Limitations of Body Surface Area–Based Activity Calculation for Radioembolization of Hepatic Metastases in Colorectal Cancer

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ABSTRACT

Purpose: To calculate absorbed radiation doses in patients treated with resin microspheres prescribed by the body surface area (BSA) method and to analyze dose-response and toxicity relationships.

Materials and Methods: A retrospective review was performed of 45 patients with colorectal carcinoma metastases who received single-session whole-liver resin microsphere radioembolization. Prescribed treatment activity was calculated using the BSA method. Liver volumes and whole-liver absorbed doses (D_{WL}) were calculated. D_{WL} was correlated with toxicity and radiographic and biochemical response.

Results: The standard BSA-based administered activity (range, 0.85–2.58 GBq) did not correlate with D_{WL} (mean, 50.4 Gy; range, 29.8–74.7 Gy; $r = -0.037$; $P = .809$) because liver weight was highly variable (mean, 1.89 kg; range, 0.94–3.42 kg) and strongly correlated with D_{WL} ($r = -0.724$; $P < .001$) but was not accounted for in the BSA method. Patients with larger livers were relatively underdosed, and patients with smaller livers were relatively overdosed. Patients who received $D_{WL} > 50$ Gy experienced more toxicity and adverse events (> grade 2 liver toxicity, 46% vs 17%; $P < .05$) but also responded better to the treatment than patients who received $D_{WL} < 50$ Gy (disease control, 88% vs 24%; $P < .01$).

Conclusions: Using the standard BSA formula, the administered activity did not correlate with D_{WL}. Based on this short-term follow-up after salvage therapy in patients with late stage metastatic colorectal carcinoma, dose-response and dose-toxicity relationships support using a protocol based on liver volume rather than BSA to prescribe the administered activity.

ABBREVIATIONS

BSA = body surface area, CEA = carcinoembryonic antigen, D_{WL} = whole-liver absorbed dose, mCRC = metastatic colorectal carcinoma, RECIST = Response Evaluation Criteria in Solid Tumors, REILD = radioembolization-induced liver disease, SPECT = single photon emission computed tomography, ^{99m}Tc-MAA = technetium-99m macroaggregated albumin, ^{90}Y = yttrium-90

Yttrium-90 (^{90}Y) radioembolization is an emerging treatment modality for treatment of both primary and secondary liver malignancies, including from metastatic colorectal carcinoma (mCRC) (1–3). Different methods have been developed and used for activity calculation and prescription (4,5). The standard method for glass microspheres (TheraSphere; Nordion, Inc, Ottawa, Ontario, Canada) is based on liver weight and the assumption of homogeneous distribution of microspheres (TheraSphere [package insert]. Ottawa, Canada: Nordion, Inc: 2004.). The whole-liver absorbed dose (D_{WL}) is calculated using a method derived from the medical internal radiation dosimetry (MIRD) equations for dose calculation (6), assuming an absorbed dose of 50 Gy for every 1 GBq activity/kg tissue. For resin

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microspheres (SIR-Spheres; Sirtex Medical Ltd, Lane Cove, Australia), a different method is recommended by the manufacturer and by consensus, referred to as the body surface area (BSA) method (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.). This method was developed after the initial method, the empiric method, proved to have an unacceptable toxicity profile in a clinical trial (7). The BSA method is based on the patient's BSA, the fractional liver involvement by tumor, and the proportion of the liver to be treated (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.). A third, more sophisticated method is the partition method. It is based on tumor and normal liver volumes and expected activity distribution, predicted by single photon emission computed tomography (SPECT) imaging (8,9). The partition method is applicable only in patients with discrete and limited disease and is not currently feasible in patients with diffuse metastatic disease that precludes defining the tumor and normal parenchymal compartments (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.). A more recently proposed treatment algorithm for resin microspheres concluded that only the BSA method was suitable for patients with bilobar disease from mCRC (10), particularly for small, hypovascular, multifocal lesions with diffuse margins.

Although the BSA method for resin microspheres has been accepted as adequately safe in patients with mCRC, a dose-response relationship is unclear, and activity calculation remains an inexact estimation (12). In clinical practice, some patients do not respond to treatment, raising uncertainty about insufficient administered activity or radiation resistance or both. Other patients appear to be overdosed and develop complications such as radioembolization-induced liver disease (REILD) (13). It is logical that a dose-response relationship should exist, not only for efficacy but also for toxicity. The aim of this study was to evaluate the consistency and validity of the BSA method and to establish a dose-response relationship based on retrospective calculation of liver volume and absorbed dose. The calculated D_{WL} was correlated with toxicity and radiographic and biochemical response.

MATERIALS AND METHODS

The primary aim of this study was to study the limitations of the BSA method for radioembolization activity calculation. The mean absorbed dose in the liver from treatment with resin microsphere radioembolization was calculated in patients with mCRC and compared with the administered activity prescribed using the BSA method. As a secondary aim, a dose-effect relationship was derived with regard to both toxicity and efficacy parameters.

