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ORIGINAL ARTICLE

Retrospective Study

Factors associated with increased incidence of severe toxicities following yttrium-90 resin microspheres in the treatment of hepatic malignancies

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Abstract

AIM: To further define variables associated with increased incidences of severe toxicities following administration of yttrium-90 (^{90}Y) microspheres.

METHODS: Fifty-eight patients undergoing 79 treatments were retrospectively assessed for development of clinical and laboratory toxicity incidence following ^{90}Y administration. Severe toxicity events were defined using Common Terminology Criteria for Adverse Events version 4.03 and defined as grade $\geqslant$ 3. Univariate logistic regression analyses were used to evaluate the effect of different factors on the incidence of severe

toxicity events. Multicollinearity was assessed for all factors with $P < 0.1$ using Pearson correlation matrices. All factors not excluded due to multicollinearity were included in a multivariate logistic regression model for each measurement of severe toxicity.

RESULTS: Severe (grade $\geqslant$ 3) toxicities occurred following 21.5% of the 79 treatments included in our analysis. The most common severe laboratory toxicities were severe alkaline phosphatase (17.7%), albumin (12.7%), and total bilirubin (10.1%) toxicities. Decreased pre-treatment albumin (OR = 26.2, P = 0.010) and increased pre-treatment international normalized ratio (INR) (OR = 17.7, P = 0.048) were associated with development of severe hepatic toxicity. Increased pre-treatment aspartate aminotransferase (AST; OR = 7.4, P = 0.025) and decreased pre-treatment hemoglobin (OR = 12.5, P = 0.025) were associated with severe albumin toxicity. Increasing pre-treatment model for end-stage liver disease (MELD) score (OR = 1.8, P = 0.033) was associated with severe total bilirubin toxicity. Colorectal adenocarcinoma histology was associated with severe alkaline phosphatase toxicity (OR = 5.4, P = 0.043).

CONCLUSION: Clinicians should carefully consider pre-treatment albumin, INR, AST, hemoglobin, MELD, and colorectal histology when choosing appropriate candidates for ^{90}Y microsphere therapy.

Key words: Yttrium-90 microspheres; Liver metastases; Multivariate analysis; Toxicity incidence; Colorectal adenocarcinoma

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Core tip: Factors associated with the development of severe (grade $\geqslant$ 3) toxicities were identified using multivariate logistic regression models using Common Terminology Criteria for Adverse Events version 4.03. We found that severe toxicities were present following 21.5% of treatments. Abnormal pre-treatment albumin and international normalized ratio (INR) were associated with development of severe hepatic toxicity. Abnormal pre-treatment aspartate aminotransferase (AST) and hemoglobin were associated with development of severe albumin toxicity. Increasing pre-treatment model for end-stage liver disease (MELD) was associated with severe total bilirubin toxicity, and colorectal adenocarcinoma with severe alkaline phosphatase toxicity. Pre-treatment albumin, INR, AST, hemoglobin, MELD, and colorectal histology should be considered when selecting appropriate candidates for ^{90}Y microsphere therapy.

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INTRODUCTION

Yttrium-90 (^{90}Y) microsphere brachytherapy has emerged as an important modality for the treatment of unresectable primary or secondary hepatic malignancies. Although surgery provides the greatest chance for cure, > 70% of hepatic malignancies are considered unresectable[1,2]. While normal liver parenchyma primarily receives blood from the portal vein, hepatic malignancies receive most of their blood from the hepatic artery[3]. Administration of beta-emitting ^{90}Y microspheres into the hepatic artery exploits this dual blood supply to preferentially deliver tumoricidal radiation to hepatic malignancies while sparing normal liver parenchyma.

^{90}Y microspheres are primarily used in the setting of salvage therapy as there is increasing evidence that they provide benefits in both time to progression and overall survival[4,5], leading to their approval for treatment of colorectal liver metastases and extensive off-label use for various other hepatic malignancies[6]. Despite these benefits, ^{90}Y is associated with several toxicities of which clinicians must be aware. Toxicities include constitutional symptoms including nausea, vomiting, fatigue, abdominal pain, and fever, all of which comprise the transient post-embolization syndrome (PES)[7-9]. Furthermore, gastrointestinal (GI) and liver toxicities, including elevated liver function tests (LFTs), have also been reported[9-11].

