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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Improved Tumor Response in Patients on Metformin Undergoing Yttrium-90 Radioembolization Segmentectomy for Hepatocellular Carcinoma

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Abstract
Purpose Metformin is associated with improved outcomes after external radiation and chemotherapy but has not been studied for Y-90 radiation segmentectomy (RS). This study evaluates the effect of metformin on tumor response after Y-90 RS in patients with hepatocellular carcinoma (HCC).
Methods and Materials A retrospective analysis of patients with HCC who underwent Y-90 RS between 2014–2018 was performed. Comparisons were made between all patients taking and not taking metformin, and diabetic patients taking and not taking metformin. Tumor response was analyzed with logistic regression to compare absolute and percent change in total tumor diameter (TTD) and modified Response Evaluation Criteria in Solid Tumors (mRECIST). Overall survival (OS) was evaluated using Kaplan–Meier estimation and log-rank analysis.
Results A total of 106 patients underwent 112 Y-90 RS, of which 40 were diabetic (38.8%) and 19 (18.4%) were on metformin. At baseline, the two groups of patients on metformin and not on metformin had no significant difference in age, Child–Pugh score, MELD score, ALBI grade, total tumor diameter, and size of dominant tumor. The only significant baseline difference was ECOG status. Uni- and multivariate analysis demonstrated a larger reduction in TTD and objective response by mRECIST criteria for patients undergoing Y-90 RS on metformin compared to those not on metformin. OS was similar between patients taking and not taking metformin ($p = 0.912$).
Conclusion Metformin may be associated with increased tumor response after Y-90 RS in patients with HCC.
Level of Evidence III, Retrospective Study.

Keywords Metformin · Y-90 radiation segmentectomy · Y-90 radioembolization

Introduction

Yttrium-90 (Y-90) radioembolization segmentectomy (RS) is a procedure in which radiolabeled Y-90 microspheres are injected into a hepatic artery that feeds the tumor to be treated [1]. In carefully selected patients with unresectable hepatocellular carcinoma (HCC), Y-90 RS improves tumor response and survival compared to systemic therapies [2–5]. This therapy can also be effective for downstaging HCC or bridging to liver transplantation [6–8].

The incomplete response of HCC to locoregional therapy, including Y-90 RS, is a relatively common occurrence in large tumors. Growing evidence suggests that this may

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be related to an insufficient tumor dose or alterations in the tumor's genetics and microenvironment, which can confer resistance to radiotherapy [9, 10]. For example, Kurebayashi et al. demonstrated that newly formed blood vessels from HCC are hypoxic, which triggers the expression of hypoxia-inducible factor 1-alpha (HIF-1 α) and upregulation of radioresistant genes [11]. This has warranted further efforts to optimize dosing strategies and improve tumor sensitivity to Y-90 RS treatment.

Increasing evidence suggests that the commonly used diabetes drug metformin has a potential role in improving outcomes in oncology [12] by altering tumor angiogenesis, cancer-associated fibroblasts, and tumor-associated macrophages to disrupt the tumor microenvironment. Several analyses examining patients with various malignancies have demonstrated improved survival after chemotherapy and external beam radiation when taking metformin [13, 14]. The use of metformin in type 2 diabetics has also been associated with a reduced incidence of HCC in the setting of cirrhosis [15], and improved treatment response for patients with HCC after chemotherapy, external beam radiation, and resection [16–20]. Despite the encouraging data of metformin as a sensitizing agent, the potential therapeutic benefit in patients with HCC undergoing Y-90 RS has not been studied. The purpose of this paper is to compare tumor response after Y-90 radiation segmentectomy in patients with hepatocellular carcinoma on metformin compared to those who were not.

Methods and Materials

Study Selection

The Institutional Review Board approved this study. A retrospective analysis was performed on consecutive adult patients who underwent Y-90 radiation segmentectomy between 2014 and 2018. All patients were referred to interventional radiology for Y-90 RS through multidisciplinary tumor boards. Data was collected from two large university-affiliated tertiary care hospitals at a single institution. Inclusion criteria included patients who underwent Y-90 RS to a single segment or subsegmental branch supplying the targeted tumor(s). Exclusion criteria included patients who had lobar Y90 treatment, bi-lobar disease, prior Y-90 RS therapy to the same lesion, or absence of baseline and follow up imaging (contrast-enhanced liver protocol MRI or CT within three months of Y-90 RS). Patients included in this study were evaluated for concurrent metformin use. All patients on metformin had diabetes Per ACR guidelines metformin was not withheld before or after the procedure for any patients [21].

