Administered activity and outcomes of glass versus resin ^{90}Y microsphere radioembolization in patients with colorectal liver metastases

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Background: Given the differences in size, specific activity, and dosing methods for glass yttrium-90 microspheres (^{90}Y-glass) and resin ^{90}Y microspheres (^{90}Y-resin), these therapies may expose the liver to different amounts of radiation, thereby affecting their efficacy and tolerability. We aimed to compare the prescribed activity of ^{90}Y-glass and ^{90}Y-resin for real-world patients undergoing selective internal radiation therapy (SIRT) for liver-dominant metastatic colorectal cancer (mCRC) and to assess efficacy and safety outcomes in these patients.

Methods: We examined the records of 28 consecutive patients with unresectable colorectal liver metastases treated with SIRT between June 2008 and May 2011 at our institution. Using baseline CT and MR images, we calculated a projected activity as if we had used the other product and compared it to the actual prescribed activity of ^{90}Y-glass and ^{90}Y-resin for each SIRT treatment per manufacturer guidelines. Progression and adverse events were evaluated at follow up visits. Survival was analyzed by the Kaplan-Meier method.

Results: For ^{90}Y-glass treatments with a mean prescribed ^{90}Y activity of 1.77 GBq, the mean projected ^{90}Y-resin activity was 0.84 GBq. For ^{90}Y-resin treatments with a mean prescribed ^{90}Y activity of 1.05 GBq, the mean projected ^{90}Y-glass activity was 2.48 GBq. The median survival was 9.3 months versus 18.2 months for ^{90}Y-glass and ^{90}Y-resin, respectively (P=0.292). During the second year after SIRT, the hazard ratio of death for patients treated with ^{90}Y-glass versus ^{90}Y-resin was 4.0 (95% CI: 1.3, 12.3; P=0.017). No significant difference in progression, adverse events or liver toxicity was observed.

Conclusions: Using manufacturer recommended guidelines, ^{90}Y-resin delivers significantly less activity than ^{90}Y-glass to patients with liver-dominant mCRC undergoing SIRT with no significant difference in adverse events and a trend toward improved survival.

Keywords: Yttrium-90 (^{90}Y); colorectal cancer; liver metastases; brachytherapy

Introduction

Colorectal cancer is the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed each year (1). Approximately 50–60% of patients with colorectal cancer present with or develop hepatic metastases through the course of their disease (2,3). Surgical liver resection offers the best prognosis for these patients but is only an

option for 10–20% of patients diagnosed with colorectal liver metastases (2,4).

Over the past 2 decades, selective internal radiation therapy (SIRT) using yttrium-90 (^{90}Y) microspheres (also called radioembolization) has emerged as an effective and safe treatment option for patients with unresectable metastatic colorectal cancer with liver-dominant metastases (5). [90]Y microspheres emit beta radiation within a relatively small radius (mean 2.5 mm), delivering tumoricidal radiation doses to localized regions in the liver while limiting the dose to healthy liver tissue (6,7). Currently, 2 different ^{90}Y microsphere products are commercially available: glass ^{90}Y microspheres (TheraSphere®; Biocompatibles UK Ltd., Surrey, England) and resin ^{90}Y microspheres (^{90}Y-resin; SIR-Spheres®; SIRTeX Medical Limited, North Sydney, NSW, Australia) (6). Glass ^{90}Y microspheres (^{90}Y-glass) measure 20–30 μm in size and contain approximately 2,500 Bq per sphere, while resin ^{90}Y microspheres (^{90}Y-resin) measure 20–60 μm in size and contain 50 Bq per sphere. A compartmental model is the manufacturer-recommended method to calculate the appropriate activity of ^{90}Y-glass, and the body surface area (BSA) method is recommended for the activity calculation of ^{90}Y-resin (5,8).

Both ^{90}Y-glass and ^{90}Y-resin have shown efficacy in patients with unresectable liver metastases (9,10), however given their differences in specific activity, size, and dosimetry methods, these products may expose the liver to different amounts of radiation, thereby affecting their efficacy and tolerability. To date, no individual study has directly compared the dosimetry of ^{90}Y-glass versus ^{90}Y-resin used in SIRT in patients with unresectable hepatic metastases from colorectal cancer.

