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SHORT COMMUNICATION

Hepatocellular carcinoma radiation segmentectomy treatment intensification prior to liver transplantation increases rates of complete pathologic necrosis: an explant analysis of 75 tumors

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Abstract

Purpose To verify the correlation between yttrium-90 glass microsphere radiation segmentectomy treatment intensification of hepatocellular carcinoma (HCC) and complete pathologic necrosis (CPN) at liver transplantation.

Methods A retrospective, single center, analysis of patients with HCC who received radiation segmentectomy prior to liver transplantation from 2016 to 2021 was performed. The tumor treatment intensification cohort ($n=38$) was prescribed radiation segmentectomy as per response recommendations identified in a previously published baseline cohort study ($n=37$). Treatment intensification and baseline cohort treatment parameters were compared for rates of CPN. Both cohorts were then combined for an overall analysis of treatment parameter correlation with CPN.

Results Sixty-three patients with a combined 75 tumors were analyzed. Specific activity, dose, and treatment activity were significantly higher in the treatment intensification cohort (all $p<0.01$), while particles per cubic centimeter of treated liver were not. CPN was achieved in 76% ($n=29$) of tumors in the treatment intensification cohort compared to 49% ($n=18$) in the baseline cohort ($p=0.013$). The combined cohort CPN rate was 63% ($n=47$). ROC analysis showed that specific activity ≥ 327 Bq (AUC 0.75, $p<0.001$), dose ≥ 446 Gy (AUC 0.69, $p=0.005$), and treatment activity ≥ 2.55 Gbq (AUC 0.71, $p=0.002$) were predictive of CPN. Multivariate logistic regression demonstrated that a specific activity ≥ 327 Bq was the sole independent predictor of CPN ($p=0.013$).

Conclusion Radiation segmentectomy treatment intensification for patients with HCC prior to liver transplantation increases rates of CPN. While dose strongly correlated with pathologic response, specific activity was the most significant independent radiation segmentectomy treatment parameter associated with CPN.

Keywords Radioembolization · Yttrium-90 · Radiation segmentectomy · Transplantation · Pathologic response

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Abbreviations

BCLC	Barcelona Clinic Liver Cancer
CPN	Complete pathologic necrosis
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
MRI	Magnetic resonance imaging
MIRD	Medical Internal Radiation Dose

MELD	Model for End-stage Liver Disease
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
ROC	Receiver operating characteristic

Radioembolization has recently been incorporated to the Barcelona Liver Cancer Clinic (BCLC) treatment algorithm for patients with BCLC stage 0-A disease and has been FDA approved for the treatment of solitary hepatocellular carcinoma (HCC).[1, 2] There is prospective, randomized, evidence in support of radioembolization treatment intensification demonstrating improved tumor response for the treatment of advanced HCC.[3] For patients with coexistent cirrhosis, neoadjuvant transarterial radioembolization has demonstrated safety and efficacy in bridging or downstaging HCC prior to liver transplantation.[4] Tumor response to local therapy has been associated with improved recurrence free survival after liver transplantation and current organ allocation policies require durable outcomes in patients with low biological model for end-stage liver disease (MELD) scores.[5, 6]

Radiation segmentectomy has shown ablative capabilities as treatment for early-stage HCC.[7] Identifying radiation segmentectomy treatment parameters that optimize tumor response may allow more patients access to liver transplantation with fewer treatments and improve post-transplant outcomes.[4] Vouche et al. and Gabr et al. have previously demonstrated an association between HCC complete pathologic necrosis (CPN) and a radioembolization radiation dose ≥ 190 Gy and ≥ 400 Gy, respectively.[8, 9] Toskich et al. reported pathologic outcomes of HCC radiation segmentectomy prior to liver transplantation which both validated these prior studies and suggested that microsphere specific activity ≥ 297 Bq predicted ≥ 99% pathologic necrosis.[10]

This study sought to verify whether radiation segmentectomy treatment intensification by increasing dose and specific activity was associated with increased tumor CPN when compared to a previously published, baseline cohort.[10] It also presents the largest cumulative radiopathologic analysis to date of patients treated with radiation segmentectomy prior to liver transplantation.

Consecutive patients treated with radiation segmentectomy for HCC as a neoadjuvant to liver transplantation from November 2016 to October 2021 at a single, tertiary care, destination medical care center were evaluated. Inclusion criteria were HCC diagnosed with either imaging or biopsy, complete coverage of the tumor by the treatment angiosome per mapping angiography contrast-enhanced cone-beam computed tomography, no other therapy to the target tumor, and available gross pathology for analysis.