Y-90 Angiographic Mapping and Procedure

Patients selected for Y-90 RS underwent routine pre-procedural angiography, which included administration of 99mTc macro aggregated albumin (Tc-99 m MAA) into the hepatic artery vasculature feeding tumor for evaluation of extra-hepatic shunting. Procedures were performed as described in prior literature [1]. Briefly, prior to Tc-99 m MAA administration, angiography was performed for procedural planning, and embolization was performed in branch vessels thought to be at high risk for non-target embolization. Cone-beam computed tomography was then performed to ensure perfusion of the entire targeted tumor(s). If the entire tumor(s) were not perfused from the microcatheter location, the location was adjusted, and the process was repeated to ensure the entire treatment tumor was covered. Approximately 4 mCi of Tc-99 m MAA was administered in total. Within 1 h after administration of Tc-99 m MAA, planar imaging was performed to calculate hepatopulmonary shunting. SPECT/CT was subsequently performed for radiotracer localization and determination of possible extra-hepatic activity.

Dose calculation was performed in accordance with procedures described in prior literature published in part by our institution [22]. Briefly, administered activity was calculated based on the manufacturer recommendation for glass microspheres – administered in all radiation segmentectomies in this study – using the Medical Internal Radiation Dosimetry (MIRD) model [23]. The mass of the liver lobe was calculated based on the imaging measurement and three-dimensional analysis using medical imaging software (MIM Software, Columbus, OH, USA), assuming a density of 1.03 g/cm^3 of liver tissue. Additionally, desired radiation dose to the targeted segment/subsegment was calculated to be 190 Gy, as previously reported by Riaz et al. [24]. Dose modifications were performed in patients with elevated lung shunt fractions (typically $> 20\%$) to ensure a single treatment lung dose less than 30 Gy and a cumulative lifetime lung dose less than 50 Gy. After appropriate dose calculation, patients underwent Y-90 RS using glass microspheres.

Data Collection and Analysis

Comparisons were made between all patients who were concurrently taking metformin and those who were not. Sub-analyses were performed examining only diabetic patients who were on metformin and those who were not. All patients were evaluated for baseline demographic factors including age, sex, etiology of HCC, diabetic condition, Eastern Cooperative Oncology Group (ECOG) status, Child–Pugh (CP) score, model for end-stage liver disease (MELD) score, Barcelona Clinic Liver Cancer (BCLC)

staging, Albumin Bilirubin (ALBI) score, and qualification for transplant using the Milan criteria. Age groups were defined as < 65 years old and > 65 years old. MELD scores were grouped as either < 8 or ≥ 8, and Child–Pugh scores were grouped as being either Child–Pugh A or Child–Pugh B/C. BCLC stages were grouped as stage A or $>$ A (BCLC B-D), since our dataset did not include patients with a BLCL = 0.

Baseline Hba1c was compared between diabetic patients on metformin and diabetic patients who were not. Pre-procedural imaging was performed in all included patients with liver-protocol of either contrast-enhanced CT or MRI. Tumor response was assessed at post-procedure imaging, typically performed at 12 weeks after Y-90 RS.

Diameter of the largest treated tumor, number of lesions, and cumulative total tumor diameter (TTD) of the three largest lesions were evaluated. Largest tumor size was compared using chi-square analysis by grouping tumors as having a tumor size of < 4 cm or ≥ 4 cm. Similarly, TTD was compared using chi-square analysis by grouping tumors as having a TTD < 5 cm or ≥ 5 cm. All patients followed up within 3 months of Y-90 RS treatment by undergoing contrast-enhanced liver protocol MRI or CT. Lesions were considered viable if there was nodular, mass-like, or thick irregular tissue along the treatment bed with any of the following: arterial phase hyperenhancement, washout, or enhancement similar to pre-treatment. Tumor response was assessed using both absolute and percent change in TTD and objective response by change in modified Response Evaluation Criteria in Solid Tumors (mRECIST) category after treatment. Baseline characteristics between groups were compared using Pearson's chi-squared, Fisher's exact test, and t-test analysis, with a p-value less than 0.05 considered statistically significant. Post-procedural imaging was interpreted by academic fellowship-trained abdominal imaging radiologists with multiple years of post-fellowship experience.

Outcome and follow up data between groups were compared with Pearson's chi-squared, Fisher's exact test, t-test analysis. A p-value of less than 0.05 was considered statistically significant. Multivariate analysis with logistic regression was performed for change in TTD and mRECIST criteria among patients who were on metformin and those who were not.

