has been shown to more accurately predict oncologic outcomes as compared to RECIST when patients are treated with TARE, RECIST data is presented in supplemental data (22). An objective RR (ORR) was defined as a complete or partial response. RR was evaluated with independent review by a body-radiologist; comparing their interpretation to the initial report with discrepancies resolved by mutual consensus. OS, time-to-progression (TTP) and local-TTP were considered to be time from first TARE procedure until death, progression at any site, or target lesion progression respectively.

Particle-load: specific activity calculations

$$\text{Number of resin Particles} = 44.48 \times 10^6 \times \frac{\text{Delivered Activity GBq}}{3 \text{ GBq} \times 2 \left(\frac{\text{Hours Before 6 PM EST}}{64.1 \text{ hours}} \right)} \quad [1]$$

$$\text{Number of glass Particles} = \text{Activity at calculation (GBq vial ordered)} \times 400,000 \text{ particles/GBq} \quad [2]$$

$$\text{Specific activity} = \frac{\text{Activity delivered}}{\text{Particle load}} \quad [3]$$

Where activity delivered was calculated by measuring the predelivery activity with a dose calibrator (Mirion Technologies Inc.) on the day of and immediately prior to the delivery.

TARE technique

TARE was performed in previously described manner (5-17). However, in brief after presentation at a multi-disciplinary conference patients which were not surgical candidates were considered for TARE. After consultation a mapping angiogram utilizing technetium-99m MAA (Tc99mMAA) followed by SPECT-CT to evaluate liver distribution, lung shunt fraction (LSF), and extra-hepatic distribution. Performing physician preference determined dose calculation method [medical internal radiation dose (MIRD), partition, body-surface-area (BSA) and a voxel based multi-compartment method were all utilized during the study period] and dose target. The microsphere (resin or glass) utilized was also at the performing physicians discretion, however, there was a tendency to utilize resin more early in the study period and glass more late in the study period. Patients returned for delivery and underwent post-delivery bremsstrahlung SPECT-CT.

Calculation of absorbed dose

Pretreatment contrast enhanced magnetic resonance imaging (MRI)s or CTs were utilized along with a dosimetry software [Simplicit90y™ (Mirada Medical, Denver, CO)] to calculate absorbed dose. A single physician with ≥6 years of experience drew 3D-regions of interest (ROI) (23). The lowest relevant isodose curve was used to contour the normal and tumoral tissues within the perfused-volume. Anatomic structures within the yttrium-90 bremsstrahlung SPECT-CT were utilized to evaluate and adjust the fit of the Co-registration. The activity delivered and LSF (calculated using standard planar method) was entered into Simplicit90y™, and the below calculation was utilized.

Dose to tumor

$$Dt = \frac{\left[\left(\frac{Ai}{Ci} \right) Ct \right] \times 50 \times (1 - LSF) \times (1 - R)}{pVt} \quad [4]$$

Where Dt is the tumor absorbed dose in Gy, Ai is the perfused volume injected activity in GBq, Ci represents the perfused volume counts, Ct represents the counts in the

Table 2 Radiologic response according to EASL criteria at three months post treatment

Radiologic response	EASL, n (%)
Entire cohort	n=26
Progressive disease	2 (7.7)
Stable disease	2 (7.7)
Partial response	13 (50.0)
Complete response	9 (34.6)
Glass only	n=17
Progressive disease	0
Stable disease	1 (5.8)
Partial response	8 (47.1)
Complete response	8 (47.1)
Resin only	n=9
Progressive disease	2 (22.2)
Stable disease	1 (11.1)
Partial response	5 (55.6)
Complete response	1 (11.1)

EASL, European Association for the Study of Liver.

segmented tumor volume, ρ represents tumor tissue density (kg/cm^3), V_t is the tumor volume (cm^3), LSF is lung shunt fraction, and R is residual activity.

Statistical analysis

Quantitative variables are expressed as mean \pm standard deviations or median [interquartile-range (IQR)]. Qualitative variables are expressed as frequencies followed by percentages in parentheses. Student T-test or ANOVA were used to analyze continuous variables and Chi-Squared or Fisher exact tests were utilized to evaluate categorical data. To determine the relationship between RR and various variables a receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis was performed. Youden-index analysis was utilized to identify thresholds on the ROC. Further analysis with univariate and multivariate regression was performed. Kaplan-Meier survival curves and Cox proportional hazard ratios were also calculated to analyze overall survival and time to progression variables. R (Version 3.4.1, The R Foundation for Statistical Computing) was used for the analysis and P values of <0.05 were considered statistically significant.

Results

Results for the RECIST classification of response can be found in supplemental materials ([Appendix 1](#)).

