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Clinical Investigation: Gastrointestinal Cancer

Safety of ^{90}Y Radioembolization in Patients Who Have Undergone Previous External Beam Radiation Therapy

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Summary

Prior exposure of the liver to external beam radiation therapy (EBRT) may lead to increased liver toxicity after yttrium-90 (^{90}Y) radioembolization (RE) treatment, depending on fractional liver exposure and dose level. Retrospective analysis of a cohort of 201 patients showed that RE can be performed safely in patients who have previously undergone EBRT only if they received limited hepatic exposure. We recommend using RE with caution if the prior V30 of the liver exceeds 10%.

Purpose: Previous external beam radiation therapy (EBRT) is theoretically contraindicated for yttrium-90 (^{90}Y) radioembolization (RE) because the liver has a lifetime tolerance to radiation before becoming vulnerable to radiation-induced liver disease. We analyzed the safety of RE as salvage treatment in patients who had previously undergone EBRT.

Methods and Materials: Between June 2004 and December 2010, a total of 31 patients who had previously undergone EBRT were treated with RE. Three-dimensional treatment planning with dose−volume histogram (DVH) analysis of the liver was used to calculate the EBRT liver dose. Liver-related toxicities including RE-induced liver disease (REILD) were reviewed and classified according to Common Terminology Criteria for Adverse Events version 4.02.

Results: The mean EBRT and RE liver doses were 4.40 Gy (range, 0-23.13 Gy) and 57.9 Gy (range, 27.0-125.9 Gy), respectively. Patients who experienced hepatotoxicity (≥grade2; n = 12) had higher EBRT mean liver doses (7.96 ± 8.55 Gy vs 1.62 ± 3.39 Gy; $P = .037$), the only independent predictor in multivariate analysis. DVH analysis showed that the fraction of liver exposed to ≥30 Gy (V30) was the strongest predictor of hepatotoxicity (10.14% ± 12.75% vs 0.84% ± 3.24%; $P = .006$). All patients with V30 >13% experienced hepatotoxicity. Fatal REILD (n = 2) occurred at the 2 highest EBRT mean liver doses (20.9 Gy and 23.1 Gy) but also at the highest cumulative liver doses (91.8 Gy and 149 Gy).

Conclusions: Prior exposure of the liver to EBRT may lead to increased liver toxicity after RE treatment, depending on fractional liver exposure and dose level. The V30 was the strongest predictor of toxicity. RE appears to be safe for the treatment of hepatic malignancies only in patients who have had limited hepatic exposure to prior EBRT.

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Conflict of interest: Daniel Sze is on the medical or scientific advisory boards for Surefire Medical, Inc, Treus Medical, Inc, RadGuard Medical, Inc, and Jennerex Biotherapeutics, Inc; is on the speaker's bureau for W. L. Gore, Inc; and has consulted for Biocompatibles, Inc and Sirtex, Inc The other authors report no conflict of interest.

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Introduction

External beam radiation therapy (EBRT) is a mainstay tool in cancer treatment. Targeting and delivery techniques have greatly improved, including advances in simulation and radiation planning, image guidance, and tumor immobilization, tracking or both, which has greatly increased the precision of accuracy of treatment (1).

Despite these advances, EBRT still exposes the normal adjacent tissues and organs to significant doses, and radiation-induced collateral damage to nontarget tissues continues to be a dose-limiting factor for effective treatment. The liver has been shown to be a radiosensitive organ at risk for radiation-induced liver disease (RILD) when tumors in the liver or in the abdomen are treated (2).

Yttrium-90 (^{90}Y) radioembolization (RE) is a form of radiation brachytherapy in which high doses of radiation may be delivered by a beta-emitting isotope incorporated in to microspheres, which are injected directly into the arteries feeding the tumors (3). RE has been shown to benefit selected patients with unresectable hepatic malignancies (4). This method of treatment takes advantage of the safety margin provided by distributing relatively little radiation in a partial liver volume primarily perfused by the portal vein while allowing arterially perfused tumors to receive tumoricidal doses of radiation. EBRT provides a more uniform field over tissue volumes, whereas ^{90}Y microspheres provide millions of scattered point sources of radioactivity that are concentrated inside the tumor (3).