Overall survival (OS) was defined as the time from the date of Y-90 to the date of death or last follow up. OS was compared using Kaplan–Meier estimation and log-rank analysis.

Results

Baseline Characteristics

106 patients with HCC underwent a total of 112 Y-90 RS treatments. Among these patients, 40 (37.7%) had diabetes, with 19 patients (18.4%) concurrently taking metformin. All patients had eGFR > 30 ml/min/1.73 m^2.

Of the 112 Y-90 RS treatments, 19 cases were performed on patients taking metformin and the remaining 93 were performed on patients who are not taking metformin. Demographic factors of age, gender, and ethnicity did not differ significantly between the two groups. Additionally, the number of patients undergoing more than one treatment (90.3% vs. 100%, $p = 0.157$), baseline Child–Pugh score (Child–Pugh score A: 89.2% vs. 100%, $p = 0.134$), baseline ALBI grade (ALBI 1: 28% vs. 26.3%; ALBI 2: 66.7% vs.73.7%; ALBI 3: 5.4% vs. 0%, $p = 0.562$), and the proportion of patients qualifying for Milan criteria were not significantly different.

Between the metformin and non-metformin group, there was no statistically significant difference in BCLC stage (BCLC stage A: 63.4% vs. 68.4%, $p = 0.68$). MELD score did not differ significantly between groups (MELD < 8: 12.9% vs. 5.3%, $p = 0.343$). Additionally, there were no differences in dominant tumor size (> 4 cm: 52.7% vs. 36.8%, $p = 0.208$), second largest tumor size, and TTD (> 5 cm: 38.7% vs. 36.8%, $p = 0.879$) between patients taking and not taking metformin (Fig. 1; Table 1). Diabetic patients on metformin had a lower ECOG status (ECOG 0: 94.7 vs. 47.7%; $p < 0.001$). Compared to patients without

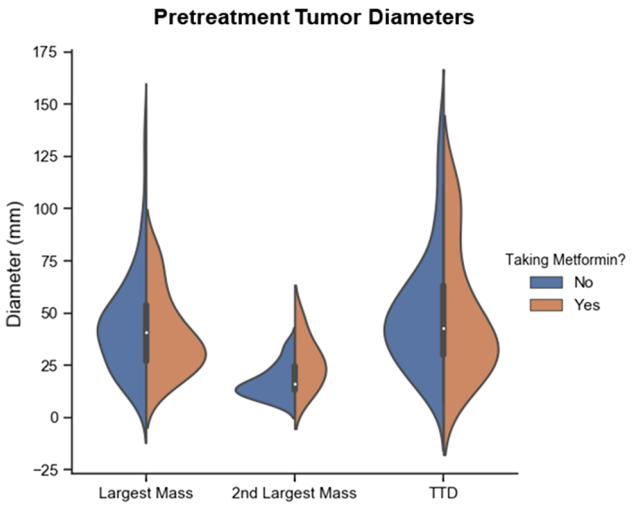

Fig. 1 Violin plot comparing the largest liver mass, 2nd largest mass, and TTD prior to Y-90 RS. Patients on metformin (orange) had no statistical difference in the largest liver mass or total tumor diameter ($p > 0.05$), when compared to patients not on metformin (blue). However, the second largest mass diameter was greater in patients on metformin (26.00 vs. 17.26 mm; $p = 0.029$)

Table 1 Comparison of baseline characteristics of patients on metformin and not on metformin

Baseline Factor	Metformin	No Metformin	P-value (*)
Age in Years (mean)	64.5	63.9	0.804
Male Gender (%)	68.4	80.2	0.356
Etiology (most common category)	HCV	HCV	0.700
ECOG 0 (%)	94.7	72.1	0.008*
Childs-Pugh A (%)	100	87.2	0.208
MELD Score (mean)	9.48	10.30	0.163
BCLC A (%)	57.9	38.3	0.483
ALBI Grade (most common category)	2	2	0.632
Met Milan Criteria (%)	52.6	51.2	1.0
Met UCSF Criteria (%)	57.9	58.1	1.0
Mean Dominant Tumor Size Diameter (mm)	40.05	44.72	0.434
Mean Total Tumor Diameter (mm)	50.21	50.83	0.934
Mean Total Number of Lesions	1.47	1.48	0.989
Lung Shunt Fraction (%)	6.04	7.75	0.144
Liver Dose (Gy)	113.62	111.23	0.681