RR by microparticle type

RR can be found in for the entire, glass only, and resin only cohorts in *Table 2*. When comparing glass to resin there was no significant difference in the likely hood of obtaining an ORR (16/17, 94.1% glass *vs.* 6/9, 66.7% resin, $P=0.1$). When looking at the likelihood of obtaining a complete response (CR) again no significant difference was seen between glass (8/17, 47.1%) and resin (1/9, 11.1%) ($P=0.098$).

RR and relationship to dose

Glass only

The mean tumor dose (MTD) for stable disease (SD) (1/17, 5.8%), partial response (PR) (8/17, 47.1%), and CR (8/17, 47.1%) by EASL was 294 ± 0 , 465.4 ± 292.4 and 951.8 ± 666.5 Gy respectively ($P=0.039$).

Resin only

The MTD for PD (2/9, 22.2%), SD (1/9, 11.1%), PR (5/9, 55.6%), and CR (1/9, 11.1%) by EASL was 126.8 ± 9.4 , 128.4 ± 0 , 144.5 ± 105 and 132.8 ± 0 Gy, respectively ($P=0.42$).

ROC analysis for ORR

A ROC curve analysis could not be performed for those who did and did not achieve an ORR by EASL in the glass only cohort as only a single patient failed to achieve an ORR. For the resin only cohort the AUC was 0.583 ($P=0.75$). Youden index analysis demonstrated a cutoff point of >103.2 Gy resulted in a sensitivity of 50% and a specificity of 100% for achieving an ORR.

ROC analysis for CR

A ROC curve analysis evaluating tumor dose in those who achieved a CR by EASL was performed for the glass only patients. Similar analysis could not be performed for resin only patients as only a single patient achieved a CR. The AUC of this analysis was 0.738 ($P=0.038$), for the glass only patients, with Youden-index analysis demonstrated a cutoff point of >541.7 Gy (sensitivity: 55.56%; specificity: 92.86%).

RR and relationship to particle-load and specific activity

The median particle-load and specific activity by RR category

Table 3 Particle load and specific activity by radiologic response (EASL criteria)

Variable	PD or SD	PR	CR	P value
Glass only				
Particle load (particles)	2,000,000 (IQR: 0)	4,000,000 (IQR: 1,100,000)	2,200,000 (IQR: 600,000)	0.1
Specific activity (Bq)	605 (IQR: 0)	814.9 (IQR: 800.5)	1,477.8 (IQR: 270)	0.12
Resin only				
Particle load (particles)	11,116,232 (IQR: 6,813,721)	9,379,321 (IQR: 6,716,057)	45,041,559 (IQR: 0)	0.3
Specific activity (Bq)	–	–	–	–

PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; EASL, European Association for the Study of Liver.

Table 4 Univariate and multivariate regression analysis of factors which may affect achieving a complete radiologic response by European Association for the Study of Liver criteria at 3 months

Variable	Univariate regression		Multivariate regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Tumor dose	1.26 (1.08–1.58)	0.017	1.22 (0.99–1.61)	0.28
Specific activity	1.16 (1.01–1.31)	0.045	1.01 (0.98–1.37)	0.48
Perfused volume	0.99 (0.94–1.16)	0.28	–	–
Particle load	1 (0.98–1.03)	0.74	–	–
Tumor size	0.75 (0.53–1.05)	0.086	0.94 (0.61–1.45)	0.79
Pretreatment CA 19-9	0.97 (0.94–1.45)	0.18	–	–
Yttrium-90 material (resin or glass)	0.14 (0.01–1.38)	0.07	2.99 (0.05–3.89)	0.61
Prior chemotherapy	7.3 (1.46–14.71)	0.008	6.88 (0.49–15.40)	0.15

Please note that all listed variables were included in the multiple regression model presented. OR, odds ratio.

can be found in *Table 3*. No significant differences were found between the particle load or specific activity in the glass cohort when compared between those with a PD or SD, PR, and CR. Similarly, no significant differences were seen between these groups in the resin only cohort when looking at particle load. Specific activity for the resin cohort could not be analyzed as all treatments had the same specific activity.

Univariate and multivariate regression analysis of achieving a CR by EASL

Results of this analysis are presented in *Table 4*, however, no tested variables remained significant on multivariate analysis. The entire cohort was included in this analysis given the small numbers and the breath of particle load and specific activity which is introduced by including both microsphere types.

TTP and OS analysis

Figure 1 demonstrates KM OS curves for those who did and did not achieve a CR by EASL criteria (P=0.01, Cox HR: 4.79 (95% CI: 1.41–16.25)).