The objectives of this paper are to further define factors associated with increased incidences of severe toxicities and to identify the frequency of liver, constitutional, and GI toxicities following administration of ^{90}Y microspheres in a sequential cohort of heterogeneous patients.

MATERIALS AND METHODS

Inclusion criteria and ^{90}Y procedure

We reviewed the charts of all patients who received ^{90}Y resin microsphere radioembolization at our institution between October 1, 2010, and September 30, 2014. All patients who received either ^{90}Y treatment to a single lobe or sequential bilobar treatments, did not have underlying liver cirrhosis, and were seen in follow-up were included in our analysis. Patients with underlying liver cirrhosis were excluded due to its potential to complicate post-treatment liver toxicities. For the purposes of this analysis, each procedure was considered a separate event as sequential treatments were always to the other liver lobe.

All patients were initially presented at a multidisciplinary hepatobiliary conference in which radiographic

imaging and labs were reviewed to determine the best course of treatment. Patients for whom ^{90}Y treatment was recommended underwent arterial catheterization to rule out aberrant arterial anatomy and perform prophylactic coil embolization of the gastroduodenal artery and other routes of collateral flow. Patients also underwent a nuclear medicine hepatopulmonary shunt study using technetium-99m-labeled macro-albumin aggregates injected into the hepatic arteries and visualized with static anterior and posterior images. ^{90}Y treatment was contraindicated for patients with a shunt > 20%, while shunts of 11%-15% and 16%-20% required a reduction in ^{90}Y dosage of 20% and 40%, respectively, to decrease the risk of patients developing radiation pneumonitis[12].

Approximately two weeks later, patients received ^{90}Y microspheres whose dose was calculated using the body surface area method adjusted for lobar involvement[13-15]. Resin microspheres of 20-60 μm (SIR spheres®, SIRTeX Medical Limited, North Sydney, N.S.W. Australia) labeled with beta-emitting ^{90}Y with a 64.2 h half-life were selectively delivered *via* the right or left hepatic artery to vessels supplying the malignancies under treatment[16].

Data collection and endpoints

Patients were typically seen in follow-up at 1-, 3-, and 6-mo post-treatment. Baseline laboratory values were defined as pre-treatment laboratory values closest to the treatment date, often measured the day of treatment prior to administration of ^{90}Y microspheres. For patients receiving sequential bilobar treatments, a new baseline for the second treatment was defined using pre-treatment laboratory values closest to the second treatment's date. The 1-mo laboratory values were defined as those closest to 1-mo from the day of treatment and between 3-wk and 2-mo post-treatment, the 3-mo laboratory values were defined as those closest to 3-mo and between 2- and 4.5-mo, and the 6-mo laboratory values were defined as those closest to 6-mo and between 4.5- and 8-mo. LFT toxicities included international normalized ratio (INR), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin and were determined using Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03)[17].

Patients were recorded as having LFT toxicities if both their post-treatment CTCAE grade was 2 or higher and this grade was increased from their pre-treatment grade. Patients with baseline LFTs meeting criteria for grade 2 toxicity which did not increase to a higher grade post-treatment were not considered to have treatment toxicity. Patients were also recorded as having severe toxicities if they had post-treatment CTCAE grade $\geqslant$ 3 laboratory measurements. Incidence of other adverse outcomes was determined from clinician notes at follow-up visits. Radiographic response at 3-mo and 6-mo post-treatment was assessed using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[18]. This study was approved by our institutional review board and was compliant with Health Insurance Portability and Accountability Act. Patients signed informed consent.

Statistical analysis

Univariate logistic regression was performed for each variable listed in Supplementary Table 1 to test their effect on the development of severe (grade $\geqslant$ 3) liver toxicities. Within each regression model, denominators were adjusted to account for missing laboratory data. Variables associated with development of severe toxicity at a significance level of $P < 0.10$ on univariate analysis were used to generate multivariate logistic regression models for each severe toxicity. Multicollinearity was assessed using Pearson correlation matrices; for variables with $r > 0.4$, only the one with greater significance on univariate analysis was included in multivariate analysis. Overall survival was estimated using the Kaplan-Meier method. A P value < 0.05 was considered statistically significant in two-tailed statistical tests. All analyses were conducted using SPSS Statistics 22.0 for Windows (IBM SPSS, Chicago, IL) with statistical review by a biomedical statistician.