Radiation toxicity to the liver is cumulative, with a lifetime threshold of approximately 30 Gy before the onset of RILD, a clinical syndrome consisting of hepatomegaly, nonicteric ascites, and elevated liver enzymes occurring from 2 weeks to 6 months after radiation exposure (2). In contradistinction, RE-induced liver disease (REILD) includes symptoms of RILD but also manifests as elevated serum bilirubin and jaundice, and it seldom includes hepatomegaly (5). Prior EBRT is considered to be a relative contraindication to RE because of a theoretical but undefined elevation in the risk of development of REILD (6, 7). The purpose of this study was to determine the risk of REILD in patients treated with RE who had previously received EBRT, and to identify dose–volume parameters predictive of the occurrence of hepatotoxicity after prior EBRT.

Methods and Materials

All data were handled in compliance with the Health Insurance Portability and Accountability Act. The institutional review board of our institution approved this retrospective study.

Patient characteristics

Between June 2004 and December 2010, a total of 201 patients with hepatic malignancy (unresectable, refractory, and liver dominant) underwent RE by use of either resin microspheres (SIR-spheres; Sirtex, Lane Cove, Australia; n = 161) or glass microspheres (TheraSphere; Nordion, Ottawa, Ontario, Canada; n = 40). The mean age was 60.1 years (range, 20-92 years). Of these patients, a total of 31 (15.4%) had previously received EBRT. The mean age of these patients was 58.4 years (range, 31-80 years). They received EBRT at a mean time interval of 22.5 months (range, 0.7-112.2 months) before receiving RE. The characteristics of the patients and tumors are shown in Table 1. The large majority of the patients received resin microspheres (29 patients), and only 2 received glass.

External beam radiation therapy treatment and dosimetric analysis

Of the 31 patients, 13 patients had undergone EBRT at our institution, and 18 patients had received EBRT treatment at an outside hospital. The dose–volumetric values were calculated on the basis of dose–volume histograms (DVH) and dose distributions on each axial computed tomographic plane. The dose–volumetric parameters analyzed were the mean dose delivered to the liver and the percentage of the normal nontumorous liver volume receiving 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), 45 Gy (V45), and 50 Gy (V50). All calculations were performed with the Eclipse system software (Varian Medical Systems, Palo Alto, CA).

Radioembolization treatment procedure

The RE treatments were prescribed and performed according to consensus recommendations (6-9). Patients who were being treated by systemic therapies had these treatments withheld for at least 1 week (4 weeks for bevacizumab) before the commencement of angiographic procedures. All patients underwent preparatory angiography, during which endovascular skeletonization of the hepatic artery was performed to prevent nontarget RE. All parasitized and select variant arteries were embolized to consolidate arterial inflow (10, 11). Technetium-99m macroaggregated albumin was injected for simulation scintigraphy, to calculate the lung shunt fraction, to characterize the intrahepatic distribution of injected tracer, and to detect extrahepatic deposition. At the treatment session, any evidence of collateralization was addressed and embolized in the same way as during the preparatory angiogram (12), followed by administration of the prescribed activity of ^{90}Y microspheres. Activity was calculated by standard body surface area method for resin microspheres and by the standard method for glass microspheres using a 120-Gy default target dose (9). All prescribed activities were recalibrated on the day of treatment.

Evaluation of radiation-induced hepatic toxicity

Serum metabolic laboratory tests—total serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and albumin—were obtained at baseline and 2, 4, and 8 weeks after RE treatment. Clinical follow-up with physical examination was obtained at 1 and 3 months by the interventional radiologist and approximately every 2-4 weeks by the medical oncologist additionally. Laboratory and clinical toxicities were graded by the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.02. Imaging follow-up was obtained 10 to 12 weeks after RE, or earlier if the patient presented with any notable symptoms or complications.