Figure 2 demonstrates the KM curves for local TTP, TTP, and OS comparing the outcomes between patients receiving the two different device types. There was no significant difference in the local TTP [HR: 1.69 (95% CI: 0.32–8.88), P=0.53] and TTP [HR: 1.64 (95% CI: 0.58–4.64), P=0.35]. However, OS [HR: 5.02 (95% CI: 1.23–20.55), P=0.025] was significantly longer in the glass as compared to resin cohorts.

Adverse events

The only Grade 3 or greater adverse events occurred in a

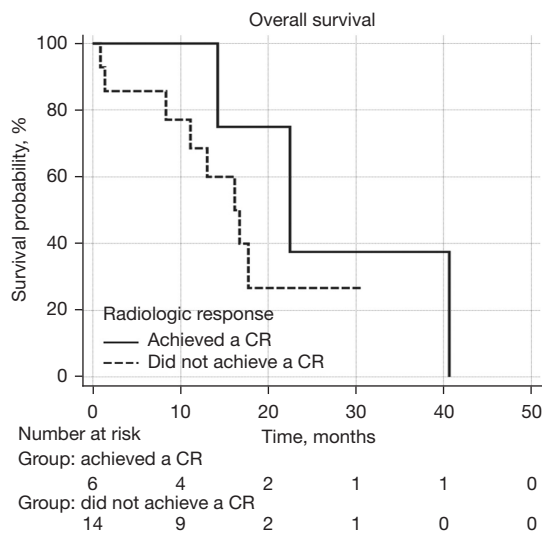


Figure 1 Kaplan Meier curves evaluating the overall survival of those who did and did not achieve a CR by EASL. CR, complete response; EASL, European Association for the Study of Liver.

single patient who had grade 3 elevation in total bilirubin, aspartate aminotransferase (AST), and alanine transaminase (ALT) at 1 month. Of the 17 treatments in 13 patients which were done concomitantly with chemotherapy 7/17 (41.2%) required a delay in chemotherapy, however all patients reinitiated chemotherapy after a delay.

Discussion

ICC is a rare primary hepatic malignancy which can be challenging to treat. While initial studies have demonstrated promise when adding TARE to the treatment algorithm, further data is needed (8-17). In particular more data on dose thresholds is needed, as emphasized by recent studies in hepatocellular carcinoma (HCC) which have demonstrated the importance of dose thresholds (24,25). This study demonstrated a significant difference in the tumoral dose seen across various radiologic response categories in the glass but not the resin cohorts. Furthermore, the study found an AUC of 0.738 (P=0.038) when evaluating glass patients who did and did not have a complete radiologic response, confirming the apparent association between dose and radiologic response. Using Youden’s index to evaluate a ROC curve, this study would suggest that providers should target at least 541.7 Gy to the tumor when using glass. The tumoral values are higher than a prior study which demonstrated that a minimum of 158 Gy