In this retrospective analysis of patients undergoing radioembolization for colorectal liver metastases at a single institution, we assessed the calculated prescribed radiation activity in patients treated with ^{90}Y-glass versus ^{90}Y-resin and compared efficacy and adverse event outcomes.

Methods

Patients

This study was a single-institution retrospective analysis of patients with unresectable colorectal liver metastases treated with ^{90}Y microsphere radioembolization at Cleveland Clinic between June 11, 2008, and May 16, 2011.

Patient records, including contrast enhanced computed tomography (CT) or magnetic resonance (MR) images,

were retrospectively reviewed. This study was approved by Cleveland Clinic's Institutional Review Board and is compliant with the Health Insurance Portability and Accountability Act.

Radioembolization

Radioembolization was delivered via a hepatic artery catheter infusion with either ^{90}Y-glass (TheraSphere®; Biocompatibles UK Ltd., Surrey, England) or ^{90}Y-resin (SIR-Spheres®; SIRTeX Medical Limited, North Sydney, NSW, Australia) as previously described (5,11). The treatment strategy of either bilobar treatment, sequential lobar, or whole-liver ^{90}Y radioembolization was at the discretion of the interventional radiologist. Selection of ^{90}Y-glass or ^{90}Y-resin was also determined by the managing interventional radiologist with discussion from the nuclear medicine authorized user, as needed.

[90]Y activity calculations

[90]Y activity was determined according to the manufacturer and recommended practice guidelines at the time of treatment (5,12-15).

For glass ^{90}Y microspheres (TheraSphere®):

Target liver lobar volume was multiplied by 1.03 g/cm^3 conversion factor to calculate target liver lobe mass. Target ^{90}Y activity was determined by the following formula, using 120 Gy as the desired dose (5,15):

$$TheraSphere^{®}\ activity\,(GBq) = \frac{Desired\ dose\,(Gy) \times Mass\ of\ selected\ liver\ target\ lobe\,(kg)}{50} \quad [1]$$

For resin ^{90}Y microspheres (SIR-Spheres):

The target activity was calculated using the body surface area (BSA) method, adjusted for the fraction of the liver to be treated (5,12-14):

$$BSA(m^2) = 0.20247 \times (Height(m))^{0.725} \times (Weight(kg))^{0.425} \quad [2]$$

$$Sir-Sphere\ Activity\,(GBq) = \left[(BSA - 0.2) + \frac{Tumor\ lobar\ volume}{Treated\ lobar\ volume}\right] \times \frac{Treated\ lobar\ volume}{Total\ liver\ volume} \quad [3]$$

Prescribed ^{90}Y activity was obtained from patient records. For each ^{90}Y-glass treatment, the corresponding projected activity of ^{90}Y-resin was calculated using the formula

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above, using tumor and liver volumes determined by MIM® software (Cleveland, OH, USA) analysis of baseline CT or MR images. For each ^{90}Y-resin treatment, the corresponding projected activity of ^{90}Y-glass was calculated using the formula above.

Evaluation of response and survival

CT or MR imaging was performed at baseline and at follow-up, typically 1 to 3 months posttreatment. Response assessment was performed according to Response Evaluation Criteria in Solid Tumors combined with necrosis criteria (mRECIST). Time to progression and overall survival time in months was calculated as the difference from the date of first ^{90}Y radioembolization to date of the event or last observation date in case of censoring. The date of death was obtained from patient records. For patients lost to follow-up, date of death was obtained by searching available public records.

Toxicity assessments and adverse events

Laboratory data from tests performed at baseline and at follow-up observations were obtained from the patients' charts, including liver function tests, hemoglobin, and blood cell counts. The presence and severity of adverse events occurring within 90 days of radioembolization and deemed to be related to the treatment were obtained from patient records, including fatigue, nausea/vomiting, abdominal pain, jaundice, cholecystitis, and gastritis. Liver enzyme toxicities were classified using the National Cancer Institute common terminology criteria for adverse events v4.03 (16).