Patients

From June 2004 to September 2011, 247 consecutive patients (143 men and 104 women; mean age, 62 y; range, 20–92 y) underwent radioembolization. A homogeneous subset was selected for this analysis. Inclusion criteria for this cohort were whole-liver treatment in one session (for toxicity analysis), colorectal carcinoma liver metastasis (one tumor type), and resin microspheres only. These criteria were met by 45 patients. Baseline characteristics are summarized in Table 1. To qualify for treatment, all patients maintained Eastern Cooperative Oncology Group performance status of 0–2 and baseline laboratory values within acceptable ranges. All 45 patients were included in this retrospective analysis. Data were

Table 1. Demographics, Baseline Characteristics, and Oncologic Histories of the Total Cohort

Characteristic	Patients, n (%)
Sex, male/female	24/21
Age (y), mean (range)	58 (25–80)
Previous systemic treatment	
Chemotherapy	44 (98%)
Antiangiogenic agents	40 (89%)
Anti-EGFR agents	19 (42%)
Previous liver-directed treatment	
Partial liver resection	17 (38%)
Radiofrequency ablation	11 (24%)
Transarterial embolization	1 (2%)
External-beam radiotherapy	1 (2%)
ECOG performance status	
0	28 (62%)
1	17 (38%)
Baseline laboratory values, median (range)	
WBC count (10^9/L)	7.1 (3.4–33.6)
Platelet count (10^9/L)	254 (94–506)
Hemoglobin (g/dL)	12.5 (9.9–15.4)
Serum AST (IU/L)	37 (11–165)
Serum ALT (IU/L)	40 (13–221)
Serum total bilirubin (mg/dL)	0.6 (0.1–2.7)
Serum alkaline phosphatase (IU/L)	163 (64–713)
Serum albumin (g/dL)	3.5 (2.3–4.5)
CEA (ng/mL)	33 (1–18,590)
Liver tumor involvement (%), median (range)	25 (5–65)
BSA (m^2), median (range)	1.90 (1.37–2.39)
Calculated activity (GBq), median (range)	1.86 (1.07–2.68)
Calculated lung shunt (%), median (range)	6.4 (0–15.0)
Administered activity (GBq), median (range)	1.84 (0.85–2.58)
Liver weight (kg), mean (range)	1.89 kg (0.94–3.42)
D_{WL} (Gy), mean (range)	50.4 (29.8–74.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CEA = carcinoembryonic antigen; D_{WL} = whole-liver absorbed dose; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; WBC = white blood cells.

handled in accordance with the Health Insurance Portability and Accountability Act. The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived. This article was written in compliance with research reporting standards for radioembolization (13).

Radioembolization

All procedures were performed by experienced interventional radiologists at a Sirtex designated Center of Excellence. Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) was used for simulation imaging after coil embolization of all relevant hepaticoenteric vessels during preparatory angiography. Radioembolization with ^{90}Y resin microspheres followed 1–2 weeks later. Activity calculations and treatments were performed in compliance with international consensus guidelines (4,5,14). All activities were calculated according to the standard BSA formula for resin microspheres based on BSA and liver tumor involvement, planning for whole liver treatment (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.):

$$\text{Prescribed activity (GBq)} = \text{BSA (m}^2\text{)} - 0.2 + \% \text{ tumor involvement}/100$$

In the case of significant hepatopulmonary shunting, the prescribed activity was reduced according to recommendations on the package insert (shunt 10%–15%, 20% reduction; shunt 15%–20%, 40% reduction; shunt > 20%, no treatment). A maximum of 10% difference in prescribed and prepared activity was accepted. The administered activity was determined by correcting the prepared activity for residual activity as well as the lung shunt. Pretreatment V-vial and posttreatment V-vial, tubing, and catheter activity were measured in a "leak-proof" Nalgene container (Bicron Electronics, Co., Canaan, Connecticut) using a Thermo/Bicron Micro-Rem meter (Thermo Fisher Scientific, Inc., Waltham, Massachusetts) at a set standard geometry. Measurements were processed by calibrated conversion algorithms (Sirtex Medical Ltd) to calculate the percentage of residual activity. Residual activity < 5% was accepted. A partition method was not used because accurate partitioning of the tumor compartment and normal liver compartment was not feasible in these patients with disseminated disease including diffuse, heterogeneous, infiltrating, necrotic, and miliary tumors (10,11) (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.). Follow-up consisted of clinical and laboratory follow-up examinations at 2, 4, and 8 weeks and imaging follow-up examination at 3 months and at intervals prescribed by the medical oncologist thereafter. Toxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02.

Imaging

Minimal requirements for radioembolization treatment included anatomic (computed tomography [CT] or magnetic resonance imaging) or functional imaging (positron emission tomography [PET] or PET/CT), or both, before treatment for patient selection and estimation of liver tumor involvement. Digital subtraction angiography images were obtained using (micro) catheters to obtain a complete hepatic arterial map and to identify extrahepatic and parasitized branches in need of prophylactic embolization. Since 2006, C-arm CT has been used as an adjunct to digital subtraction angiography when end-organ tissue perfusion or vascular anatomy was unclear. In addition, C-arm CT was performed to delineate the vascular territory served by the planned catheter placement and to predict distribution of the microspheres (15). Subsequently, patients underwent ^{99m}Tc-MAA administration and planar and SPECT imaging to measure the proportion shunted into the lungs and to evaluate for any extrahepatic deposition.

Follow-up imaging replicating the modality employed before treatment was used for objective response analysis at 3 months after radioembolization, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and World Health Organization criteria with a focus on liver response only (16). One radiology-trained author (M.G.E.H.L., blinded for activity and dose calculations) performed readings of all clinical film interpretations and defined radiographic response according to RECIST 1.1. PET imaging before and after treatment was not available in most patients.