All patients were treated with Y90-containing glass microspheres (TheraSphere™, Boston Scientific, Marlborough, MA) as advised by a multidisciplinary tumor board. Radiation segmentectomies were performed utilizing a previously reported technique and dose was calculated using the Medical Internal Radiation Dose (MIRD) single compartment methodology.[11] The baseline cohort included a broad range of radiation segmentectomy dose and specific activity as previously published.[10] Given the superior rates of tumor necrosis observed with higher doses and specific activities in the baseline cohort, our practice adopted a dose ≥ 400 Gy and specific activity ≥ 297 Bq for the treatment intensification cohort, when feasible.[9, 10]

Follow-up magnetic resonance imaging (MRI) was performed for all patients at 1 month and every 3 months after radioembolization until liver transplantation. Target tumor response and progression within the treatment angiosome (in-field) were assessed by board certified abdominal radiologists with greater than 5 years of experience using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Best imaging response was used for analysis.

Histopathologic examination was performed by board-certified pathologists on tissue fixed in formalin and sectioned at approximately 4-mm intervals to assess for treatment response. CPN was defined as the absence of any cell identifiable as HCC. In cases with residual HCC at explant, the percentage of pathologic necrosis was calculated using the volume of histologically viable tumor relative to the pre-treatment MRI tumor volume, as per the baseline cohort.[10]

Sixty-three patients and a combined 75 tumors with a median size of 2.2 cm (range: 1.0–6.7) were analyzed. Dose was significantly higher in the treatment intensification cohort, with a median of 536 Gy compared to 314 Gy in the baseline cohort ($p < 0.001$) (Table 1). Thirty-three (87%) tumors in the treatment intensification cohort were treated with a dose ≥ 400 Gy compared to 16 (43%) tumors in the baseline cohort ($p < 0.001$). Specific activity was significantly higher in the treatment intensification cohort, with a median of 715 Bq compared to 321 Bq in the baseline cohort ($p < 0.001$). All (100%) tumors in the treatment intensification cohort were treated with a specific activity ≥ 297 Bq compared to 24 (65%) tumors in the baseline cohort ($p < 0.001$) (Supplementary Table 1). The number of particles per cc of treated liver was not significantly different between cohorts.

Target tumor post-treatment imaging overall response was 100% (89% complete response) and 92% (76% complete response) in the treatment intensification and baseline cohorts, respectively (Table 1). Median time from radiation segmentectomy to liver transplantation was 188 days (range: 32–1105) in the combined cohort, 183 days (range:

Table 1 Treatment parameters and tumor response in baseline and treatment intensification cohorts

	Baseline cohort ($n=37$)	Treatment intensification cohort ($n=38$)	p-value
Treatment parameter, median (IQR 1, 3)			
Specific activity (Bq)	321 (244, 680)	715 (708, 925)	<0.001
Particles/cc of liver treated ($\times 10^3$)	16.7 (12.6, 26.1)	15.9 (11.0, 20.7)	0.114
Dose (Gy)	314 (245, 491)	536 (461, 728)	<0.001
Total treatment activity (GBq)	1.09 (0.60, 1.71)	2.85 (1.74, 4.29)	<0.001
Estimated number of particles ($\times 10^6$)	2.4 (1.8, 4.0)	4.0 (2.0, 5.4)	0.080
Total angiosome volume (cc)	175 (100, 274)	250 (144, 350)	0.035
Binary treatment parameters, frequency (percentage)			
Dose			
≥190 Gy	34 (92%)	38 (100%)	0.115
≥400 Gy	16 (43%)	33 (87%)	<0.001
≥500 Gy	8 (22%)	21 (55%)	0.003
Specific activity ≥297 Bq	24 (65%)	38 (100%)	<0.001
Imaging response, frequency (percentage)			
mRECIST target tumor			
CR	28 (76%)	34 (89%)	0.265
PR	6 (16%)	4 (11%)	
SD	2 (6%)	0	
PD	1 (3%)	0	
mRECIST overall response	34 (92%)	38 (100%)	0.115
Pathologic response, frequency (percentage)			
CPN	18 (49%)	29 (76%)	0.013
≥99%	25 (68%)	30 (79%)	0.356
≥95%	28 (76%)	34 (89%)	0.115

IQR, interquartile range; *Bq*, Becquerel; *cc*, cubic centimeter; *Gy*, Gray; *GBq*, Gigabecquerel; *mRECIST*, modified Response Evaluation Criteria in Solid Tumors; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *CPN*, complete pathologic necrosis