Statistical analyses

Differences in baseline characteristics between the treatment groups were evaluated by a Wilcoxon rank sum test for ordinal variables and a Fisher's exact test for categorical variables. Overall survival probabilities were evaluated using the Kaplan-Meier method with 95% confidence intervals (95% CI) for the difference in median survival time between ^{90}Y-resin and ^{90}Y-glass patients constructed with the percentile bootstrap method. Ten thousand bootstrap samples were generated, each sampled with replacement at the patient level. Fisher's exact test was used to assess differences in the rate of disease progression

(or death) between ^{90}Y-resin and ^{90}Y-glass patients at 3 and 6 months after first ^{90}Y treatment. A Cox proportional hazards model was used to assess the effect of treatment on survival while adjusting for age and tumor extent at first treatment. In this model, treatment (^{90}Y-glass *vs.* ^{90}Y-resin) was included as the main predictor of interest, while age and tumor extent at first treatment were included as covariates. A significance level of 0.05 was used for all analyses.

Results

Patient characteristics and treatment strategy

Between June 11, 2008, and May 16, 2011, a total of 28 consecutive patients with colorectal liver metastases underwent transarterial radioembolization with ^{90}Y microspheres at Cleveland Clinic. Fifteen patients received 29 treatments with ^{90}Y-glass, and 13 patients received 22 treatments with ^{90}Y-resin. All patients had received prior chemotherapy, typically multiple lines of chemotherapy. Baseline demographics and liver enzymes were similar between the 2 groups (*Table 1*). The median time from diagnosis of liver metastases to ^{90}Y treatment was more than twice as long for ^{90}Y-resin-treated patients *vs.* ^{90}Y-glass–treated patients (448 *vs.* 184 days, respectively; P=0.025). The ^{90}Y-glass prescribed activity per treatment was significantly higher than that of ^{90}Y-resin [mean 1.77 gigabecquerel (GBq) *vs.* 1.05 GBq; P=0.007]. The mean administered activity per patient over the entire course of treatment was almost 3 times higher among ^{90}Y-glass–treated patients compared to ^{90}Y-resin–treated patients (mean: 3.5 *vs.* 1.3 GBq; P<0.001). Differences in lobar involvement and treatment plan also existed between the ^{90}Y-resin and ^{90}Y-glass groups. ^{90}Y-resin–treated patients with bilobar involvement received treatment for each lobe on the same day, while ^{90}Y-glass–treated patients typically received sequential lobar treatments ≤1 month apart.

^{90}Y activity prescribed with glass vs. resin ^{90}Y microspheres

By contouring tumors on baseline CT or MR images from patients in the ^{90}Y-glass group, we calculated the ^{90}Y-resin projected activity (*Figure 1A,B*) for each ^{90}Y-glass radioembolization treatment. Conversely, by contouring the liver lobes on baseline CT or MR images from patients in the ^{90}Y-resin group, we calculated the ^{90}Y-glass projected activity (*Figure 1C*) for each ^{90}Y-resin radioembolization treatment.

Table 1 Patient characteristics and treatment strategy

Parameter	Glass ^{90}Y [n=15]	Resin ^{90}Y [n=13]
Sex, n [%]		
Male	9 [60]	7 [54]
Female	6 [40]	6 [46]
Age, years	65 [31–86]	63 [35–80]
BSA, m^2	1.9 [1.7–2.5]^a	1.8 [1.5–2.4]^a
ECOG PS, n [%]		
0	2 [13]	1 [8]
1	4 [27]	5 [38]
2	1 [7]	1 [8]
3	2 [13]	1 [8]
Not available	6 [40]	5 [38]
Liver tumor burden , n [%]^b		
<5%	8 [53]	6 [46]
5–15%	4 [27]	2 [15]
15–25%	2 [13]	2 [15]
25–35%	0 [0]	2 [15]
35–45%	1 [7]	1 [8]
Liver laboratory values		
ALT, U/L	22 [6–45]	22 [10–53]
AST, U/L	28 [19–46]	26 [19–101]
Alkaline phosphatase, U/L	136 [54–285]	138 [51–1,392]
Bilirubin, mg/dL	0.4 [0.2–1.7]	0.5 [0.2–1.7]
Time to ^{90}Y treatment, days^c	184 [18–574]*	448 [43–2,029]*
Concurrent chemotherapy, n [%]^d	7 [47]	4 [31]^a
Lobes treated, n [%]		
Unilobar, 1 dose	2	7
Unilobar, 2 doses, segmental	0	1
Bilobar, sequential	11	0
Bilobar, simultaneous	2	4
Bilobar, multiple doses, sequential	0	1
Total liver dose, GBq-mean [SD]	3.5 [1.2]†	1.3 [0.6]†