Dosimetry

The BSA-based prescribed activity was used retrospectively to calculate DWL for each patient. D_{WL} was calculated using the MIRD formula of 50 Gy per 1 GBq activity/kg tissue (6). CT was used to calculate the liver volume (including metastatic lesions), converted to weight by the relationship 1 mL = 1.029 g. D_{WL} was calculated assuming homogeneous intrahepatic microsphere distribution and absorption of all the administered activity and energy in the liver, using the following formula (6):

$$D_{WL}(\text{Gy}) = [A_{Y90}\,(\text{GBq})/\text{LW(kg)}] \times 50\ (\text{J/GBq})$$

Where A_{Y90} was the administered activity in GBq corrected for the lung shunt, LW was the liver weight in kg, and D_{WL} was the whole-liver absorbed dose in Gy. Dose-response and dose-toxicity relationships were analyzed using D_{WL}.

Statistical Analysis

A commercial statistical software package (SPSS for Windows, version 19.0; SPSS Inc, Chicago, Illinois) was

used for data analysis. All continuous variables were tested for normal distribution probability using Kolmogorov-Smirnov tests and normality plots. Median and range were reported for nonnormal distributed variables, and mean and range were reported for normal distributed variables. For comparison between groups, nonparametric Mann-Whitney test (continuous variables) and Fisher exact test (categorical variables) were used. For individual correlation of two continuous variables, Pearson or Spearman correlation coefficient was used, depending on normality. Linear regression analysis was used to describe linear relationships between continuous variables. A P value $< .05$ was considered statistically significant.

RESULTS

Patient demographics are listed in Table 1. A visual estimated median of 25% of the liver volume (range, 5%–65%) consisted of tumor tissue with a median carcinoembryonic antigen (CEA) level of 33 ng/mL (range, 1–18,590 ng/mL). All patients were treated in a salvage setting and had been treated before embolization with platinum-based systemic chemotherapy regimens (98%), bevacizumab (89%), and several liver-directed treatments, including partial liver resections (38%) or radiofrequency ablation (24%). All patients had been removed from antiangiogenesis treatment for at least 6 weeks at the time of radioembolization treatment. The median administered activity was 1.84 GBq (range, 0.85–2.58 GBq), leading to a wide range of D_{WL} (mean, 50.4 Gy; range, 29.8–74.7 Gy). Stasis during administration was encountered in 13 patients (28.9%), leading to incomplete administrations in 6 patients (71%–93% administered). Of these 13 patients, 12 had received prior bevacizumab (92.3%).

No correlation was found between administered activity and D_{WL} ($r = -0.037$, $P = .809$). Although BSA correlated with liver weight ($r = 0.635$, $P < .001$) and liver weight correlated with administered activity ($r = 0.662$, $P < .001$), this did not result in a correlation between administered activity and D_{WL} (Fig 1a). Instead, a correlation was found between liver weight and D_{WL} ($r = -0.723$, $P < .001$) (Fig 1b). Patients with larger livers were relatively underdosed, and patients with smaller livers were relatively overdosed (Fig 2a–d). The wide range of D_{WL} was predominantly caused by a wide range in liver weight spanning almost a 4-fold difference (mean, 1.89 kg; range, 0.94–3.42 kg), whereas the BSA varied by < 2-fold (1.37–2.39 m^2). Linear regression analysis revealed the relation:

$$D_{WL}(Gy) = -13.7 * LW(kg) + 76.2$$

Where D_{WL} was the whole-liver absorbed dose in Gy, and LW was liver weight in kg. D_{WL} was equal to the mean of 50.4 Gy at a liver weight of 1.88 kg (Fig 1b).

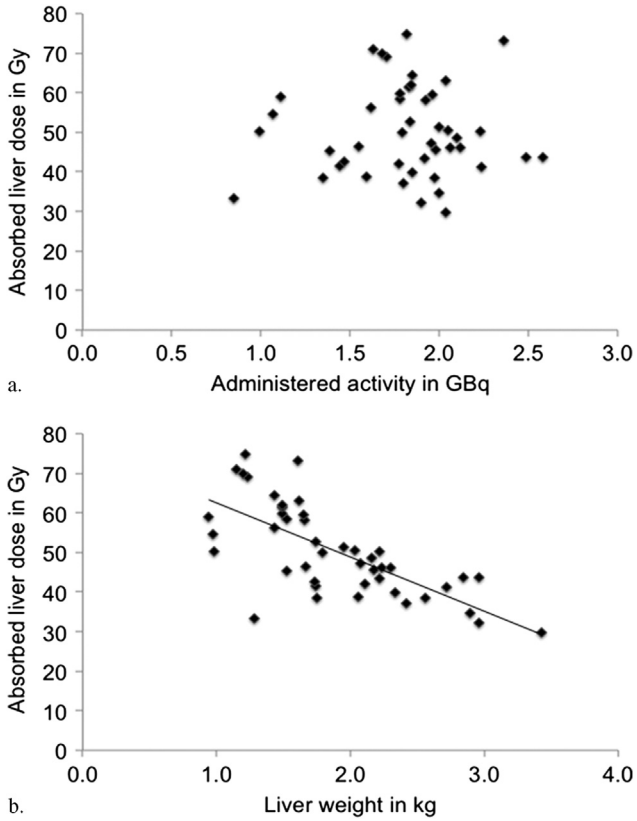

Figure 1. D_{WL} was not correlated to the administered activity ($r = -0.037$, $P = .809$) **(a)**. Instead, liver weight, a factor that is not taken into account in the BSA activity calculation method, proved to be negatively correlated with D_{WL} ($r = -0.723$, $P < .001$) **(b)**. Linear regression analysis showed the relation D_{WL} (Gy) = −13.7 * LW (kg) + 76.2. Larger livers were relatively underdosed, and smaller livers were relatively overdosed.