*$p < 0.05$

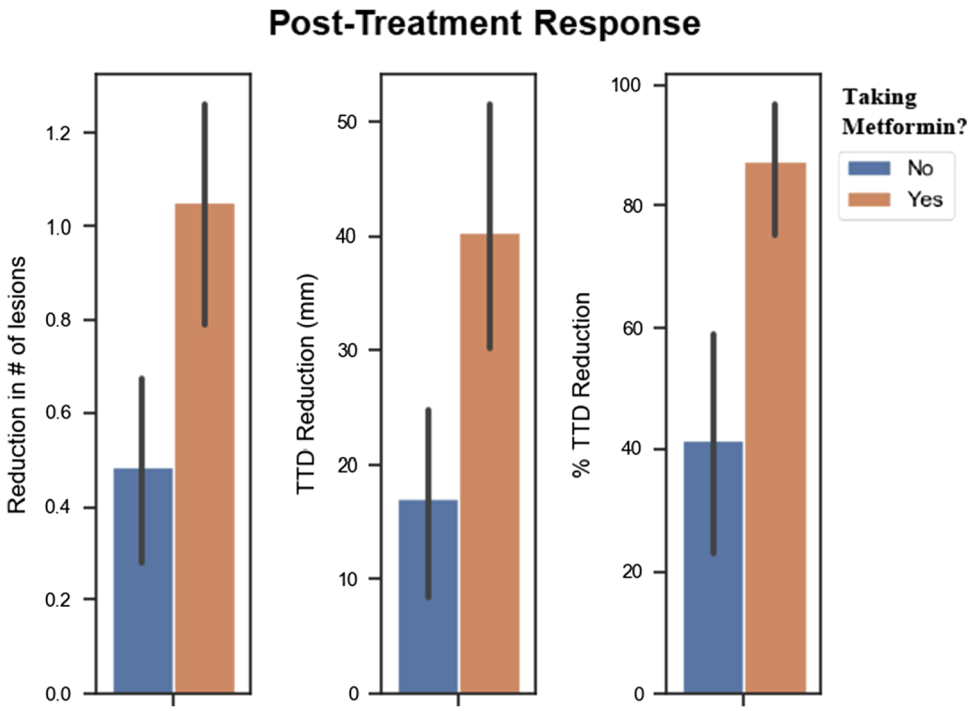

Fig. 2 Histograms comparing post-treatment tumor response. On follow-up imaging, patients on metformin (orange) compared to those not taking metformin (blue) had a greater mean reduction in viable lesion (1.05 vs. 0.49 lesions; $p = 0.001$), a greater reduction in total tumor diameter (40.4 vs. 17.1 mm; $p = 0.018$), and a greater percent reduction in total tumor diameter (87.47 vs. 41.6%; $p < 0.001$)

diabetes, patients with diabetes were more likely to have NASH cirrhosis (22.5 vs. 4.6%; $p = 0.009$), and less likely to have HCV cirrhosis (42.5 vs. 66.2%; $p = 0.025$). There was no difference in Hba1c between diabetic patients on metformin and diabetic patients not on metformin (6.25 vs. 7.34; $p = 0.062$).

Treatment Response and Survival

On follow-up imaging, patients on metformin had a greater mean reduction of viable lesions of 1.05 compared to 0.49 in patients not on metformin ($p = 0.001$; Fig. 2). Patients taking metformin had a greater mean TTD reduction of 40.4 mm compared to 17.1 mm in patients not on metformin ($p = 0.018$; Fig. 2). A mean percent reduction of $> 50\%$ in viable TTD was greater in patients on

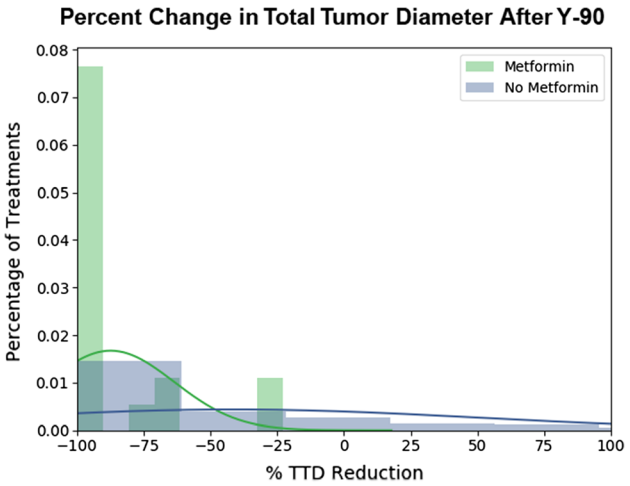

Fig. 3 Patients taking metformin (green) had an average percent decrease of 87.47% in total tumor diameter compared to an average decrease of 41.6% in patients not taking metformin (blue; $p < 0.001$)