Patients were classified according to the occurrence of hepatotoxicity, defined as grade 2 to grade 4 laboratory toxicity, and fatal REILD, defined as new or worsened hepatic toxicity in the absence of progressive malignant disease, accompanied by nonmalignant ascites and jaundice, typically occurring 1 to 2 months after the completion of RE, resulting in death.

Table 1 Baseline characteristics of patients who underwent RE with or without prior EBRT

Characteristic	RE only (n=170)	%	EBRT + RE (n=31)	%	*P* value*
Age, y: ≤60/>60	79/91	47/53	13/18	42/58	.641
Sex: M/F	100/70	59/41	17/14	55/45	.679
ECOG performance status					.241
0	88	51.8	20	64.5	
1	74	43.5	8	25.8	
2	7	4.1	3	9.7	
3	1	0.6	0	-	
Tumor type					.017
Primary malignancy†	55	32.4	3	9.7	
Secondary malignancy‡	115	67.6	28	90.3	
Treatment approach					.187
Whole liver	120	70.6	26	83.9	
Lobar/segmental	50	29.4	5	16.1	
Liver involvement (%)§	30 ± 16		27 ± 16		.428
Microspheres					.049
Resin	132		29		
Glass	38		2		
Administered activity (GBq)§	2.25 ± 1.29		1.96 ± 1.09		.321
Prior therapy					
TACE	35	20.6	5	16.1	.569
Surgery (resection)	33	19.4	4	12.9	.394
RFA	18	10.6	6	19.4	.223
Systemic chemotherapy	102	60.0	22	71.0	.251
Antiangiogenic agents	75	44.1	13	41.9	.822
Anti-EGFR agents	22	12.9	3	9.7	.614
Baseline laboratory values§					
AST, IU/L	59 ± 53		50 ± 30		.457
ALT, IU/L	50 ± 34		47 ± 28		.385
Total bilirubin, mg/dL	0.7 ± 0.4		0.6 ± 0.3		.041
Alkaline phosphatase, U/L	234 ± 171		175 ± 99		.063
Albumin, g/dL	3.4 ± 0.5		3.4 ± 0.5		.497

Abbreviations: EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; RE = radioembolization; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

* Univariate analysis.

† Hepatocellular carcinoma (40); cholangiocarcinoma (18).

‡ Colorectal carcinoma (68); neuroendocrine carcinoma (30); melanoma (7); renal cell carcinoma (5); breast carcinoma (5); sarcoma (4); pancreas carcinoma (4); ovarian carcinoma (3); miscellaneous (17).

§ Mean ± standard deviation.

Statistical analysis

Univariate analysis (Mann-Whitney) was performed for comparison of parameters between groups and to identify those parameters with significance $P<.10$ for inclusion as covariates in multivariate analysis (binary logistic regression). The conditional step-forward method was used with $P<.05$ for entry and $P>.10$ for removal from the model. Receiver operating characteristic (ROC) curve analysis was performed to identify at which EBRT dose level the DVH analysis best predicted liver toxicity. A commercial statistical software package (SPSS for Windows, version 19.0; SPSS Inc., Chicago, IL) was used for data analysis.

Results

Of the 31 patients who had undergone EBRT before RE treatment, the mean EBRT liver dose was 4.40 Gy (range, 0-23.13 Gy). Eighteen patients had a mean liver dose of 0 Gy, 6 patients 0 to 10 Gy, 5 patients 10 to 20 Gy, and 2 patients >20 Gy (Fig. 1). Sixteen patients (51.6%) were exposed to radiation in the abdominopelvic region; of those, the liver was included directly in the field of radiation in 5 patients (16.1%). However, EBRT outside the abdominopelvic region did not preclude radiation exposure to the liver. Three patients received EBRT to the thorax and had calculated mean liver doses of 1.23 Gy, 2.13 Gy, and 8.05 Gy, respectively. Univariate analysis of patients who received EBRT to the abdominopelvic area compared with those who received EBRT to any other part of the body revealed statistically higher dose−volumetric parameters at every dose level. For patients who underwent EBRT to the abdominopelvic region, the mean liver dose was 7.81 Gy, significantly higher than the mean liver dose of 0.76 Gy in patients who underwent EBRT to other parts of the body (mainly thorax).