To evaluate the dose-response relationship for D_{WL}, the study cohort was stratified into two groups with D_{WL} below or above the mean of 50 Gy (Table 2). The low D_{WL} group received a D_{WL} mean of 41.1 Gy compared with a D_{WL} mean of 60.0 Gy in the high D_{WL} group ($P < .001$). No differences were found with regard to demographics, baseline characteristics, and treatment history, and the interval from baseline CT scan to follow-up CT scan and the interval between treatment and follow-up scan were not different between groups (mean, 5.1 vs 4.6 mo and 2.9 vs 2.9 mo, respectively). BSA proved to be significantly higher in the low D_{WL} group compared with the high D_{WL} group (2.03 m^2 vs 1.76 m^2; $P < .01$), leading to higher calculated (2.00 GBq vs 1.79 GBq; $P = .02$) and administered activities (1.92 GBq vs 1.83 GBq; $P = .39$). Although administered activity was higher in the low D_{WL} group, this still led to lower D_{WL} because of the significantly larger livers in this group compared with the high D_{WL} group (2.26 kg vs 1.49 kg; $P < .001$).

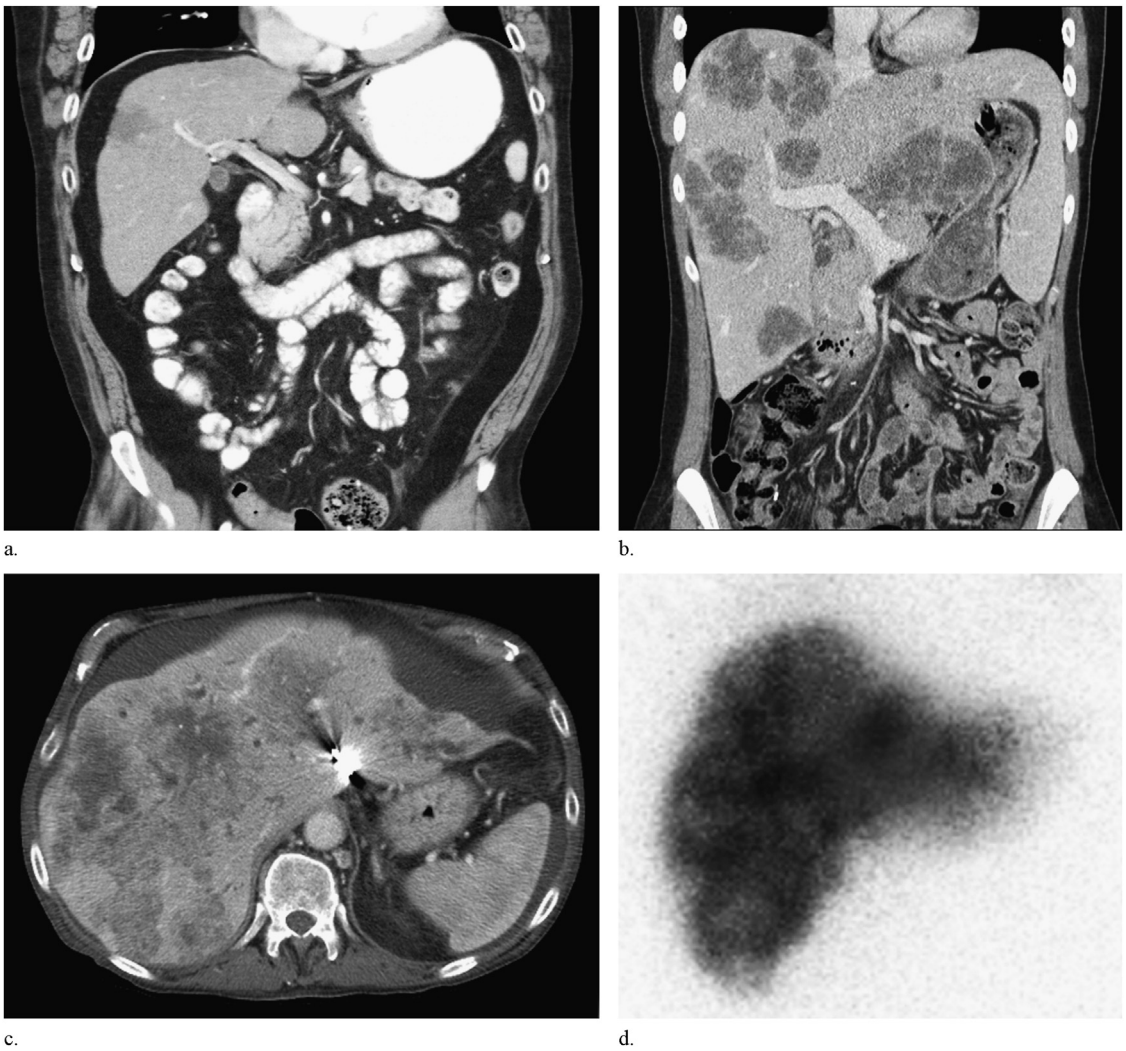

Figure 2. Coronal reformats of contrast-enhanced CT images at the level of the portal vein before treatment **(a, b)**. One patient developed REILD **(a)**. In this patient, an administered activity of 1.82 GBq (BSA, 1.78 m^2; estimated tumor fraction, 15%) and a small liver weighing 1.22 kg resulted in a high D_{WL} of 74.7 Gy. Another patient **(b)** received 1.85 GBq (BSA, 1.50 m^2; estimated tumor fraction, 45%) but had a large liver of 2.33 kg, resulting in a D_{WL} of only 39.7 Gy. The same administered activity resulted in very different absorbed doses in these two patients. The partition method could not be accurately applied to this population because many patients presented with multiple confluent or indistinct tumors on imaging **(c)** and ^{99m}Tc-MAA SPECT **(d)**.

