CLINICAL STUDY

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.