RESULTS

Baseline Characteristics

During 2010-2014, 76 patients underwent 104 ^{90}Y microsphere treatments. All 104 treatments were considered for inclusion in our analysis while 58 patients undergoing 79 treatments ultimately met our inclusion criteria. One patient underwent three lobar treatments with the initial sequential treatments occurring in 2011 and the third treatment in 2013. This third treatment was excluded due to the inability to rule out the effect of previous treatments on the development of any subsequent toxicities. Ten treatments (9.6%) were excluded due to underlying liver cirrhosis, and 14 treatments (13.5%) were excluded due to lack of follow-up. Mean time to initial follow-up for all treatments was 45 d (± 31; range, 4-165 d), and mean total follow-up was 274 d (± 332; range, 14-1427 d).

Baseline characteristics for each patient and treatment are presented in Table 1. Thirty-two patients who underwent 46 treatments had extrahepatic disease, while 12 treatments occurred in patients with unilobar disease. Patients typically returned home the day after treatment (n = 75; 94.9%). In three cases, discharge was delayed by 1-2 d for pain, nausea and vomiting, or port infection.

Toxicity analysis

Table 2 presents the incidence of all toxicities while Table 3 presents the incidence of severe toxicities.

Table 1 Baseline characteristics

Characteristics	Values[1]
Patient characteristics (n = 58)	
Sex	
Female	28 (48.3)
Male	30 (51.7)
Race	
White	44 (75.9)
Black	14 (24.1)
Age at primary diagnosis	57.64 ± 10.18 (32-84)
< 65	47 (81.0)
⩾ 65	11 (19.0)
Primary diagnosis	
Colorectal adenocarcinoma	30 (51.7)
Neuroendocrine	12 (20.7)
Cholangiocarcinoma	5 (8.6)
Other primaries	11 (19.0)
Age at liver diagnosis	58.45 ± 10.43 (32-86)
< 65	44 (75.9)
⩾ 65	14 (24.1)
Liver steatosis	7 (12.1)
Number hepatic lesions	
< 10	11 (19.0)
⩾ 10	47 (81.0)
Prior treatment	
None	6 (10.3)
Radiofrequency ablation	6 (10.3)
Surgery	11 (19.0)
TACE	3 (5.2)
EBRT	2 (3.4)
Chemotherapy	52 (89.7)
Number chemo regimens	1.78 ± 1.38 (0-7)
Treatment characteristics (n = 79)	
Age at treatment	59.54 ± 10.99 (32-86)
Years from primary diagnosis	2.68 ± 2.79 (0.14-12.88)
Years from liver diagnosis	1.85 ± 1.80 (0.12-8.49)
< 65	53 (67.1)
⩾ 65	26 (32.9)
KPS	
< 80%	11 (13.9)
⩾ 80%	68 (86.1)
Child-Pugh	
A	74 (93.7)
B	5 (6.3)
MELD score	7.61 ± 1.49 (6-13)
Max primary index tumor size (mm)	61.03 ± 41.65 (9-223)
Sum primary index tumors (mm)	82.18 ± 49.08 (9-223)
Lobe treated	
Right	55 (69.6)
Left	24 (30.4)
BMI (kg/m^2)	26.5 ± 4.46 (18.40-36.65)
BSA (m^2)	1.89 ± 0.24 (1.46-2.65)
Total liver	
Volume (mL)	1927.67 ± 779.16 (1002-6243)
Tumor volume (mL)	336.56 ± 460.83 (5.1-3096)
% Tumor	14.35 ± 11.90 (0.27-49.59)
< 25%	62 (78.5)
⩾ 25%	17 (21.5)
Treated liver	
Volume (mL)	1124.06 ± 585.45 (346-3946)
Tumor volume (mL)	253.73 ± 435.82 (3-3096)
% Tumor	17.26 ± 16.97 (0.29-78.46)
< 25%	58 (73.4)
⩾ 25%	21 (26.6)
Lung shunt (%)	7.11 ± 3.62 (1.3-17.4)
Calculated dose (mCi)	27.5 ± 9.68 (8.2-56.8)
Unadjusted[2]	47.61 ± 9.51 (22.9-77.7)
Administered dose (mCi)	27.48 ± 9.91 (8.2-56.9)
Unadjusted	47.76 ± 10.64 (10.6-77.8)
Difference in dose (mCi)	-0.02 ± 1.71 (-9.53-3.2)
% Difference	-0.25 ± 8.31 (-53.84-10.46)
Dose to lung (Gy)	3.4 ± 1.77 (0.55-8.41)
Intra-procedural complications	
Stasis	10 (12.7)
Reflux	