Most patients tolerated treatment well with minor and expected symptoms such as transient nausea and pain related to the postradioembolization syndrome. Some patients experienced more serious adverse events, including gastrointestinal ulceration (five patients) and REILD (one patient). The initial high rate of ulceration was attributed to administration via the proper hepatic artery, a practice that was later discontinued (17). During the first 2 months, laboratory test toxicity was mostly confined to grade 1–2. Only five patients (median $D_{WL} = 63.2$ Gy) had grade 3 toxicity (leukopenia in one patient, thrombocytopenia in two patients, bilirubinemia in one patient, and anemia with high alkaline phosphatase in one patient). Grade 4 toxicity was not encountered. However, REILD was diagnosed in one patient with a maximum bilirubin level of 9.7 mg/dL, increased transaminases and alkaline phosphatase, and decreased albumin, together with jaundice, nausea, peripheral edema, and ascites. However, metastases in this patient responded well to treatment with stable disease on CT and a CEA decrease of 85%. The patient died 6 months after treatment.

Grade 2 or greater liver toxicities occurred less frequently in the low D_{WL} group (17% vs 46%; $P < .05$). Significant correlations were found between changes in laboratory values over time versus D_{WL} (aspartate aminotransferase, alanine aminotransferase, and total serum bilirubin in week 4; aspartate aminotransferase, total serum bilirubin, and albumin in week 8; $P < .05$). Figure 3a,b illustrates the difference in toxicity between the low and high D_{WL} groups with regard to laboratory changes over time. The patient with REILD who had

Table 2. Baseline Characteristics of Low Dose versus High Dose Group

Variable	< 50 Gy	> 50 Gy	*P* Value
No. Patients	23	22	
Sex, male/female	14/9	10/12	NS
Age (y)	58 (25–80)	52 (33–65)	NS
Previous systemic treatment			
Chemotherapy	22 (96%)	22 (100%)	NS
Antiangiogenic agents	20 (87%)	20 (91%)	NS
Anti-EGFR agents	8 (35%)	11 (50%)	NS
Previous liver-directed treatment			
Partial liver resection	7 (30%)	10 (46%)	NS
Radiofrequency ablation	6 (26%)	5 (23%)	NS
Transarterial embolization	1 (4%)	0 (0%)	NS
External-beam radiotherapy	1 (4%)	0 (0%)	NS
ECOG performance status			NS
0	16 (70%)	12 (55%)	
1	7 (30%)	10 (46%)	
Baseline laboratory values			
WBC count (10^9/L)	7.1	7.2	NS
Platelet count (10^9/L)	261	238	NS
Hemoglobin (g/dL)	12.4	13.3	NS
Serum AST (IU/L)	45	33	NS
Serum ALT (IU/L)	42	39	NS
Serum total bilirubin (mg/dL)	0.6	0.6	NS
Serum alkaline phosphatase (IU/L)	163	167	NS
Serum albumin (g/dL)	3.3	3.7	< .05
CEA (ng/mL)	49	22	NS
Liver tumor involvement (%)	25	20	NS
BSA (m^2)	2.03	1.76	< .01
Calculated activity (GBq)	2.00	1.79	< .05
Calculated lung shunt (%)	6.8	6.0	NS
Administered activity (GBq)	1.92	1.83	NS
Liver weight (kg)	2.26	1.49	<.001
D_{WL} (Gy)	41.1	60.0	<.001
Follow-up imaging			
Interval baseline—follow-up (d)	155	140	NS
Interval radioembolization—follow-up (d)	89	87	NS

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CEA = carcinoembryonic antigen; D_{WL} = whole-liver absorbed dose; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NS = not significant; WBC = white blood cells.

been treated with 1.82 GBq (BSA, 1.78; estimated liver tumor involvement, 15%) had the highest D_{WL} in the cohort (74.7 Gy) because of a low liver weight of only 1.22 kg despite no cirrhosis and no prior resections.

Efficacy was variable throughout the study cohort. Median changes in CEA level compared with baseline were −28.8% (range, −84.2 to +75%) at week 2, −48.6% (range, −94.7 to +71.2%) at week 4, and −36.7% (range, −94.7 to +85.4%) at week 8. The mean interval between baseline and follow-up CT was 4.9 months and between radioembolization treatment and follow-up was 2.9 months. The target lesions showed a median change of −1.5% (range, −35 to +73%) by RECIST and −3% (range, −56 to +193%) by World Health Organization criteria at 3-month follow-up. Objective response classification was identical by RECIST and by World Health Organization criteria. The overall response rate (complete response plus partial response) was low (17%) compared with the overall disease control rate, which included stable disease (63%). No complete responses were observed. Median overall survival after diagnosis was 37.9 months and after radioembolization treatment was 11.2 months.