Data given as median (range) unless otherwise stated; BSA, body surface area; ALT, alanine aminotransferase; AST, aspartate aminotransferase. *, P=0.025; †, P<0.001. ^{a}, Data missing for 1 patient; ^{b}, percentage of whole liver; ^{c}, time from diagnosis of hepatic metastases to first ^{90}Y microsphere treatment; ^{d}, chemotherapy treatment either concurrent or initiated within 1 month of last ^{90}Y treatment.
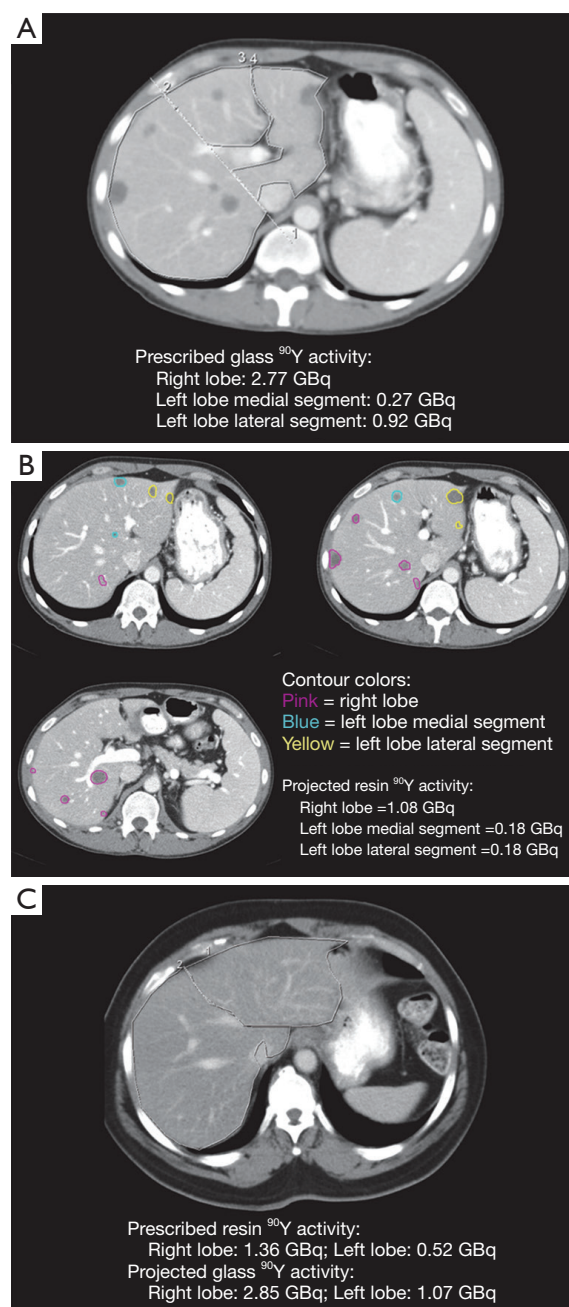

Figure 1 Pre-radioembolization CT images: examples of lobar and tumor contours used in calculating ^{90}Y activity. (A) Right lobe, left lobe medial segment and left lobe lateral segment contours used to determine glass microsphere prescribed dose in a 35-year-old male patient; (B) tumor contours used to determine projected resin microsphere activity in the same 35-year-old male patient; (C) right lobe and left lobe contours used to determine projected glass microsphere activity in a 57-year-old male patient who received a separate resin microsphere treatment for each lobe.