[1]Values presented as numbers (percentage) or mean ± SD (range); [2]Unadjusted indicates dose prior to being adjusted for lobar treatment. TACE: Transcatheter arterial chemoembolization; EBRT: External beam radiation therapy; KPS: Karnofsky Performance Status; MELD: Model for End-Stage Liver Disease; BMI: Body mass index; BSA: Body Surface Area; mCi: Millicurie; Gy: Gray.

Table 2 Toxicity incidence

Toxicity	*n*[1] (%)
Post-embolization syndrome[2]	11 (12.79)
Constitutional toxicities[2]	48 (55.81)
Fatigue	41 (47.67)
Loss of appetite	15 (17.44)
Weakness	11 (12.79)
Fever	6 (6.98)
Weight loss	5 (5.81)
Flu-like symptoms	5 (5.81)
Malaise	4 (4.65)
Chills	2 (2.33)
Gastrointestinal toxicities[2]	47 (55.29)
Abdominal pain	34 (40.00)
Nausea	23 (27.06)
Emesis	10 (11.76)
Constipation	6 (7.06)
Diarrhea	3 (3.53)
Abdominal Cramps	1 (1.18)
Hepatic toxicities[2]	38 (44.19)
Alkaline phosphatase	27 (34.18)
Albumin	21 (26.58)
Total bilirubin	18 (22.78)
Aspartate aminotransferase	9 (11.39)
INR	3 (4.29)
Encephalopathy	2 (2.33)
Jaundice	2 (2.33)
Ascites	1 (1.16)

[1]*n* for this Table was determined based on the number of the original 104 patients included in our study with clinical or laboratory follow-up. There were 86 patients with clinical follow-up but only 79 patients with laboratory follow-up, 9 of whom did not have post-treatment INR values obtained; [2]High incidence of toxicity. INR: International normalized ratio.

Treatment type was not associated with a difference in either clinical or laboratory toxicity (see Supplementary Table 2).

Univariate and multivariate binary logistic regression models were generated for the presence of any severe toxicity, severe albumin toxicity, severe ALP toxicity, and severe total bilirubin toxicity. Results of the multivariate analyses are included in Table 4 (see Supplementary Table 1 for univariate analyses). Multivariate analyses found several associations: decreased pre-treatment albumin (OR = 26.2, P = 0.010) and increased pre-treatment INR (OR = 17.7, P = 0.048) with severe hepatic toxicity, increased pre-treatment AST (OR = 7.4, P = 0.025) and decreased pre-treatment hemoglobin (OR = 12.5, P = 0.025)

Table 3 Severe toxicity incidence

Severe toxicities	Our patients		Time to toxicity development			Literature
	n	%	mean ± SD	range	Number of resolved[1]	
Any	17	21.5				7%-38%[7,9,39]
INR	1	1.4	25.00 ± 0.00		0	1.3%-1.8%[20,27]
Albumin	10	12.7	97.80 ± 40.59	(35-174)		0%-2%[9,27,40]
AST	2	2.5	98.00 ± 19.80	(84-112)	0	0%-8%[7,9,20,22,23,27,40]
ALT	0	0.0				
ALP	14	17.7	86.46 ± 58.37	(3-182)	5	0.5%-20%[7,9,20,23,40]
Total bilirubin	8	10.1	80.75 ± 51.63	(14-182)	1	0%-27%[7,9,20,22,23,27,40]

[1]Toxicities were considered irreversible if values remained grade ⩾ 3 until last recorded measurement. INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