Of the 31 patients who had previously undergone EBRT, 26 patients (83.9%) received whole liver RE treatment either in the same session or sequentially in 2 separate sessions. The mean lung shunt was 6.7% (range, 1.5-16.0%), the mean activity of ^{90}Y

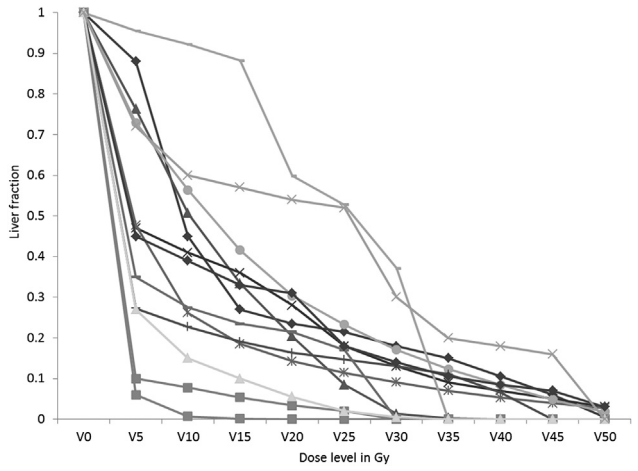

Fig. 1. Dose−volume histogram parameters of liver doses in patients who underwent external beam radiation therapy before receiving ^{90}Y radioembolization.

delivered was 1.96 GBq (range, 0.39-7.30 GBq), and the mean liver dose was 57.9 Gy (range, 27.0-125.9 Gy). Twenty-two patients received doses between 50 and 100 Gy, and only 1 patient received more than 100 Gy. The EBRT and RE mean liver doses are depicted in Figure 2.

Complete follow-up laboratory test results were available for 28 patients. Laboratory values showed a maximum change from baseline at week 8, with a mean change of +134.5% for total serum bilirubin, +30.7% for AST, +10.5% for ALT, +63.9% for alkaline phosphatase, and −7% for albumin (Fig. 3a). A total of 12 patients (38.7%) experienced grade 2 or higher hepatotoxicity (Fig. 3b).

Two patients experienced fatal REILD. One patient (ECOG 2) received whole liver RE treatment in 1 session with 1.46 GBq resin microspheres (body surface area 1.40 m^2; liver weight 1009 g; mean liver dose 70.9 Gy) for metastatic gastroesophageal carcinoma, with a history of prior systemic chemotherapy and EBRT on the primary tumor site 3 months previously, resulting in a mean liver dose of 20.93 Gy. Six weeks after RE, he experienced REILD with grade 4 laboratory toxicities, nausea, jaundice, ascites, and fatigue. Transjugular wedged hepatic venous pressures indicated portal hypertension with an estimated gradient of 12 to 16 mm Hg, and biopsy confirmed venoocclusive disease (VOD). He died 60 days after receiving RE. The second patient (ECOG 0) received whole liver RE treatment in 2 sessions with a total of 7.30 GBq glass microspheres (125.9 Gy) for hepatocellular carcinoma, with a history of prior transarterial chemoembolization (once), sorafenib, and EBRT on the left lobe 5 months previously (mean liver dose 23.1 Gy). This patient had complete replacement of the left lobe by hepatocellular carcinoma with portal vein tumor thrombus and was intentionally treated with a supratherapeutic 172-Gy glass microsphere dose to this lobe (radiation lobectomy) (13) and a more conventional dose of 111 Gy to the right lobe 5 weeks later, which was only 15% replaced by tumor. Again, 6 to 8 weeks after RE he experienced progressive REILD with grade 3 laboratory toxicity, abdominal distension, jaundice and fatigue. He refused further treatment and died 122 days after receiving RE. Including these 2 patients, 6 of 201 patients (3.0%) in the total cohort had signs and symptoms of REILD.