If patients in the ^{90}Y-glass group had been treated with ^{90}Y-resin, their mean radiation activity per treatment would have been 53% lower (mean prescribed ^{90}Y-glass activity =1.77 GBq; mean projected ^{90}Y-resin activity =0.84 GBq; *Figure 2A*). Likewise, if patients in the ^{90}Y-resin group had been treated with ^{90}Y-glass, their mean radiation activity per treatment would have been 136% higher (mean projected ^{90}Y-glass activity =2.48 GBq; mean prescribed ^{90}Y-resin activity =1.05 GBq; *Figure 2B*).

Time to progression and overall survival

Eleven of 14 patients (79%) treated with ^{90}Y-glass and 8 of 13 patients (62%) treated with ^{90}Y-resin progressed ≤3 months posttreatment (P=0.420). By 6 months, 79% of ^{90}Y-glass–treated patients and 85% of ^{90}Y-resin–treated patients showed progression (P=0.999).

The date of death was obtained for all 28 patients. Public records confirmed the date of death for 17 ^{90}Y microsphere patients lost to follow-up (8 ^{90}Y-glass, 9 ^{90}Y-resin). Median survival was 547 days (18.2 months) for ^{90}Y-resin–treated patients as compared to 279 days (9.3 months) for ^{90}Y-glass–treated patients, although the 268 day difference was not statistically significant (95% CI: –186–458; P=0.292; *Figure 3*). Of note, 2 ^{90}Y-glass patients and 1 ^{90}Y-resin patient had prolonged survival times (1,170 days, 1,225 days, and 1,259 days, respectively), and 2 ^{90}Y-resin patients died ≤40 days. Excluding the 3 outliers with prolonged survival from the analysis revealed a significantly longer overall survival for ^{90}Y-resin–treated patients as compared with ^{90}Y-glass–treated patients (496 *vs*. 273 days, respectively; P=0.021. No significant difference in survival between ^{90}Y-glass–treated patients and ^{90}Y-resin–treated patients was observed when 2 ^{90}Y-resin patients with survival ≤40 days were excluded from the analysis (279 *vs*. 603 days; P=0.121).

After adjusting for age and hepatic tumor burden, the hazard ratio (HR) of death for ^{90}Y-glass–treated patients was an estimated 4 times greater than that of ^{90}Y-resin–treated patients during the second year after initial SIRT (HR: 4.0; 95% CI: 1.3,12.3; P=0.017).

Total administered activity and survival

In all but 1 ^{90}Y-glass—treated patient, the total ^{90}Y administered activity was higher in ^{90}Y-glass—treated patients than in ^{90}Y-resin–treated patients. After adjusting

for age and hepatic tumor burden the observed survival tended to be higher for ^{90}Y-resin–treated patients (*Figure 4*), although this difference was not statistically significant (HR ^{90}Y-glass *vs*. ^{90}Y-resin: 1.8; 95% CI: 0.8,4.3; P=0.156).

Clinical and laboratory toxicities

Fatigue was the most common reported symptom (^{90}Y-glass group: 53%; ^{90}Y-resin group: 77%; *Tables 2,3*). Most adverse events were mild and occurred within a month of the first ^{90}Y treatment. Abdominal pain resolved without surgical intervention. No deaths were deemed to have resulted as a direct consequence of the treatments themselves. No patient experienced radioembolization-induced liver disease (REILD). Similar liver toxicities were observed in patients receiving ^{90}Y-glass and ^{90}Y-resin treatments.

Conclusions

Using dosimetry calculations based on CT and MR images of real-world patients, we found that the treatment of a particular volume of liver tissue required significantly less ^{90}Y activity with ^{90}Y-resin when compared to ^{90}Y-glass. Our results suggest a trend toward improved survival in patients receiving ^{90}Y-resin, particularly during the second year following SIRT.

One of the core principles of radiation therapy is to keep radiation exposure as low as reasonably achievable (17). In our study, patients in the ^{90}Y-glass group received almost 3 times the total liver radiation activity over the entire course of treatment than the ^{90}Y-resin group received. When we compared the prescribed and corresponding projected activity for each ^{90}Y treatment, we found that ^{90}Y-glass treatment would more than double the ^{90}Y activity that would be used if the same patient were treated with ^{90}Y-resin. This significant finding raises the question of whether radiation dosage to normal liver tissue can be minimized by using ^{90}Y-resin or by altering the dosimetry for ^{90}Y-glass.