Table 4 Multivariate analyses of severe toxicities

Toxicity	Factor	Univariate		Multivariate		
		P value	OR	*P* value	OR	95%CI
Any						
	Pre-treatment albumin	0.001	33.600	0.010	26.166	2.194-312.072
	Pre-treatment INR	0.016	9.231	0.048	17.743	1.027-306.461
	Colorectal adenocarcinoma	0.022	4.213	0.070	4.527	0.885-23.155
	Pre-treatment ALP	0.018	12.343	0.187	4.770	0.468-48.651
	Pre-treatment total bilirubin	0.031	13.071	0.327	33.100	0.030-36243.627
	Pre-treatment hemoglobin	0.047	3.467	0.449	1.881	0.366-9.674
	MELD score	0.068	1.364		Excluded[1]	
	Pre-treatment AST	0.032	3.552		Excluded[1]	
Albumin						
	Pre-treatment hemoglobin	0.040	9.265	0.025	12.492	1.349-114.011
	Pre-treatment AST	0.039	5.517	0.025	7.404	1.283-42.714
	Pre-treatment total bilirubin	0.047	8.375	0.355	3.349	0.259-43.374
Total bilirubin						
	MELD score	0.020	1.625	0.033	1.830	1.050-3.187
	Pre-treatment albumin	0.035	10.138	0.056	9.042	0.941-86.840
	Administered dose	0.099	0.933	0.117	0.922	0.833-1.020
	Pre-treatment INR	0.075	5.583	0.658	1.694	0.165-17.429
	Pre-treatment total bilirubin	0.025	11.500		Excluded[1]	
ALP						
	Colorectal adenocarcinoma	0.030	4.552	0.043	5.362	1.058-27.185
	Pre-treatment ALP	0.037	9.237	0.070	15.615	0.803-303.636
	Pre-treatment hemoglobin	0.019	6.581	0.084	4.886	0.809-29.519
	KPS	0.067	0.953	0.150	0.947	0.879-1.020
	Pre-treatment INR	0.049	5.636	0.189	4.903	0.456-52.716
	KPS < 80 *vs* KPS ⩾ 80	0.093	3.314		Excluded[1]	
	Pre-treatment AST	0.050	3.519		Excluded[1]	

[1]Variables marked as Excluded were excluded from multivariate analysis due to interdependence. INR: International normalized ratio; ALP: Alkaline phosphatase; MELD: Model for end-stage liver disease; AST: Aspartate aminotransferase; KPS: Karnofsky performance score.

with severe albumin toxicity, increasing model for end-stage liver disease (MELD) score (OR = 1.8, *P* = 0.033) with severe total bilirubin toxicity, and colorectal adenocarcinoma histology with severe alkaline phosphatase toxicity (OR = 5.4, *P* = 0.043).

Radiographic response and overall survival

Radiographic response was assessed following 55 treatments at 3 mo and 30 treatments at 6 mo. Response was not assessed for all patients due to both early expiration and lack of radiographic follow-up at our institution since it serves as a tertiary referral center. At 3 mo, 4 patients had a partial response (7.3%), and 27 patients had stable disease (49.1%) with the rest having progressive disease. At 6 mo, 7 patients had a partial response (23.3%), and 10 patients had stable disease (33.3%) with the rest having progressive disease. Median overall survival for all patients was 8.77 mo (95%CI: 6.43-11.11) from the time of first treatment. Thirty-day mortality was 0%.

DISCUSSION

Published studies on toxicities associated with ^{90}Y treatment have generally focused on their incidence. While some have focused on univariate analysis of factors predictive of increased toxicity rates, multivariate analysis to account for interaction between

these variables remains sparse. We performed this retrospective analysis to further characterize predictors of toxicity to aid in appropriate patient selection and management. Although the majority of treatments resulted in at least one toxicity, severe (grade $\geqslant$ 3) toxicities occurred after 21.5% of our treatments (see Table 2).

Although patients had PES following only 12.8% of treatments, many others had symptoms consistent with this syndrome but not ascribed to it. This observation may help explain why some studies report PES in few patients while others report PES in most[8,9]. Incidences of post-treatment ascites, jaundice, and hepatic encephalopathy in our patients was consistent with other studies[19-26]. Incidence of constitutional and GI symptoms in the literature is variable, especially for fatigue[7,19,20,24,25,27], fever[7,11,24,25,27,28], abdominal pain[7,11,19-21,23-25,27,28], and nausea[7,19,20,22,24,25,27,28]. This variability likely proceeds from their subjectivity, different thresholds for categorization, and variable diligence in seeking and documenting evidence of these toxicities. Table 3 compares the incidence of severe toxicities among our patients with that available in the literature, showing that our observed incidence was representative of the literature except for severe albumin toxicity.