Table 2 Treatment parameters for tumors with CPN vs without CPN in the combined cohort

Treatment parameter, median (IQR 1, 3)	CPN ($n=47$)	Non-CPN ($n=28$)	p-value
Specific activity (Bq)	713 (672, 870)	319 (239, 711)	<0.001
Particles/cc of liver treated ($\times 10^3$)	16.0 (11.3, 19.0)	20.0 (11.2, 28.4)	0.124
Dose (Gy)	510 (412, 587)	360 (252, 496)	0.005
Total treatment activity (GBq)	2.42 (1.09, 3.70)	1.20 (0.58, 1.86)	0.002
Number of particles ($\times 10^6$)	3.2 (2.0, 6.0)	2.8 (1.7, 4.7)	0.586
Total angiosome volume (cc)	209 (105, 350)	177 (107, 271)	0.164

IQR, interquartile range; *Bq*, Becquerel; *Gy*, Gray; *GBq*, Gigabecquerel; *cc*, cubic centimeter; *CPN*, complete pathologic necrosis

32–1105) in the treatment intensification cohort, and 206 days (range: 58–550) in the baseline cohort ($p=0.574$).

Histopathologic analysis demonstrated CPN in 29 of 38 (76%) tumors in the treatment intensification cohort compared to 18 of 37 (49%) tumors in the baseline cohort ($p=0.013$). CPN was achieved in 47 of 75 (63%) tumors within the combined cohort. There were significant differences in dose ($p=0.005$), specific activity ($p<0.001$), and total treatment activity ($p=0.002$) between tumors with CPN and those without CPN in the combined cohort (Table 2).

Receiver operating characteristic (ROC) curves were generated to study the relationship between treatment parameters and CPN in the combined cohort. Specific activity was the treatment parameter most predictive of CPN (AUC, 0.749; 95%CI, 0.625–0.873; $p<0.001$) (Fig. 1), with a cutoff of ≥327 Bq (microspheres with ≤8 days of decay after calibration) showing a sensitivity of 83% and specificity of 64%. Tumors with CPN were treated with a higher median specific activity in the combined cohort compared to those without CPN ($p<0.001$) (Table 2). ROC analysis showed that a dose ≥446 Gy was 72% sensitive and 68%