The median survival of 18.2 months (^{90}Y-resin) and 9.3 months (^{90}Y-glass) is in line with recently published studies of SIRT in patients with hepatic colorectal metastases (11,18-27). The results from these studies have shown a wide range for median survival of patients undergoing SIRT: 8.3–17.0 months with ^{90}Y-resin (19,22-27) and 9.3–15.2 months with ^{90}Y-glass (11,18,20,21). The extent of liver tumor burden, extrahepatic disease and
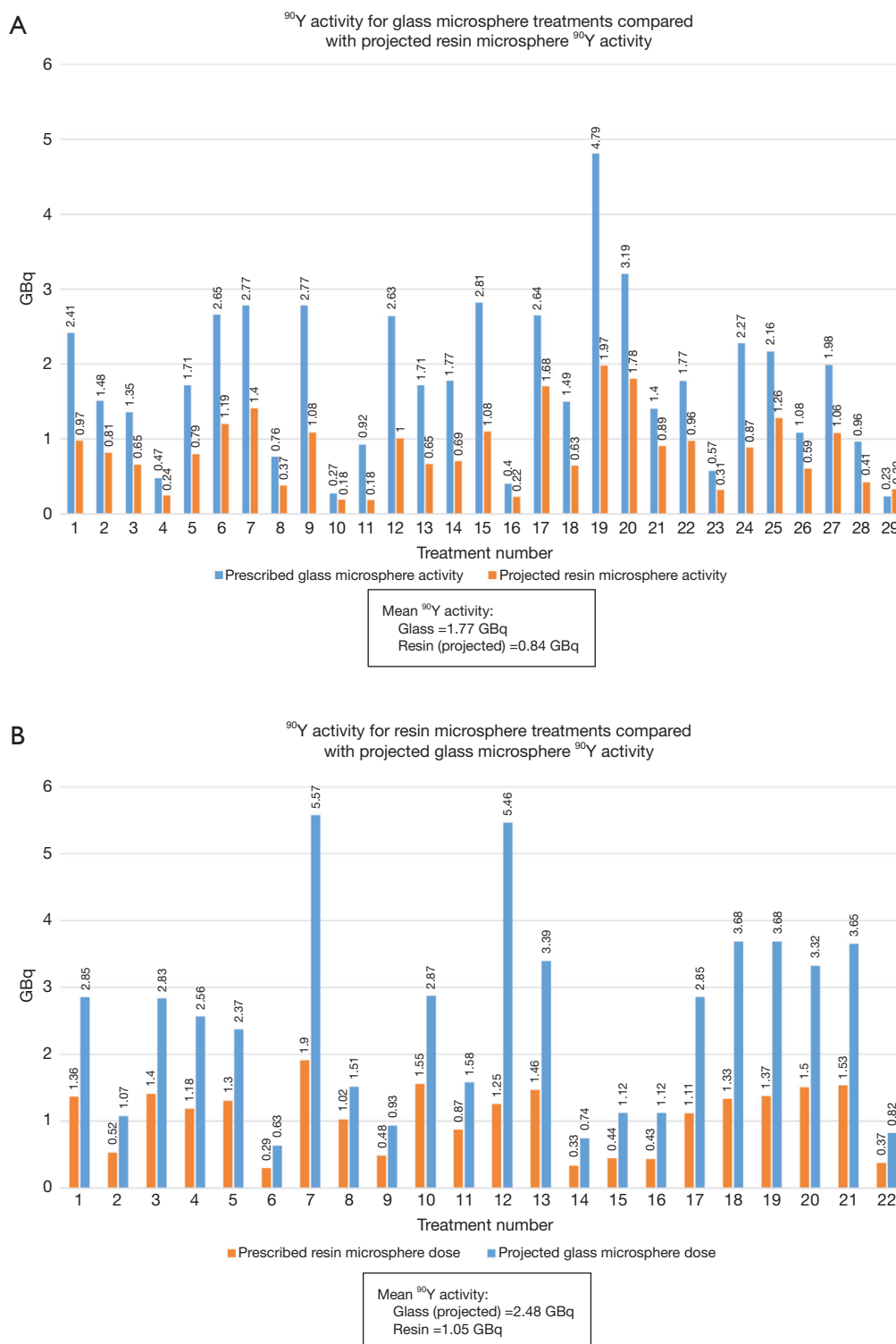
Figure 2 Comparisons of [90]Y Microsphere Activity. (A) In 29 glass ^{90}Y microsphere treatments, prescribed glass ^{90}Y activity versus projected resin ^{90}Y activity; (B) in 22 resin ^{90}Y microsphere treatments, prescribed resin microsphere ^{90}Y activity versus projected glass microsphere ^{90}Y activity.
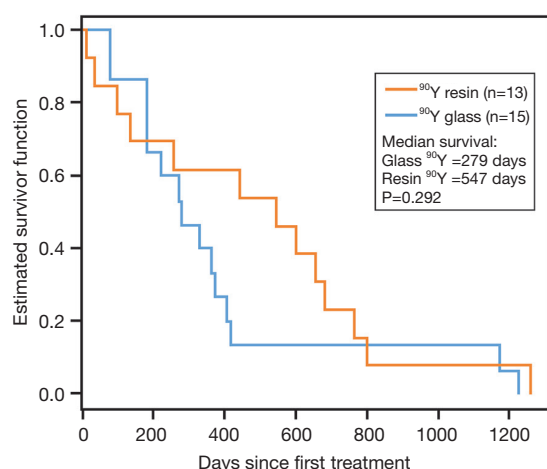
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Figure 3 Kaplan-Meier survival curves of 28 patients treated with glass or resin ^{90}Y microspheres. Overall survival in all 28 patients.
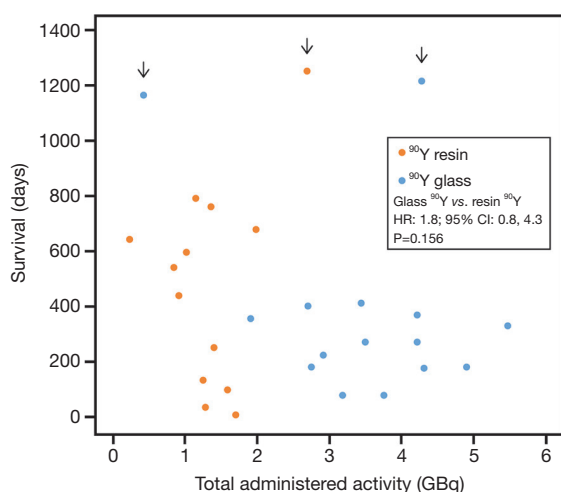