In order to assess factors which may predict development of severe toxicities, we performed a multivariate analysis for each severe toxicity. However, since records for clinical toxicities generally did not indicate severity, only LFT toxicities were included. However, we did find that each category of severe toxicity was associated with the development of at least one clinical toxicity (see Supplementary Table 3), suggesting the development of severe laboratory toxicities is clinically relevant. Besides analyzing each severe LFT toxicity individually, we also analyzed the presence of any severe LFT toxicity as this represents underlying post-treatment liver injury regardless of mode. Despite our inability to analyze severe clinical toxicities, each category of severe LFT toxicity was associated with the development of at least 1 clinical toxicity (see Supplementary Table 3), indicating that these laboratory toxicities are clinically relevant. We also did not include radiation-induced liver disease (RILD) as an endpoint as patients were not clinically assessed for the development of certain aspects of RILD. Furthermore, as ascites is a necessary component of RILD and only 1 of our patients had ascites, RILD was not present in enough patients to analyze. Finally, this patient was already included in the analysis of severe hepatic toxicities due to the development of Grade 3 albumin toxicity. We included the MELD score, as calculated using the UNOS modified formula[29], among our variables as an indicator of overall pre-treatment liver function despite it not being validated among this patient population as this is a widely utilized metric of liver function.

Results of our multivariate analyses revealed that pre-treatment laboratory values were important predictors for the presence of post-treatment liver injury. Goin *et al*[23] previously found pre-treatment total bilirubin and increased liver doses to be associated with liver toxicities. Another study[30] found increased pre-treatment bilirubin and AST were both associated with the development of RILD on univariate analysis. Others have provided further support that increased liver dose was associated with liver toxicities[13,31] and RILD[26]. Our binary logistic regression analysis found only pre-treatment albumin levels < 3.4 gm/dL (OR = 26.2, P = 0.010) or pre-treatment INR levels > 1.2 (OR = 17.7, P = 0.048) predicted development of any severe LFT toxicity. Although increased pre-treatment AST and total bilirubin were significant on univariate analysis, neither were significant on multivariate analysis, and multicollinearity excluded AST, demonstrating the need to assess factors significant on univariate analysis with multivariate analysis. As our patients were treated using the body surface area method without post-treatment SPECT imaging, accurate liver doses could not be determined and could not be included in our analysis.

We further analyzed specific LFTs, including INR and albumin, markers of severe dysfunction of the liver's biosynthetic capacity[32-34]. Although incidence of post-treatment INR toxicities was only 1.4% and could not be analyzed further, multivariate analysis of severe albumin toxicity showed that pre-treatment AST level > 40 units/L (OR = 7.4, P = 0.025) or pre-treatment hemoglobin level < 11.2 gm/dL in women and < 13.4 gm/dL in men (OR = 12.5, P = 0.025) were predictors. Another study found liver decompensation, including INR toxicity, to be associated with pre-treatment Child-Pugh Class B[31]. Interestingly, no treatment in patients with Class B had severe albumin toxicity in our study, though this may be due to the low incidence of such patients in our cohort.

We did not analyze markers of severe direct hepatocellular injury, AST and ALT[35], due to their low incidence; however, analysis of severe ALP toxicity, a marker of cholestasis leading to liver injury[36] showed colorectal adenocarcinoma histology to be associated with severe ALP toxicity (OR = 5.4, P = 0.043). Of the 14 treatments with severe ALP toxicity, 11 occurred in patients with colorectal adenocarcinoma (78.6%), while none of the 23 treatments in patients with neuroendocrine tumors or cholangiocarcinoma led to severe ALP toxicity.

Multivariate analysis on severe total bilirubin toxicity, a marker of the liver's ability to transport ions[37], revealed that increasing pre-treatment MELD was associated with increased risk of toxicity (OR = 1.8, P = 0.033). Prior studies had found total bilirubin toxicities could be predicted by both cirrhosis[38] and Child-Pugh Class B[31]. Since underlying cirrhosis was an exclusion criterion, we are unable to comment on its predictive ability. Child-Pugh class was not included in multivariate analysis as it had a P = 0.462 on

univariate.