Table 2 Logistic regression determining independent factors predicting > 50% total tumor diameter in patients who underwent Y-90 radiation segmentectomy

Baseline Factor	Exp(B)	Standard Error	P-value (*)
Age	0.93	0.537	0.893
Ethnicity	1.055	0.490	0.913
ECOG Status	1.521	0.52	0.420
Albi Grade	1.038	0.556	0.947
MELD Score	0.681	0.794	0.628
Child–Pugh score	7.407	0.959	0.037*
BCLC Stage	6.285	0.616	0.003*
Largest tumor size	0.297	0.636	0.056
Total tumor diameter	1.617	0.865	0.578
Milan criteria	2.515	0.815	0.258
Metformin	9.351	0.934	0.017*
Number of treatments	0.220	0.938	0.123

*$p < 0.05$

metformin (89.5%) than patients not on metformin (60.2% $p = 0.015$; Fig. 3). Among all patients taking metformin, there was a larger proportion of patients with complete response by mRECIST criteria (65.6 vs. 89.5% treatments, p = 0.039).

Multivariate analysis using logistic regression demonstrates that metformin was an independent predictor of > 50% reduction in viable TTD ($p = 0.017$) and objective response ($p = 0.040$;Tables 2 and 3). Additionally, both CP A score and BCLC A stage were also found to be independent predictors of > 50% reduction in viable TTD and objective response (Tables 2 and 3).

OS in the metformin group, 38.2 months, did not statistically differ from OS in patients not on metformin, 40.3 months ($p = 0.912$; Fig. 4). When comparing diabetic patients on metformin to diabetics not taking metformin, diabetic patients on metformin had a greater absolute decrease in TTD (40.4 vs. 13.9 mm; $p = 0.036$), but not percent change (87.5 vs. 39.0%; $p = 0.081$) or decrease in number of lesions (1.05 vs. 0.67; $p = 0.215$). Which may be attributed to a lower number of patients in this subgroup. Overall survival was not significantly different between diabetic patients on metformin and those who were not (38.2 vs. 34.6 months; $p = 0.995$).

Table 3 Logistic regression determining independent factors predicting objective response via mRECIST in patients who underwent Y-90 radiation segmentectomy

Baseline Factor	Exp(B)	Standard Error	P-value (*)
Age	0.623	0.554	0.393
Ethnicity	0.826	0.499	0.702
ECOG Status	1.311	0.511	0.596
Albi Grade	1.04	0.565	0.944
MELD Score	1.013	0.788	0.986
Child–Pugh score	11.49	0.956	0.011*
BCLC Stage	4.20	0.609	0.018*
Largest tumor size	0.434	0.644	0.196
Total tumor diameter	0.685	0.911	0.678
Milan criteria	1.237	0.870	0.807
Metformin	5.709	0.912	0.040*
Number of treatments	0.393	0.985	0.344

*$p < 0.05$

Discussion

Metformin may have a role as an anti-tumor agent in HCC. Meta-analyses have shown improved outcomes in animals with HCC taking metformin as well as decreased rates of development of HCC in diabetic patients taking metformin [20, 25]. Furthermore, an increasing number of studies in the radiation oncology literature suggest that metformin may function as a radiosensitizing agent for patients undergoing radiation treatment of their malignancies, including HCC [13, 17]. For example, Jang et al. demonstrate that patients with HCC on metformin who underwent stereotactic body or hypofractionated radiotherapy experienced greater overall and progression-free survival [17]. Prospective trials in patients with HCC undergoing Y-90 RS would be required to elucidate the therapeutic benefits and optimal dosing strategy of metformin.