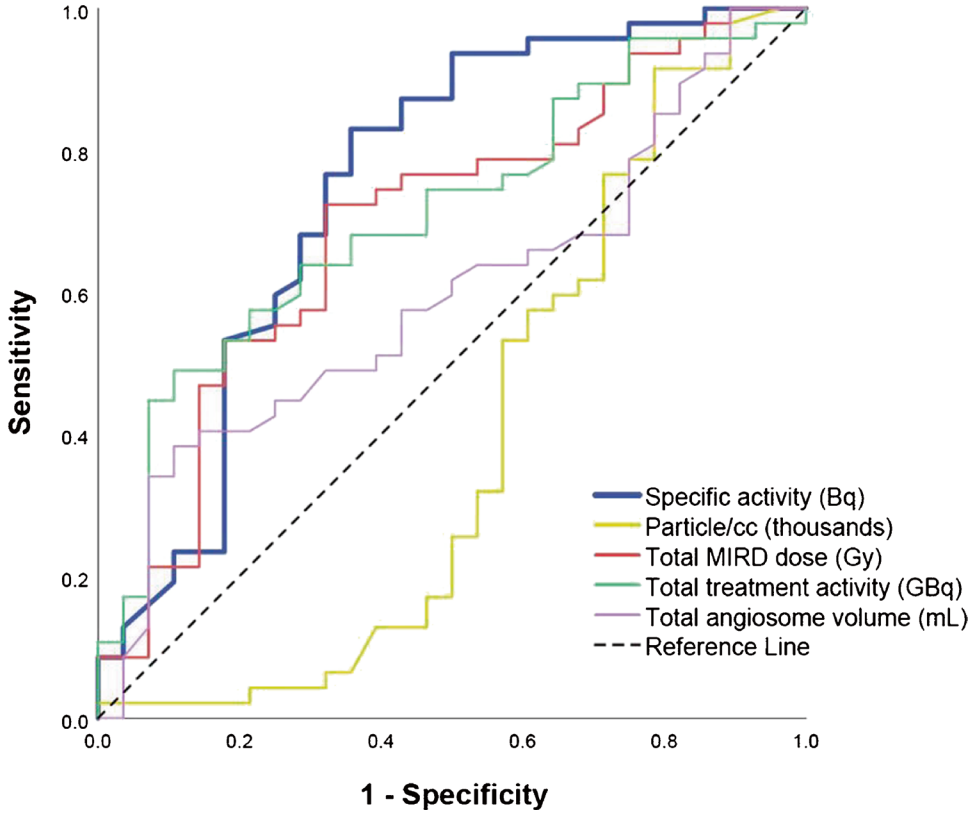

Fig. 1 ROC curve for CPN

Treatment parameter	AUC (95% CI)	*p*-value
Specific activity	0.749 (0.625-0.873)	<0.001
Particles/cc	0.393 (0.244-0.542)	0.124
Total MIRD dose	0.695 (0.570-0.820)	0.005
Total treatment activity	0.710 (0.592-0.829)	0.002
Total angiosome volume	0.597 (0.466-0.727)	0.164

specific in predicting CPN ($p=0.005$). Total treatment activity ≥ 2.55 GBq was 49% sensitive and 89% specific for CPN ($p=0.002$). A Spearman's correlation coefficient for specific activity and dose was 0.484 ($p<0.001$), demonstrating a moderate correlation, but below the conventional cutoff of 0.8–0.9 in screening for collinearity.[12] Multivariate logistic regression analyses demonstrated that specific activity was the sole independent treatment parameter predictive of CPN, both as a continuous ($p=0.013$) and binary variable with a cutoff of ≥ 327 Bq ($p=0.013$) (Table 3). The variance inflation factor for dose and specific activity in predicting CPN was 1.36, further supporting the lack of significant collinearity.[13, 14]

Treatment parameters associated with ≥ 99% pathologic necrosis (73%, $n=55/75$) were assessed due to limitations in detecting microscopic disease at the time of treatment, potential for sampling error in explant slide preparation, and the lack of viability staining. Specific activity ($p=0.001$), dose ($p=0.013$), and total treatment activity ($p=0.005$) were associated with ≥ 99% pathologic necrosis (Supplementary Fig. 1). Similarly to the previously published baseline cohort study, multivariate logistic regression analyses showed that specific activity was the sole predictor of ≥ 99% pathologic necrosis (Supplementary Table 2).

Angiosome volume was also increased in the treatment intensification cohort compared to the baseline cohort ($p=0.035$), despite a similar tumor size (median 2.0 vs 2.3 cm). While the effects of increasing radiation segmentectomy volume were not previously analyzed, the contribution of this parameter to the outcomes of this study is

Table 3 Logistic regression analyses for CPN in the combined cohort

Treatment parameter	Odds ratio (95% CI)	*p*-value
Univariate		
Specific activity ≥ 327 (Bq)	7.5 (2.6–22.1)	< 0.001
Dose (Gy)	1.004 (1.001-1.006)	0.011
Dose ≥ 446 (Gy)	5.5 (2.0–15.3)	0.001
Total angiosome volume (cc)	1.0 (1.0–1.0)	0.447
Total treatment activity (GBq)	1.7 (1.2–2.5)	0.006
Total treatment activity ≥ 2.55 (GBq)	5.7 (1.7–19.1)	0.004
Estimated number of particles ($\times 10^6$)	1.1 (0.9–1.3)	0.495
Particles/cc of liver treated ($\times 10^3$)	0.9 (0.9–1.0)	0.050
Tumor size (cm)	0.9 (0.6–1.4)	0.556
Multivariate model 1		
Specific activity (Bq)	1.003 (1.001–1.005)	0.013
Dose (Gy)	1.002 (0.999–1.005)	0.297
Multivariate model 2		
Specific activity ≥ 327 (Bq)	4.5 (1.4–15.2)	0.013
Dose ≥ 446 (Gy)	2.8 (0.9–9.1)	0.084

CI, confidence interval; *cc*, cubic centimeter; *Bq*, Becquerel; *GBq*, Gigabecquerel

indeterminate. With regard to adverse events of treatment intensification, the biochemical safety of ablative radioembolization as a function of percent liver has been previously published by our group.[15]

As previously described by Pasciak et al., decreasing microsphere density may also reduce tumor dose, but this relationship is likely of little clinical significance when treatments are above 5000 microspheres per cubic centimeter (cc).[16] Conversely, the present study found that reducing specific activity to increase particle number was associated with decreased pathologic necrosis, which highlights complexities of the radioembolization microdose environment. Given the median microsphere density of approximately 16,000 microspheres/cc in the present study, it is plausible that microsphere clusters within the tumor were sufficiently optimized and that higher activity of an individual cluster conveyed a greater therapeutic benefit. As such, when performing radiation segmentectomy with ablative intent, the authors recommend that specific activity should not be reduced in order to increase particle number when treating small tumors. If more particles are desired, the total activity and dose should be increased in lieu of reducing specific activity, if the volume of liver to be treated is expendable.