The anatomic decrease in size of the target lesions correlated with D_{WL} ($P < .05$), leading to significant differences between the low and high D_{WL} groups (Fig 4a,b). A lower response rate was found in the low D_{WL} group (8% vs 31%; $P = .36$), but the difference was more striking when looking at disease control (24% vs 88%; $P < .01$). About three quarters of the patients who

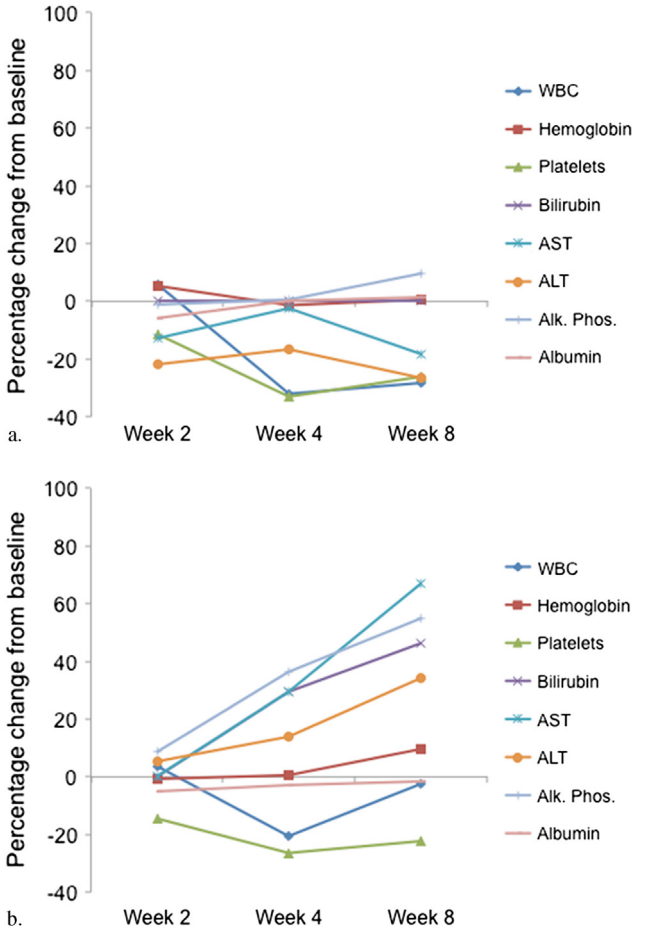

Figure 3. **(a)** During follow-up, the laboratory values in the low D_{WL} group did not show any significant changes except for minor decreases in platelet and white blood cell counts. **(b)** The high D_{WL} group showed significant increases in total serum bilirubin and liver enzymes and significant declines in serum albumin levels, platelet counts, and white blood cell counts. Values represent means of percentage changes. Alk. Phos. = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell count. (Available in color online at *www.jvir.org*.)

had been treated with D_{WL} < 50 Gy had progressed within an interval of 3 months. Serum CEA levels showed a variable response over time and were possibly influenced by extrahepatic disease in two thirds of the patients (lung and lymph nodes mostly). Favorable changes in CEA levels were more pronounced in the high D_{WL} group (**Fig 4c**).

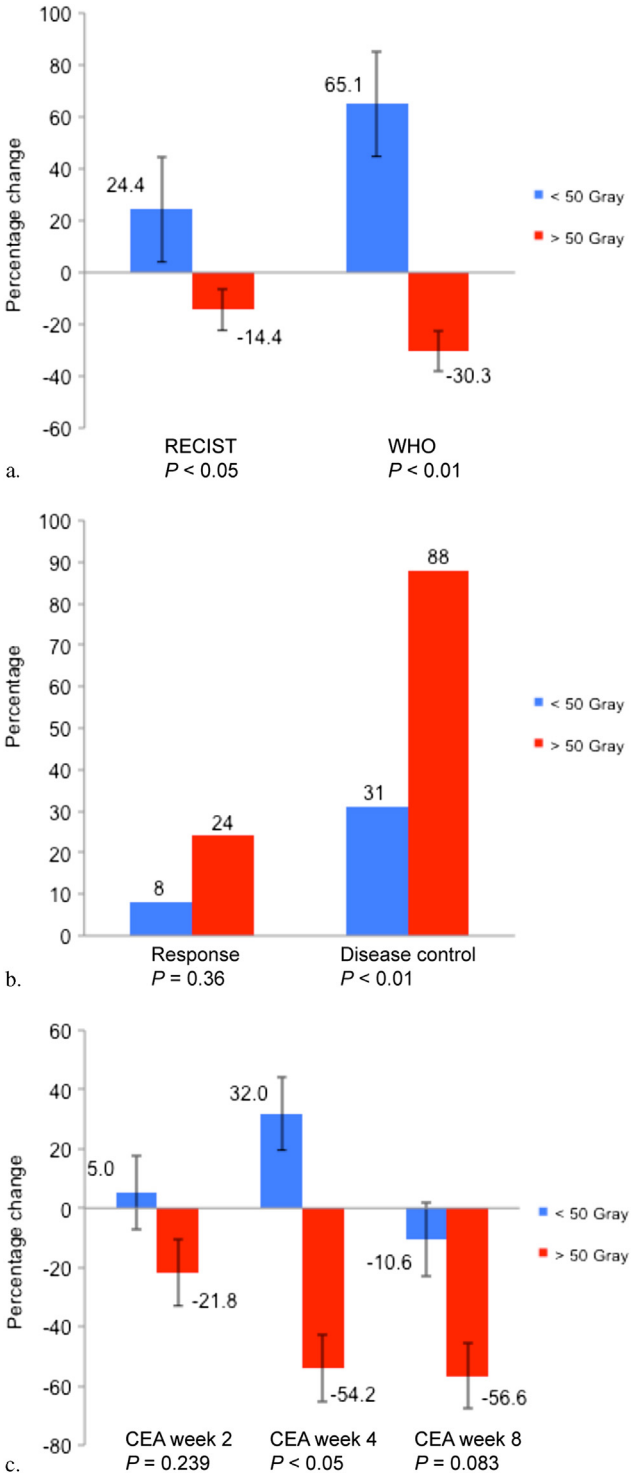

Figure 4. Parameters of response. **(a)** A significant difference in target lesion size change was observed between the low D_{WL} and high D_{WL} groups at 3-month follow-up. **(b)** This difference translated to differences in response rates (complete response and partial response) and disease control rates (response plus stable disease). **(c)** Changes in CEA levels were more pronounced in the high D_{WL} group. WHO = World Health Organization. (Available in color online at *www.jvir.org*.)