Figure 4 Effect of total administered activity on patient survival in glass and resin ^{90}Y-treated patients. Arrows indicate three outliers with relatively prolonged survival times (1,170, 1,225 and 1,259 days).

Table 2 Adverse events and liver toxicities (I)

Adverse event (general)[a]	Glass ^{90}Y, n [%]	Resin ^{90}Y, n [%]
Fatigue	8 [53]	10 [77]
Nausea/vomiting	4 [27]	4 [33]
General pain	2 [13]	2 [15]
Abdominal pain	0 [0]	2 [15]

[a], As reported in patient records without grade distinctions; no general adverse events were reported for 5 patients receiving glass ^{90}Y treatment.

Table 3 Adverse events and liver toxicities (II)

Adverse event (hepatic)[b]	Glass ^{90}Y, n [%]		Resin ^{90}Y, n [%]	
	All grades	Grade 3/4	All grades	Grade 3/4
ALT	2 [13]	0 [0]	3 [23]	0 [0]
ALP	11 [73]	0 [0]	9 [69]	1 [8]
AST	5 [33]	0 [0]	3 [23]	0 [0]
Bilirubin	3 [20]	0 [0]	1 [8]	1 [8]

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase. [b], CTCAE v4.03.

number of prior chemotherapy lines have been shown to have a significant impact on overall survival following SIRT and may explain the variation in overall survival seen in our and prior studies (11,18,19,27,28). For the most part, our patients had ≤25% liver tumor burden with no recorded extrahepatic disease and were being treated in a salvage setting. The 3 ^{90}Y-resin patients with >25% tumor burden died at 15, 40, and 547 days; the 1 ^{90}Y-glass patient with >25% tumor burden died at 83 days. The longer interval between the diagnosis of liver metastases and SIRT in the ^{90}Y-resin cohort might predict that this cohort would have a shorter overall survival compared to the ^{90}Y-glass cohort, however we observed a nonsignificant trend toward longer survival in the ^{90}Y-resin cohort. Due to the small size of this study and the significant difference in the interval between the diagnosis of metastases and SIRT, we cannot draw any strong conclusions when comparing overall survival with ^{90}Y-resin and ^{90}Y-glass.