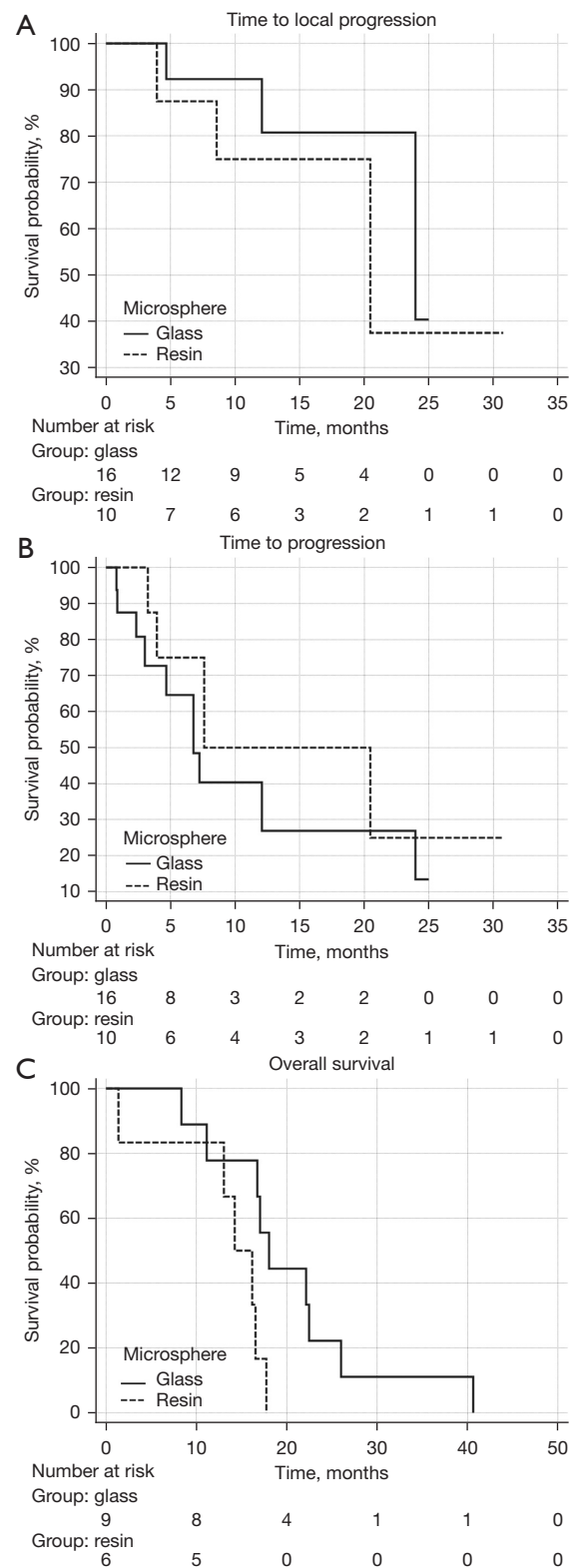


Figure 2 Kaplan Meier curve evaluating local time to progression (A), time to progression (B), and overall survival (C) in those who received glass and resin microspheres.

was needed to induce a response (18). This difference may be secondary to the small cohorts in both studies, however further data is needed. The study also confirms the OS benefit of achieving a CR in this patient cohort.

The current study also evaluated the importance of particle load on radiologic response. Particle load has been shown to be an important factor in areas such as tumor to normal ratio (TNR) in prior publications evaluating treatment of other primary liver cancers (23). While significant differences were not seen among RR and particle load in either the glass or resin cohort, the subject warrants further evaluation. A related factor, specific activity could not be evaluated in the resin cohort as all resin treatments utilized day of calibrations. While there was a trend toward higher specific activity being associated with better RR in glass treatments this was not significant. Again, this variable warrants further evaluation, especially given the emerging evidence supporting their importance in TARE for HCC (23,26,27). In line with this there was a significant difference noted in OS between those receiving glass and resin. These differences may have occurred for a number of reasons, however, the devices primarily differ in their relative particle loads and specific activities, again emphasizing the importance of these variables in future investigations.

One important consideration with any treatment are adverse events. There were very few adverse events in this cohort, consistent with prior studies (5-17). A specific concern expressed by the medical oncology community is the inability to continue systemic therapy during/after TARE. This study did show that of the 13 patients who underwent 17 TARE treatments while undergoing systemic therapy delay in the next cycle of therapy occurred after 7 (41.2%) treatments. However, perhaps more importantly all patients did continue with chemotherapy after a delay. These results are fairly consistent with Edeline *et al.* who showed fairly low levels of toxicity in those patients undergoing simultaneous TARE and systemic therapy, particularly when whole liver TARE was not performed (8). These findings should help give confidence to multidisciplinary teams when offering a combined treatment strategy.

This study has a number of limitations, most importantly it is a single center retrospective study with a limited patient cohort. No pathologic data was available for the cohort, and thus radiologic response was used as a surrogate. Radiologic response is known not to mirror pathologic response perfectly (25,28). Finally, patients were treated at a

quaternary referral center and the experience there may not reflect other centers experience.

Conclusions

In conclusion, a relationship between tumor dose and radiologic response in patients treated for ICC with TARE appears to exist. Furthermore, activity per particle and particle load may be associated with response as well and further evaluation of these variables may be of benefit.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-210/rc>

Data Sharing Statement: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-210/dss>

Peer Review File: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-210/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-210/coif>). SY have received consulting fees, been a part of the speaker bureau, and received funds for travel from Boston Scientific, and also received consulting fees from Mirada as well as served in leadership roles for both the Society of Interventional Radiology and the GEST meeting. DD have received consulting fees, been a part of the speaker bureau, and received funds for travel from Sirtex as well as served in leadership roles for both the Society of Interventional Radiology and the GEST meeting. JG have received consulting fees, been a part of the speaker bureau, and received funds for travel from Sirtex as well as served in leadership roles for both the Society of Interventional Radiology and the GEST meeting. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the IRB of the University of Minnesota (No. STUDY00003416). Informed consent was waived by the IRB for this retrospective study but all patients were consented for the procedure.

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Cite this article as: Young S, Torkian P, Flanagan S, D'Souza D, Sanghvi T, Goltzarian J. Intrahepatic cholangiocarcinoma: a dose threshold evaluation in those undergoing transarterial radioembolization. *J Gastrointest Oncol* 2023;14(5):2202-2211. doi: 10.21037/jgo-23-210