Some may theorize that sequential bilobar treatments could complicate measurement of toxicities like cirrhosis despite treatments being to different lobes, but incidences of toxicities among our patients were independent of whether patients received treatment to a single lobe or to both (see Supplementary Table 2), and our analysis of severe toxicities revealed each category of severe toxicity was independent of treatment type. We also found that radiographic response did not influence the development of severe toxicities in any examined category (see Supplementary Table 1), indicating our results were not dependent on tumor progression. However, even if incidence of toxicities was overestimated due to inability to differentiate between progression and toxicity, this overestimation is also shared by other studies.

As with any retrospective study, a primary limitation is unintentional bias. The retrospective nature of our analysis prevented grading of clinical toxicities not graded on initial follow-up. The heterogeneity of our patient population reflects that of patients treated with ^{90}Y and reported elsewhere. Since our institution serves as a referral center, some patients were lost to follow-up, while incomplete follow-up was available for others, potentially biasing our results. Though clinicians may have had different thresholds for recording toxicities, no obvious differences were ascertained. While the small sample size of our patients prevented us from performing more extensive analysis of reported toxicities and prevented some factors from being included in multivariate analysis, we were able to perform substantive multivariate toxicity analysis. Further analysis should be performed in a larger cohort of patients both to validate our results and to determine the predictive value of those factors not included in our multivariate analysis. However, even with these limitations, our study achieved its primary objectives.

In conclusion, our multivariate analysis found that patients with decreased pre-treatment albumin were 26.2 times and elevated pre-treatment INR were 17.7 times more likely to develop severe post-treatment liver toxicity. Patients with decreased pre-treatment hemoglobin were 12.5 times more likely to develop post-treatment dysfunction of the liver's biosynthetic capacity, while patients with increased AST were 7.4 times more likely. Pre-treatment MELD was associated with the development of total bilirubin toxicity, and colorectal adenocarcinoma was associated with development of indirect liver injury. Our results indicate that clinicians should more carefully assess pre-treatment laboratory values, particularly albumin, INR, AST, and hemoglobin when determining the potential risk of ^{90}Y resin microsphere treatment and counseling patients regarding expected severe toxicities and the resultant quality of life. Clinicians should also have greater reservations when recommending ^{90}Y treatment to patients with colorectal adenocarcinoma and elevated MELD scores due to risk for increased toxicity. As such, our results provide a valuable addition to the currently sparse literature regarding multivariate analyses of predictors of severe toxicity after administration of ^{90}Y microspheres.

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COMMENTS

Background

Beta-emitting yttrium-90 (^{90}Y) microsphere brachytherapy is an important modality for the treatment of unresectable primary or secondary hepatic malignancies that preferentially delivers tumorcidal radiation to hepatic malignancies while sparing normal liver parenchyma. This therapy is associated with the development of both mild and severe toxicities. While many have performed univariate analyses of factors predictive of increased toxicity rates, multivariate analyses to account for interactions between these variables remain sparse.

Research frontiers

Current research is seeking to determine which patients will benefit the most from this therapy, including which ones are more likely to develop toxicities.

Innovations and breakthroughs

Goin *et al* have previously found pre-treatment total bilirubin and higher liver doses to be associated with liver toxicities. Multiple other studies found higher liver disease to be associated with liver toxicities and RILD. Others found increased pre-treatment bilirubin and AST to be associated with radiation-induced liver disease on univariate analysis. Another study found liver decompensation, including INR toxicity, and total bilirubin toxicity to be associated with pre-treatment Child-Pugh Class B. A final study found total bilirubin toxicities to be associated with cirrhosis.

Applications

Clinicians should more carefully assess pre-treatment laboratory values, particularly albumin, INR, AST, and hemoglobin when determining the potential risk of ^{90}Y resin microsphere treatment and counseling patients regarding expected severe toxicities and the resultant quality of life. Furthermore, clinicians should have greater reservations when recommending ^{90}Y treatment to patients with colorectal adenocarcinoma and elevated MELD scores due to risk for increased toxicity. As such, current results provide a valuable addition to the currently sparse literature regarding multivariate analyses of predictors of severe toxicity after administration of ^{90}Y microspheres. Prospective studies should also be performed to validate the results of this study.

Terminology

^{90}Y microspheres are a type of beta-emitting brachytherapy. Patients with lung shunts > 10% require dose reductions in order to limit the risk of developing radiation pneumonitis. MELD score was based on the UNOS modified formula to provide an indication of underlying liver disease.

Peer-review

This manuscript is a well-designed and well-written study detailing variables associated with the development of severe toxicities.

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