The 2 patients with grade 5 REILD received not only the highest EBRT liver doses (20.93 Gy and 23.13 Gy) but also the highest cumulative liver doses (91.8 Gy and 149.0 Gy). As such, both patients were outliers within the cohort. However, patients with hepatotoxicity also received higher EBRT doses (7.96 ± 8.55 Gy vs 1.62 ± 3.39 Gy; P=.037) with a trend toward higher cumulative doses (74.2 ± 42.6 Gy vs 53.5 ± 10.6 Gy; P=.063) (Table 2). The RE liver dose was not different between groups (66.2 ± 38.0 Gy vs 51.9 ± 11.1 Gy; P=.210). In multivariate analysis including all known clinical, laboratory, and procedural parameters, the mean EBRT liver dose proved to be the only independent predictor of hepatotoxicity in the study cohort. In fact, comparison between patients with and without hepatotoxicity revealed statistically higher DVH parameters at virtually every dose level (Table 2). The strongest difference was found at a dose level of 30 Gy. The fraction of liver exposed to at least 30 Gy was 10.14 ± 12.75% in patients who experienced hepatotoxicity versus 0.84 ± 3.24% in patients who did not (P=.006). Figure 4 illustrates the dose−effect relationship between the fraction of liver exposed to either 5 Gy (Fig. 4a) or 30 Gy (Fig. 4b) and the occurrence of hepatotoxicity or fatal REILD in this study cohort. As expected, for liver toxicity to develop, the fraction of EBRT liver exposure needed to be higher for 5 Gy than for 30 Gy. Second, for fatal REILD to develop, the fraction of liver exposure needed to be higher in comparison with hepatotoxicity.

The ROC curve analysis also identified the 30 Gy EBRT dose level as being the strongest predictor of hepatotoxicity, with an area under the curve of 0.755 (95% confidence interval 0.559-0.951; P=.023). The cutoff value for 100% specificity was

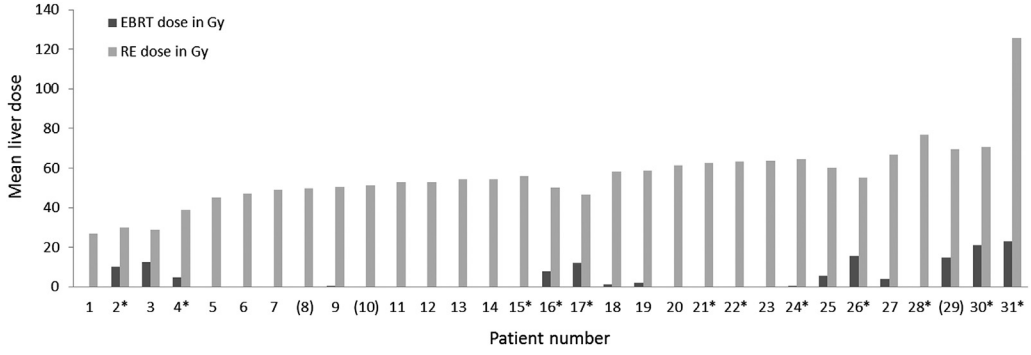

Fig. 2. Mean liver dose from prior external beam radiation therapy (EBRT) and radioembolization (RE), ranked by cumulative dose. *Patients who experienced hepatotoxicity ≥grade 2. Patients 30 and 31 experienced fatal RE-induced liver disease. Patient numbers in parentheses indicate patients who were not evaluable for liver toxicity.