Metformin exerts pleiotropic effects through various signaling pathways; however, its anti-tumoral properties are not fully understood. Multiple studies suggest that

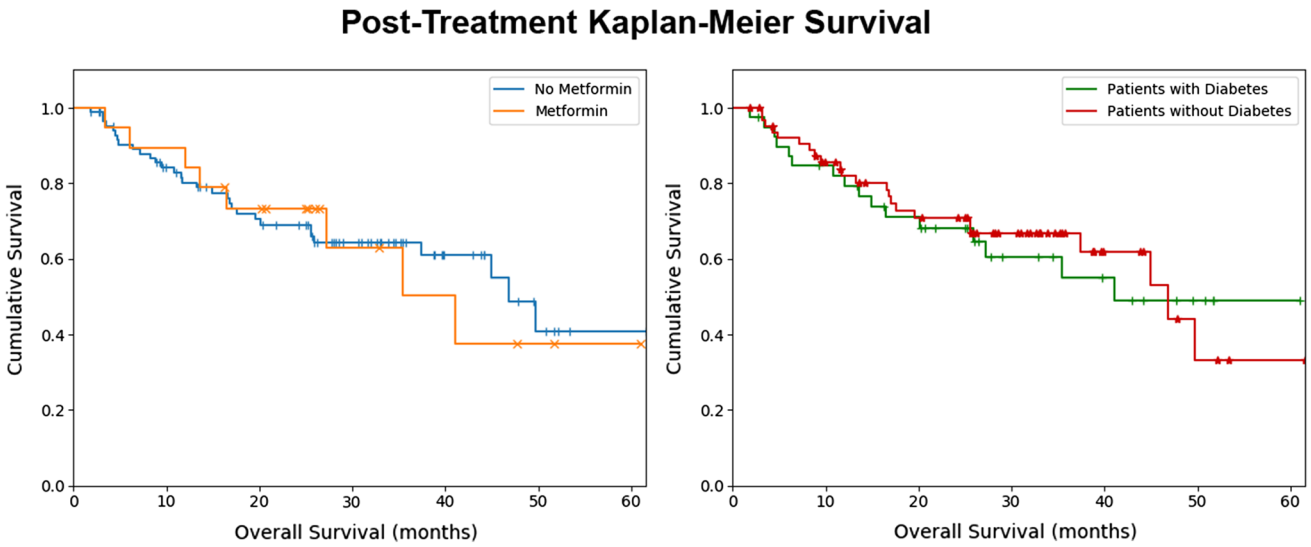

Fig. 4 Kaplan–Meier post-treatment survival plots. Patients on metformin (orange) had no difference in OS compared to patients not on metformin (blue; 33.7 vs 39.7 months; $p = 0.886$). Patients with diabetes (green) had no difference in OS compared to patients without diabetes (red; 39.5 months vs. 40.03 months; $p = 0.830$)

metformin exerts protective effects through the activation of AMP-activated protein kinase (AMPK). Above certain concentrations in the liver, AMPK activation can trigger apoptosis and limit protein synthesis, cellular proliferation, and angiogenesis [26–28]. In a rat model of cirrhosis, metformin prevented HCC development by suppressing activation of HIF-1 α-hepatic progenitor cells [29]. Metformin has also been shown to augment response to radiation therapy, as evidenced by enhanced DNA damage after radiation, which may be related to impaired DNA repair mechanisms and response to oxidative stress [30].

The results from this study add to the notion that metformin is a radiosensitizing agent and may have a potential therapeutic benefit in patients undergoing Y-90 radioembolization. In our series, patients on metformin with HCC who underwent Y-90 RS had improved response to therapy, as evidenced by a reduction in the number of viable lesions, a reduction in tumor diameter, and a greater proportion of complete response by mRECIST criteria compared to patients not taking metformin. An improved response, evidenced by a greater absolute reduction in TTD, was also observed among diabetic patients on metformin compared to diabetic patients not on metformin. Despite an improved tumor response to therapy at the first follow up appointment (within three months), patients taking metformin had no statistical difference in overall survival. This is likely at least in part related to a relatively short-term follow-up period in this cohort. This may also be related to the fact that diabetes as an independent risk factor confers a baseline lower OS.

This study is limited by its retrospective nature and small sample size, where small differences may not be appreciated. There were multiple confounding variables, which may obscure the influence of metformin, including effects on survival. Patients with diabetes were more likely to have NASH cirrhosis, while patients without diabetes were more likely to have HCV cirrhosis. Also, patients on metformin have diabetes which may lead to variations in clinical management and outcomes compared to patients without diabetes.

It is also notable that while baseline factors of age, Child–Pugh score, BCLC stage, MELD score, ALBI grade, and measured tumor sizes were not statistically different between the metformin and non-metformin groups, this may be related to a relatively small sample size which can obscure subtle effects between groups. Individualized dosimetry data was also not analyzed between groups, which may have an influence on tumor response. However, dosing was likely similar between all groups, since there were no differences in measured tumor sizes and the same dosing model (MIRD) was utilized in all patients.