DISCUSSION

Optimal dosimetry has been a challenge since the development of ^{90}Y microspheres for radioembolization in the late 1960s (18–20). In early clinical trials, the empiric method was used to calculate the prescribed activity for resin microspheres. Patients were treated with a predetermined activity that reflected only fractional tumor involvement of the liver. Tumor involvement that was < 25%, 25%–50%, or > 50% of the total liver volume was treated with 2 GBq, 2.5 GBq, or 3 GBq. In a randomized phase III trial in patients

with mCRC treated with ^{90}Y resin microspheres and chemotherapy (hepatic artery chemotherapy with floxuridine) versus chemotherapy alone, the regimen including radioembolization with empiric method activity prescription proved to be equally safe and more effective (21). However, in a subsequent study, the same group proposed the BSA-based activity calculation formula because interim analysis of the first five patients revealed signs of REILD in one (small) patient who had been treated with 2.5 GBq (7). The high risk of REILD using the empiric activity calculation method was later confirmed in a multicenter retrospective study (2), rendering the empiric method obsolete (10).

In the present study, we found that target volume and weight (ie, liver) were not adequately reflected by BSA-based activity calculations. The standard BSA-based activity calculation formula resulted in a wide variation of D_{WL}, spanning a 2.5-fold difference. A liver weight with greater deviation from the mean of 1.89 kg led to greater deviation from D_{WL} mean of 50.4 Gy. This finding suggests that for a therapy that is not systemic but is confined to the liver, BSA cannot accurately model the volume of distribution, especially when the volume of the liver may be distorted by disease involvement. Within the 2.5-fold dose range, significant correlations were found between D_{WL} and specific parameters of toxicity and efficacy, such as liver function and objective response of the treated tumors. These findings confirmed the subjective suspicions of other authors (22).

The overall objective response rate (17%), disease control rate (63%), and overall survival (median, 11.2 months) in the present study were comparable to other results reported in the literature (23–29). However, patients treated with $D_{WL} < 50$ Gy showed a significantly lower disease control rate of only 24%, accompanied by lower rates of adverse events. This dose-response relationship suggests that the low D_{WL} group might have benefited from receiving higher D_{WL}, although at the cost of higher toxicity. A true dose-escalation study reaching dose-limiting toxicity based on D_{WL} could serve to clarify this issue. Several studies using glass microspheres, albeit reflecting a mechanism of action with less emphasis on embolic effect, have shown safety with much higher D_{WL} in the 120-Gy range (30).

The main limitation of the present study is its retrospective design. It shows the limitations of the currently used BSA activity calculation method compared with an approach based on D_{WL}, but it is underpowered to provide evidence for an alternative method to improve dosimetry or to show an effect on efficacy parameters beyond liver response, such as CEA and overall survival. Follow-up for this report was limited to 3 months with only one time point for objective response assessment and only one interpreter. Later response and maximal response were not analyzed because of high variability in chronology and availability of follow-up. Molecular imaging tools such as PET may add to response assessment beyond anatomic changes only, but these were available on only a few patients of our cohort (31). The small number of patients included was due to tight selection criteria, which were deemed necessary to create a homogeneous cohort with similar cell type, previous treatment histories, and hepatic reserve.

The other limitation was the use of D_{WL} for absorbed dose. The parameter D_{WL}, which is essentially the simplified partition model routinely used for glass microsphere activity calculation, showed advantages over the BSA-based approach for prediction of activity-related toxicity and efficacy. However, it is still an overly simplified calculation of the mean absorbed dose based on the assumption of homogeneous distribution, and it does not reflect differences in tissue vascularity and the proportion of tumor involvement (32). The actual tumor absorbed dose and the normal liver absorbed dose would represent more accurate parameters for efficacy and toxicity, respectively, but accurate measurement of these partition parameters is not possible at the present time in patients with diffuse, indistinct, multiple tumor involvement (**Fig 2c, d**) (10,11) (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.).

A requisite for optimal radioembolization treatment is to administer an optimal activity for each patient. The lack of correlation found between D_{WL} and efficacy indicates that improved activity calculation methods based on accurate physiologic parameters are needed. The partition model method allows calculation of the administered activity in the tumor volume and in the healthy liver volume, assuming a defined distribution of the activity (8–10). However, this assumption is questioned by significant distribution differences between simulation dose ^{99m}Tc-MAA SPECT and ^{90}Y SPECT/PET after radioembolization (33). Specific technical solutions (ie, subselective administrations beyond major bifurcations) may help to reduce this problem, but some error is inherent to dosimetry based on ^{99m}Tc-MAA imaging. Methods to determine tumor volume and healthy tissue volume and to determine relative microsphere distribution are technically challenging and not yet validated in patients with advanced liver disease from mCRC (11). Lastly, when using a partition method, a maximum tolerable dose to normal liver tissue needs to be defined. The proposed value of 80 Gy has not been validated and should be expected to vary according to patient-specific characteristics, such as tumor type, treatment history, and comorbidities (SIR-Spheres Yttrium-90 Resin Microspheres [package insert]. Lane Cove, Australia: Sirtex Inc: 2012.). Simplification assuming uniform distribution precludes the necessity of specifying these parameters and is currently used for activity calculation for glass microspheres. New software

is being developed to allow automatic segmentation and volume and tumor involvement calculations, but physiologic microsphere distribution modeling remains elusive. These future developments should lead to safer and more effective personalized dose planning in radioembolization treatment.