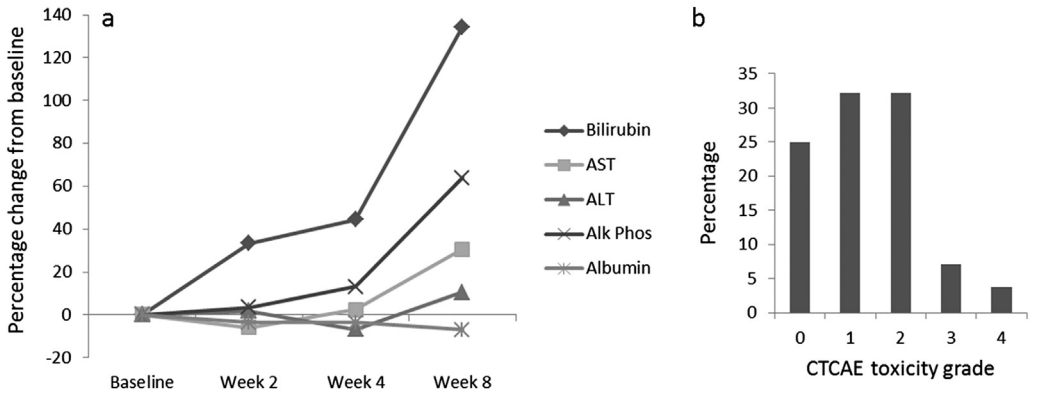

Fig. 3. Percentage change from baseline of laboratory values related to liver function (a) and liver toxicity according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.02, in percentage of total study cohort (b). Bilirubin = total serum bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Alk Phos = alkaline phosphatase.

13%. In other words, all patients with >13% of the liver exposed to at least 30 Gy experienced hepatotoxicity. For fatal REILD, the cutoff value was 30% of the liver exposed to at least 30 Gy, although this number was not significant (area under the curve 0.673, 95% confidence interval 0.171-1.0; $P = .422$).

Discussion

The treatment of hepatic malignancies with radiation is limited by the susceptibility of the liver to radiation toxicity. Tumors are typically more resistant to radiation than is the background liver, which can tolerate only about 30 Gy exposure before developing RILD, which when severe, is fatal (14-16). RE entails the deposition of a large number of finite radiation sources in a volume of distribution that includes the target tumors, taking advantage of the tumors' arterial hypervascularity to effect preferential deposition in the tumor tissue while keeping background liver deposition low enough to result in a dose of <30 Gy. Accurate prediction of deposition is not currently possible, so to limit the risk of accidental overdose to the background liver, RE is contraindicated by consensus in patients who have previously undergone EBRT (6, 7).

Table 2 Univariate analysis of dose–volumetric parameters associated with patients who experienced hepatotoxicity grade 2 or higher

Parameter	Hepatotoxicity grade 2 or higher		*P* value
	Yes (n = 12)	No (n = 16)	
Mean liver dose			
Mean EBRT liver dose, Gy	7.96 ± 8.55	1.62 ± 3.39	.037
Mean RE liver dose, Gy	66.2 ± 38.0	51.9 ± 11.1	.210
Cumulative liver dose, Gy	74.2 ± 42.6	53.5 ± 10.6	.063
Fractional liver exposure			
V5 (%)	36.40 ± 36.43	7.81 ± 14.88	.037
V10 (%)	28.93 ± 30.94	5.75 ± 12.10	.048
V15 (%)	24.23 ± 28.00	4.69 ± 10.41	.054
V20 (%)	18.85 ± 21.33	3.65 ± 8.47	.035
V25 (%)	15.05 ± 19.20	2.44 ± 5.92	.037
V30 (%)	10.14 ± 12.75	0.84 ± 3.24	.006
V35 (%)	5.10 ± 6.89	0.56 ± 2.25	.009
V40 (%)	3.91 ± 5.70	0.44 ± 1.75	.026
V45 (%)	2.64 ± 4.86	0.32 ± 1.25	.071
V50 (%)	0.63 ± 1.17	0.19 ± 0.75	.195

The biological quality factor (Q) is 1.0 for both x-rays and beta particles. EBRT x-rays are generally delivered at a high dose rate for a few seconds at a time but generally require multiple fractionated treatments over a span of days or weeks. Beta particles from radioisotope decay are constantly emitted at a low dose rate over a period of weeks, governed by the isotope's decay characteristics. It is incompletely understood whether the combined toxicity of x-ray and beta irradiation is additive, synergistic, or antergistic.