Despite the limitations of this analysis, this relatively robust multifactorial analysis suggests that metformin is an independent predictor of tumor diameter and objective response.

Conclusion

Metformin may be associated with increased tumor response in patients with HCC undergoing Y-90 RS. More human and animal-based studies are required to understand the anti-cancer effects of metformin with the goal of optimizing therapy and elucidating its mechanistic targets.

Furthermore, prospective studies examining the effects of metformin and similar pharmaceutical agents on Y-90 is warranted, as this may provide an opportunity to improve outcomes for patients with unresectable HCC.

Author contribution Mohammad Elsayed conceived the analysis, contributed the data, performed the analysis, and wrote the paper. William Wagstaff contributed the data and performed the analysis. Keywan Behbahani wrote the paper. Alexander Villalobos contributed the data and performed the analysis. Zachary Bercu contributed data. Bill Majdalany contributed the data. Mehmet Akce contributed the data. David Schuster contributed the data. David M Schuster contributed the data. Hui Mao contributed the data and performed the analysis. Nima Kokabi conceived the analysis, contributed the data, performed the analysis, and wrote the paper.

Declarations

Conflict of interest The senior author, Nima Kokabi MD, conducts Y-90 radioembolization research partially funded by Sirtex Medical Ltd. Richard Duszak, Jr., MD receives research support from the Harvey L. Neiman Health Policy Institute.

References

1. Camacho JC, Moncayo V, Kokabi N, Reavey HE, Galt JR, Yamada K, et al. 90Y Radioembolization: Multimodality Imaging Pattern Approach with Angiographic Correlation for Optimized Target Therapy Delivery. Radiographics. 2015;35(5):1602–18. https://doi.org/10.1148/rg.2015140314.
2. Bhangoo MS, Karnani DR, Hein PN, Giap H, Knowles H, Issa C, et al. Radioembolization with Yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. J gastrointest oncol. 2015;6(5):469–78. https://doi.org/10.3978/j.issn.2078-6891.2015.056.
3. Gordon AC, Gabr A, Riaz A, Uddin OM, Abouchaleh N, Ali R, et al. Radioembolization super survivors: extended survival in non-operative hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2018;41(10):1557–65. https://doi.org/10.1007/s00270-018-2008-y.
4. Wehrenberg-Klee E, Gandhi RT, Ganguli S. Patient selection and clinical outcomes of y90 in hepatocellular carcinoma. Tech Vasc Interv Radiol. 2019;22(2):70–3. https://doi.org/10.1053/j.tvir.2019.02.006.
5. Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. Journal of vascular and interventional radiology: JVIR. 2010;21(2):224–30. https://doi.org/10.1016/j.jvir.2009.10.013.
6. Levi Sandri GB, Ettorre GM, Giannelli V, Colasanti M, Sciuto R, Pizzi G, et al. Trans-arterial radio-embolization: a new chance for patients with hepatocellular cancer to access liver transplantation, a world review. Translational gastroenterology and hepatology. 2017;2:98. https://doi.org/10.21037/tgh.2017.11.11.
7. Ettorre GM, Levi Sandri GB, Laurenzi A, Colasanti M, Meniconi RL, Lionetti R, et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma Prior to Liver Transplantation. World J Surg. 2017;41(1):241–9. https://doi.org/10.1007/s00268-016-3682-z.
8. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151(6):1155-63.e2. https://doi.org/10.1053/j.gastro.2016.08.029.
9. Guo J, Li L, Guo B, Liu D, Shi J, Wu C, et al. Mechanisms of resistance to chemotherapy and radiotherapy in hepatocellular carcinoma. Translational Cancer Research. 2018;7(3):765–81.
10. Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology (Baltimore, MD). 2014;60(1):192–201. https://doi.org/10.1002/hep.27057.
11. Kurebayashi Y, Ojima H, Tsujikawa H, Kubota N, Maehara J, Abe Y, et al. Landscape of immune microenvironment in hepatocellular carcinoma and its additional impact on histological and molecular classification. Hepatology (Baltimore, MD). 2018;68(3):1025–41. https://doi.org/10.1002/hep.29904.
12. Chen K, Li Y, Guo Z, Zeng Y, Zhang W, Wang H. Metformin: current clinical applications in nondiabetic patients with cancer. Aging. 2020;12(4):3993–4009. https://doi.org/10.18632/aging.102787.
13. Samsuri NAB, Leech M, Marignol L. Metformin and improved treatment outcomes in radiation therapy - a review. Cancer Treat Rev. 2017;55:150–62. https://doi.org/10.1016/j.ctrv.2017.03.005.
14. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol. 2013;37(3):207–18. https://doi.org/10.1016/j.canep.2012.12.009.
15. Tseng C-H. Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. Liver Int. 2018;38(11):2018–27. https://doi.org/10.1111/liv.13872.
16. Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. J Clin Endocrinol Metab. 2011;96(8):2601–8. https://doi.org/10.1210/jc.2010-2415.
17. Jang WI, Kim MS, Lim JS, Yoo HJ, Seo YS, Han CJ, et al. Survival advantage associated with metformin usage in hepatocellular carcinoma patients receiving radiotherapy: a propensity score matching analysis. Anticancer Res. 2015;35(9):5047–54.
18. Seo YS, Kim YJ, Kim MS, Suh KS, Kim SB, Han CJ, et al. Association of metformin use with cancer-specific mortality in hepatocellular carcinoma after curative resection: a nationwide population-based study. Medicine. 2016;95(17):e3527. https://doi.org/10.1097/md.0000000000003527.
19. Harris K, Smith L. Safety and efficacy of metformin in patients with type 2 diabetes mellitus and chronic hepatitis C. Ann Pharmacother. 2013;47(10):1348–52. https://doi.org/10.1177/1060028013503108.
20. Li J, Hernanda PY, Bramer WM, Peppelenbosch MP, van Luijk J, Pan Q. Anti-tumor effects of metformin in animal models of hepatocellular carcinoma: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0127967. https://doi.org/10.1371/journal.pone.0127967.
21. Radiology ACo. 2020. ACR manual on contrast media. American College of Radiology
22. Camacho JC, Moncayo V, Kokabi N, Reavey HE, Galt JR, Yamada K, et al. (90)Y Radioembolization: multimodality imaging pattern approach with angiographic correlation for optimized target therapy delivery. Radiographics. 2015;35(5):1602–18. https://doi.org/10.1148/rg.2015140314.
23. TheraSphere® Yttrium-90 Glass Microspheres. Biocompatibles UK. https://btgplc.com/BTG/media/TheraSphere-Documents/PDF/TheraSphere-Package-Insert_USA_Rev-14.pdf. July 2019. .
24. Riaz A, Gates VL, Atassi B, Lewandowski RJ, Mulcahy MF, Ryu RK, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol

Phys. 2011;79(1):163–71. https://doi.org/10.1016/j.ijrobp.2009.10.062.
25. Zhang H, Gao C, Fang L, Zhao HC, Yao SK. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. Scand J Gastroenterol. 2013;48(1):78–87. https://doi.org/10.3109/00365521.2012.719926.
26. Cunha V, Cotrim HP, Rocha R, Carvalho K, Lins-Kusterer L. Metformin in the prevention of hepatocellular carcinoma in diabetic patients: a systematic review. Ann Hepatol. 2019. https://doi.org/10.1016/j.aohep.2019.10.005.
27. Li J, Hernanda PY, Bramer WM, Peppelenbosch MP, van Luijk J, Pan Q. Anti-tumor effects of metformin in animal models of hepatocellular carcinoma: a systematic review and meta-analysis. PLoS ONE. 2015;10(6):e0127967. https://doi.org/10.1371/journal.pone.0127967.
28. Zheng L, Yang W, Wu F, Wang C, Yu L, Tang L, et al. Prognostic significance of AMPK activation and therapeutic effects of metformin in hepatocellular carcinoma. Clin canc res: an official J Amer Assoc Cancer Res. 2013;19(19):5372–80. https://doi.org/10.1158/1078-0432.ccr-13-0203.
29. DePeralta DK, Wei L, Ghoshal S, Schmidt B, Lauwers GY, Lanuti M, et al. Metformin prevents hepatocellular carcinoma development by suppressing hepatic progenitor cell activation in a rat model of cirrhosis. Cancer. 2016;122(8):1216–27. https://doi.org/10.1002/cncr.29912.
30. Koritzinsky M, Metformin. 2015. A Novel Biological Modifier of Tumor Response to Radiation Therapy. Int J Rad Oncol*Biol*-Phys. 93 (2) 454–64. https://doi.org/10.1016/j.ijrobp.2015.06.003