In conclusion, the size of a liver can vary greatly in the setting of liver disease. Prescription of radioembolization activity using the BSA method results in a wide variation of actual D_{WL}, within which there is a dose-response relationship of greater efficacy and higher toxicity with higher doses. An activity calculation method based on absorbed dose could be advantageous, but further improvements in imaging and modeling are needed.

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REFERENCES

1. Coldwell D, Sangro B, Salem R, et al. Radioembolization in the treatment of uunresectable liver tumors: experience across a range of primary cancers. Am J Clin Oncol 2012; 35:167–177.
2. Kennedy AS, McNeillie P, Dezarn WA, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys 2009; 74:1494–1500.
3. Vente MA, Wondergem M, van de Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol 2009; 19:951–959.
4. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 2007; 68:13–23.
5. Kennedy A, Coldwell D, Sangro B, et al. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol 2012; 35:91–99.
6. Gulec SA, Mesoloras G, Stabin M. Dosimetric techniques in 90Y-microsphere therapy of liver cancer: the MIRD equations for dose calculations. J Nucl Med 2006; 47:1209–1211.
7. van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol 2004; 88:78–85.
8. Ho S, Lau WY, Leung TW, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med 1996; 23:947–952.
9. Ho S, Lau WY, Leung TW, et al. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur J Nucl Med 1997; 24:293–298.
10. Lau WY, Kennedy AS, Kim YH, et al. Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres. Int J Radiat Oncol Biol Phys 2012; 82:401–407.
11. Dezarn WA, Cessna JT, de Werd LA, et al. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies. Med Phys 2011; 38:4824–4845.
12. Sangro B, Gil-Alzugaray B, Rodriguez J, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 2008; 112:1538–1546.
13. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol 2011; 22:265–278.
14. Coldwell D, Sangro B, Wasan H, et al. General selection criteria of patients for radioembolization of liver tumors: an international working group report. Am J Clin Oncol 2011; 34:337–341.
15. Louie JD, Kothary N, Kuo WT, et al. Incorporating cone-beam CT into the treatment planning for yttrium-90 radioembolization. J Vasc Interv Radiol 2009; 20:606–613.
16. Shim JH, Lee HC, Kim SO, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 2012; 262:708–718.
17. Lam MG, Banerjee S, Louie JD, et al. Root cause analysis of gastroduodenal ulceration after yttrium-90 radioembolization. J Vasc Interv Radiol 2013; 36:1536–1547.
18. Gray BN, Anderson JE, Burton MA, et al. Regression of liver metastases following treatment with yttrium-90 microspheres. Aust N Z J Surg 1992; 62:105–110.
19. Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy with 90yttrium microspheres for extensive colorectal liver metastases. J Gastrointest Surg 2001; 5:294–302.
20. Gray BN, Burton MA, Kelleher DK, et al. Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. J Surg Oncol 1989; 42:192–196.
21. Gray B, van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001; 12: 1711–1720.
22. Kao YH, Tan EH, Ng CE, Goh SW. Clinical implications of the body surface area method versus partition model dosimetry for yttrium-90 radioembolization using resin microspheres: a technical review. Ann Nucl Med 2011; 25:455–461.
23. Cianni R, Urigo C, Notarianni E, et al. Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. Cardiovasc Intervent Radiol 2009; 32:1179–1186.
24. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 2010; 103: 324–331.
25. Fahmueller YN, Nagel D, Hoffmann RT, et al. Predictive and prognostic value of circulating nucleosomes and serum biomarkers in patients with metastasized colorectal cancer undergoing selective internal radiation therapy. BMC Cancer 2012; 12:5.
26. Gulec SA, Mesoloras G, Dezarn WA, et al. Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: the tumor selectivity of the treatment as a function of tumor to liver flow ratio. J Transl Med 2007; 5:15.
27. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol 2008; 19:1187–1195.
28. Kennedy AS, Coldwell D, Nutting C, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys 2006; 65:412–425.
29. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol 2011; 35:1066–1073.
30. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer 2009; 115:1849–1858.
31. Wong CY, Gates VL, Tang B, et al. Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography predicts extrahepatic metastatic potential of colorectal metastasis: a practical guide for yttrium-90 microspheres liver-directed therapy. Cancer Biother Radiopharm 2010; 25:233–236.
32. Campbell JM, Wong CO, Muzik O, et al. Early dose response to yttrium-90 microsphere treatment of metastatic liver cancer by a patient-specific method using single photon emission computed tomography and positron emission tomography. Int J Radiat Oncol Biol Phys 2009; 74:313–320.
33. Wondergem M, Smits ML, Elschot M, et al. 99mTc-macroaggregated albumin poorly predicts the intrahepatic distribution of 90Y resin microspheres in hepatic radioembolization. J Nucl Med 2013; 54: 1294–1301.