The current study provides clinical data to confirm cumulative toxicity from EBRT and RE, and the necessity for caution in patients treated by RE who have previously undergone EBRT. The mean liver dose from prior EBRT proved to be the only independent predictor of liver toxicity, not the mean liver dose from RE or the cumulative liver dose. DVH analysis revealed the V30 to be most predictive for hepatotoxicity, with a cutoff level for fractional liver exposure of 13%. This mirrors previous work on EBRT that showed a threshold for hepatotoxicity of a mean liver dose of 30 Gy (14-16).

However, the dose–response relationship for the occurrence of hepatotoxicity after RE remains unclear, owing to the uncertainty of the RE dose distribution in comparison with EBRT (9). The liver tolerates a much higher RE mean liver dose in comparison with RT, likely because of the inhomogeneity of microsphere distribution, but the actual dose to background liver is unknown and is probably kept below 30 Gy in nearly all patients by the current standard dose prescription methods. In some studies, the administered activity proved to be an important predictor for the occurrence of REILD (5, 17), but a dose–response relationship has never been established because of the difficulties with RE dosimetry in patients with diffuse multifocal disease, in whom it is virtually impossible to calculate the dose to normal liver tissue accurately. The mean target dose serves as a surrogate but was not predictive in our cohort. The incidence of REILD in our cohort (3.0%) fell within the range of published statistics (5, 17).