During the second year following SIRT ^{90}Y-glass—treated patients had roughly 4 times the hazard of death as compared to ^{90}Y-resin—treated patients. One possible explanation for this finding could be that the lower ^{90}Y activity of the ^{90}Y-resin caused less insult to normal liver tissue than ^{90}Y-glass. Recent ^{90}Y PET/CT studies in ^{90}Y-glass-treated patients have demonstrated an absorbed radiation dose of 67–94 Gy in normal parenchyma and found that complications increase with higher absorbed radiation doses to normal liver tissue (29,30). No patient in this small study experienced REILD, a rare but serious complication of SIRT that is associated with higher prescribed ^{90}Y activity in patients treated for unresectable hepatic tumors (31,32). Although we observed no significant differences in adverse events or liver toxicities between the ^{90}Y-glass or ^{90}Y-resin groups, our findings were based on medical records that may not accurately capture all

complications. Nevertheless, the authors would conjecture that the radiation exposure to normal liver parenchyma has enough biologic effect to influence overall survival, even though the exposures in both ^{90}Y-glass and ^{90}Y-resin groups do not typically reach the threshold required for inducing REILD.

A strength of this study is that these real-world patient cohorts were treated at the same institution and were similar in disease stage, prior chemotherapy, demographics, performance status, and liver function. Any cohort differences would not impact our finding that prescribed ^{90}Y activity was significantly lower with ^{90}Y-resin versus ^{90}Y-glass per treatment, as we compared the prescribed activity and the projected activity to be used for the same treatment. We acknowledge that the interpretation of overall survival data is substantially limited by the small cohort size and retrospective design. Survival results may also have been impacted by differences in the ^{90}Y-resin and ^{90}Y-glass cohorts and concurrent chemotherapy in some patients. Our institution's interventional radiologists' particular practices may account for differences in the treatment strategies for the ^{90}Y-glass and ^{90}Y-resin groups, including the significantly longer interval between diagnosis of metastases and SIRT in the ^{90}Y-resin group and the apparent preference for ^{90}Y-resin for unilobar treatments and ^{90}Y-glass for bilobar treatments. We also note that there was no uniform follow-up testing or systematic post-therapy imaging to confirm the distribution of ^{90}Y, which has recently become more common in SIRT. At the Cleveland Clinic, post-therapy ^{90}Y PET/CT has been the standard practice since 2012, but at the time of this cohort study Bremsstrahlung SPECT/CT scans were performed on only a few patients on an ad hoc basis.

In conclusion, our study shows that SIRT using ^{90}Y-resin delivers significantly less ^{90}Y activity to patients with liver-dominant colorectal metastases as compared to SIRT using ^{90}Y-glass. Our results also suggest a possible survival benefit for patients treated with ^{90}Y-resin as compared to those treated with ^{90}Y-glass and a similar adverse event profile for both products. Larger, prospective studies are warranted to examine the effect of dosimetry on SIRT efficacy and safety outcomes.

Acknowledgements

Footnote

Conflicts of Interest: S.S. has served on advisory boards for Siemens and Bayer Healthcare and as a consultant for Siemens, has received speaker honoraria from SIRTeX Medical Inc. and BTG International, Inc., and has received payment for the development of educational presentations for Bayer Healthcare. V.K. received a speaker honorarium from SIRTeX Medical Inc. Authors E.N., J.B., and A.P. declare that they have no competing interests. S.S. was affiliated with the Cleveland Clinic during the time of this study.

Ethical Statement: The study was approved by institutional ethics board of Cleveland Clinic (No. IORG0000301).

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