In conclusion, the results of this study demonstrate that radiation segmentectomy treatment intensification of HCC using a radiation dose ≥ 446 Gy and specific activity ≥ 327 Bq is more likely to achieve CPN. A CPN rate of 76% in the treatment intensification cohort confirms the ablative capacity of radioembolization and its potential for curative intent.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by S. Ali Montazeri, Cynthia De la Garza-Ramos, and Beau B. Toskich. Jason T. Lewis, Jordan D. LeGout, and David M. Sella contributed in pathologic and imaging analysis. All authors contributed in data gathering and manuscript editing. All authors read, edited, and approved the final manuscript.

Declarations

Ethics approval This retrospective study was approved by the Institutional Review Board and the need for informed consent was waived. This study was compliant with the Health Insurance Portability and Accountability Act.

Competing interests B.B.T. is an advisor for Boston Scientific, Sirtex Medical, Johnson and Johnson, AstraZeneca, Genentech, Eisai, HistoSonics, VIVOS, and Turnstone Biologics. The authors reported no other potential conflicts of interest for this work.

References

1. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update. *J Hepatol*. Published online November 2021. https://doi.org/10.1016/j.jhep.2021.11.018
2. Food and Drug Administration USD of H and HS. TheraSphere™ – P200029. Published 2020. Accessed April 25, 2021. https://www.fda.gov/medical-devices/recently-approved-devices/therasphere tm-p200029
3. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021;6(1):17–29. https://doi.org/10.1016/S2468-1253(20)30290-9.
4. Gabr A, Kulik L, Mouli S, et al. Liver transplantation following yttrium-90 radioembolization: 15-year experience in 207-patient cohort. *Hepatology*. Published online May 2020. https://doi.org/10.1002/hep.31318
5. DiNorcia J, Florman SS, Haydel B, et al. Pathologic response to pretransplant locoregional therapy is predictive of patient outcome after liver transplantation for hepatocellular carcinoma: analysis from the US Multicenter HCC Transplant Consortium. *Ann Surg*. 2020;271(4):616–24. https://doi.org/10.1097/SLA.0000000000003253.
6. Organ Procurement and Transplantation Network USD of H and HS. Organ Procurement and Transplantation Network (OPTN) policies. Published 2020. Accessed April 27, 2020. https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/optn_policies.pdf

7. Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology.* 2018;287(3):1050–8. https://doi.org/10.1148/radiol.2018171768.
8. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014;60(1):192–201. https://doi.org/10.1002/hep.27057.
9. Gabr A, Riaz A, Johnson GE, et al. Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. Eur J Nucl Med Mol Imaging. 2021;48(2):580–3. https://doi.org/10.1007/s00259-020-04976-8.
10. Toskich B, Vidal LL, Olson MT, et al. Pathologic response of hepatocellular carcinoma treated with yttrium-90 glass microsphere radiation segmentectomy prior to liver transplantation: a validation study. *J Vasc Interv Radiol,* 2021;32(4):518–526.e1. https://doi.org/10.1016/j.jvir.2020.12.019.
11. Toskich BB, Liu DM. Y90 radioembolization dosimetry: Concepts for the interventional radiologist. *Tech Vasc Interv Radiol.* 2019;22(2):100–11. https://doi.org/10.1053/j.tvir.2019.02.011.
12. Field A. *Discovering statistics using IBM SPSS statistics 5th Ed.* 2018.
13. Hahs-Vaughn, D. LomaX R. *An introduction to statistical concepts.* 2013.
14. Field A. *Discovering statistics using IBM SPSS statistics*. 2013.
15. De la Garza-Ramos C, Overfield CJ, Montazeri SA, et al. Biochemical safety of ablative yttrium-90 radioembolization for hepatocellular carcinoma as a function of percent liver treated. *J Hepatocell Carcinoma.* 2021;8:861–70. https://doi.org/10.2147/JHC.S319215.
16. Pasciak AS, Bourgeois AC, Bradley YC. A microdosimetric analysis of absorbed dose to tumor as a function of number of microspheres per unit volume in 90Y radioembolization. *J Nucl Med.* 2016;57(7):1020–6. https://doi.org/10.2967/jnumed.115.163444.