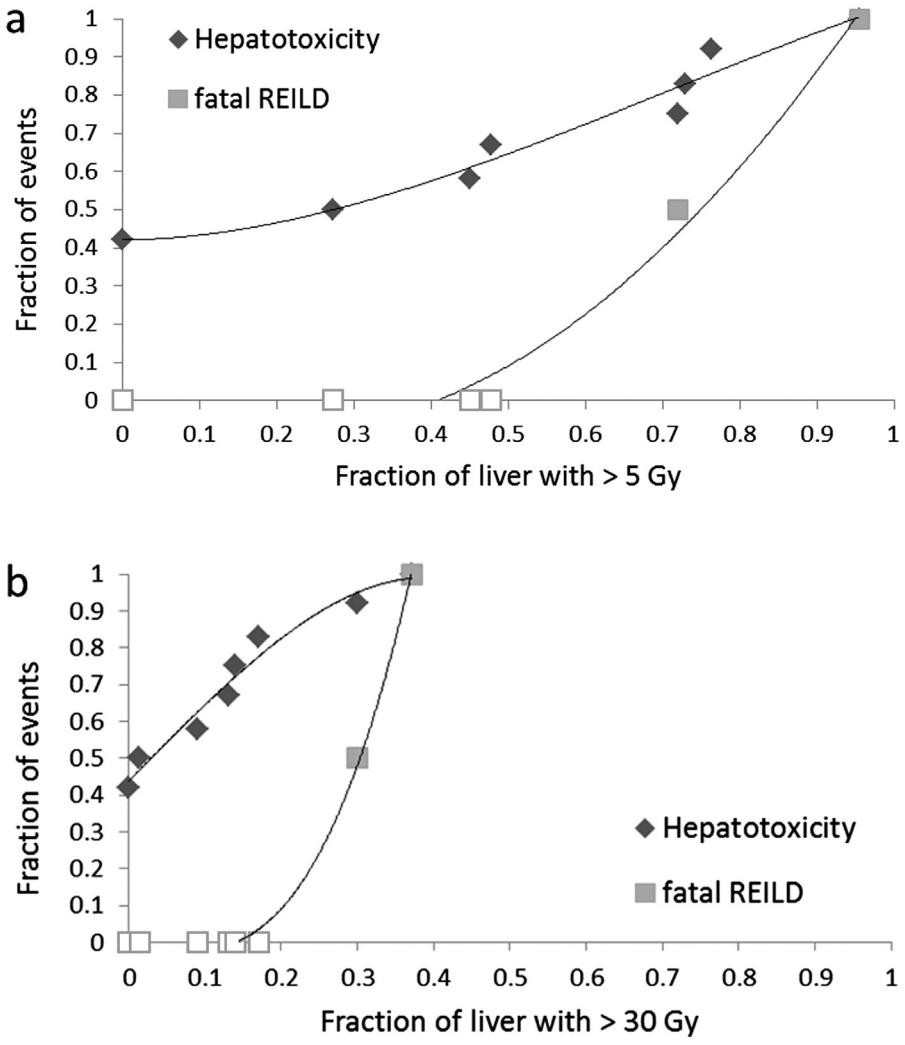

Fig. 4. Dose–effect relationship between fraction of liver exposed to an external beam radiation therapy dose >5 Gy (a) or >30 Gy (b) and occurrence of either hepatotoxicity ≥grade 2 or fatal radioembolization-induced liver disease (REILD).

The histopathologic hallmark of classic RILD and REILD is VOD. It is characterized by severe centrilobular congestion of the sinusoids, with necrosis and atrophy of perivenular hepatocytes (2). The exact pathogenesis is yet unknown, but it is hypothesized that radiation-induced fibrin deposits by endothelial cells, lining central veins and afferent sinusoids, are invaded by collagen-producing fibroblasts, leading to sinusoidal fibrosis and VOD. It appears unlikely that hepatocyte damage is the primary cause of injury. EBRT-induced RILD typically occurs 4 to 8 weeks after EBRT. Patients present with fatigue, weight gain, increased abdominal girth, ascites, and hepatomegaly. Jaundice is rare, unlike with other causes of VOD. Serum chemistries usually show marked elevation of alkaline phosphatase and moderate elevations in AST and ALT (2). REILD differs from RILD in that it causes jaundice and hyperbilirubinemia, and hepatomegaly is usually absent (5). REILD is more similar to a clinical syndrome described as combined modality induced liver disease (CMILD), a syndrome that occurs after combination systemic chemotherapy and total body irradiation performed as a conditioning treatment in preparation for bone marrow transplantation (2). Most patients treated by RE received prior systemic chemotherapy, which might explain the similarities between REILD and CMILD (5).

The liver retains a memory of toxicity from previous treatments, including some systemic chemotherapeutics, and local treatments such as EBRT and RE. Although a quantitative comparison is difficult, EBRT and RE share some pathologic pathways leading to VOD, resulting in the clinical syndromes RILD and REILD. Although limited by few subjects and its retrospective design, our study shows that previous EBRT treatment is an important predictor of liver toxicity in patients treated by RE. In part because of the deficiency of accurate segmented dosimetry for the background liver during RE treatment, exact thresholds for which RE treatment may be safely performed after EBRT cannot be established. Also, because only 2 patients were treated with glass microspheres, no direct comparison could be made with resin microspheres. Distinct differences in microsphere characteristics may lead to differences in dose distribution and toxicity, although this is currently unknown. Glass microspheres generally use higher prescribed activities and target doses, but resin microspheres are more often used for wide coverage of diffuse hepatic metastases. This may equalize REILD incidence. Our preliminary data indicate that the fraction of liver exposed to at least 30 Gy is an important predictor of toxicity, with a threshold for hepatotoxicity at around 10% liver exposure and

a threshold for serious complications such as fatal REILD at around 30% liver exposure.

Conclusion

Prior exposure of the liver to EBRT may lead to increased liver toxicity after RE treatment, depending on fractional liver exposure and dose level. DVH analysis is crucial for risk evaluation, not only for patients with previous EBRT on the liver itself but also for patients with EBRT anywhere in the truncal region. RE can be performed safely in patients who have previously undergone EBRT only if they received limited hepatic exposure. We recommend using RE with caution if the prior V30 of the liver exceeds 10%.

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