Quantitative Dosimetry for Yttrium-90 Radionuclide Therapy: Tumor Dose Predicts Fluorodeoxyglucose Positron Emission Tomography Response in Hepatic Metastatic Melanoma

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ABSTRACT

Purpose: To assess a new method for generating patient-specific volumetric dose calculations and analyze the relationship between tumor dose and positron emission tomography (PET) response after radioembolization of hepatic melanoma metastases.

Methods and Materials: Yttrium-90 (^{90}Y) bremsstrahlung single photon emission computed tomography (SPECT)/computed tomography (CT) acquired after ^{90}Y radioembolization was convolved with published ^{90}Y Monte Carlo estimated dose deposition kernels to create a three-dimensional dose distribution. Dose-volume histograms were calculated for tumor volumes manually defined from magnetic resonance imaging or PET/CT imaging. Tumor response was assessed by absolute reduction in maximum standardized uptake value (SUV_{max}) and total lesion glycolysis (TLG).

Results: Seven patients with 30 tumors treated with ^{90}Y for hepatic metastatic melanoma with available ^{90}Y SPECT/CT and PET/CT before and after treatment were identified for analysis. The median (range) for minimum, mean, and maximum dose per tumor volume was 16.9 Gy (5.7–43.5 Gy), 28.6 Gy (13.8–65.6 Gy) and 36.6 Gy (20–124 Gy), respectively. Response was assessed by fluorodeoxyglucose PET/CT at a median time after treatment of 2.8 months (range, 1.2–7.9 months). Mean tumor dose ($P = .03$) and the percentage of tumor volume receiving $\geq$ 50 Gy ($P < .01$) significantly predicted for decrease in tumor SUV_{max}, whereas maximum tumor dose predicted for decrease in tumor TLG ($P < .01$).

Conclusions: Volumetric dose calculations showed a statistically significant association with metabolic tumor response. The significant dose-response relationship points to the clinical utility of patient-specific absorbed dose calculations for radionuclide therapy.

ABBREVIATIONS

CC = correlation coefficient, DVH = dose-volume histogram, EORTC = European Organization for Research and Treatment of Cancer, HCC = hepatocellular carcinoma, PMR = partial metabolic response, SD = standard deviation, SUV_{max} = maximum standardized uptake value, ^{99m}Tc-MAA = technetium-99m-macroaggregated albumin, TLG = total lesion glycolysis, V = volume (eg, V10), ^{90}Y = yttrium-90

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Current standards of yttrium-90 (^{90}Y) radioembolization use commercially derived general calculations for delivered activity based on liver size, extent of tumor involvement, and the absorbed fraction dose calculation method (1). These standard calculations do not take into account patient-specific spatial distribution of tumors within the liver or the heterogeneous distribution of ^{90}Y microspheres after delivery. There is currently no standard method for quantifying true activity or dose delivered (1), and dose to tumor and normal liver often may remain unknown and undocumented. This uncertainty prevents the correlation of patient and treatment characteristics with dose received and clinical outcomes necessary for evidence-based improvements in treatment delivery.

The most recent consensus recommendations published from the American Association of Physicists in Medicine highlighted these challenges of ^{90}Y radioembolization and called for the use of single photon emission computed tomography (SPECT)/computed tomography (CT) systems with voxel-based dose calculation for development of three-dimensional liver, tumor, and lung distribution data to be used for careful dose-volume histogram (DVH) analysis (1). More recent publications have reported success with investigational methods using technetium-99m-macroaggregated albumin (^{99m}Tc-MAA) SPECT/CT for personalized treatment planning and dose calculation (2–4). However, because hepatic arterial infusions of ^{99m}Tc-MAA and ^{90}Y are performed as separate procedures, and because there are small physical differences between the macroaggregated albumin and the glass or resin microspheres (5), one may question whether ^{99m}Tc-MAA SPECT/CT represents the true delivered dose with high accuracy. ^{90}Y bremsstrahlung SPECT/CT is often performed after treatment as qualitative verification of ^{90}Y microsphere distribution, and investigational reports have demonstrated the feasibility of using ^{90}Y SPECT/CT for directly and quantitatively representing tumor dosimetry (6–8). In this article, we examine the clinical utility of ^{90}Y bremsstrahlung–based dosimetry models through analysis of the relationship between volumetric absorbed dose calculations and treatment response as measured by fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT in patients with hepatic metastatic melanoma.

MATERIALS AND METHODS

Patients

This is a correlative study to a single institutional prospective observational study comprising patients treated with ^{90}Y radioembolization, which was approved by the local institutional review board and compliant with the Health Insurance Portability and Accountability Act. We identified 14 consecutive patients with metastatic melanoma treated with ^{90}Y radioembolization for hepatic metastases between April 2009 and October 2010. Seven patients were excluded because no FDG-PET/CT imaging before treatment (n = 4) or after treatment (n = 3) was available. Seven patients with 30 tumors remained who had both diagnostic (before treatment) and follow-up (after treatment) FDG-PET/CT imaging for inclusion in this secondary analysis in which ^{90}Y dose-volume statistics were retrospectively calculated and correlated with FDG-PET response. All patients had confirmation of malignant melanoma based on biopsy or surgical resection and radiographic evidence of hepatic metastasis by CT, magnetic resonance (MR) imaging, or PET/CT.

The median patient age was 50 years (range, 36–75 y; standard deviation [SD], 14.1). All patients had Eastern Cooperative Oncology Group performance status ranging from 0–1. Three patients received prior systemic therapy, including interleukin-2, cisplatin, cyclophosphamide, and dacarbazine, although no patient received systemic therapy within 2 weeks of treatment. The median tumor size was 2.1 cm (range, 1.0–13.1 cm; SD, 2.6) in axial dimension and 5.1 mL (range, 0.5–956.5 mL; SD, 206.9) in volume.

^{90}Y Radioembolization

Patients underwent evaluation before treatment including ^{99m}Tc-MAA SPECT and abdominal angiography with embolization if indicated. ^{90}Y SIR-Spheres (SIRTeX; Sirtex Medical Limited, North Sydney, Australia) were administered with activity specified according to institutional modification of the SIRTeX calculation (1):

$$A = [\text{body surface area} - 0.2 + (\text{tumor volume}/\text{treated lobe volume})] \times [1 - \text{reduction factor}] \times [\text{treated lobe volume}/\text{total liver volume}]$$

Dose reductions included a 10% reduction for < 5% tumor involvement (n = 2) and a 20% dose reduction for low albumin and recent chemoembolization (n = 1). Four patients received treatment to a single lobe of the liver, and three patients were treated to each lobe in two staged procedures, separated by a median time of 1 month (range, 0.7–2.8 months). Median activity delivered per lobe was 21.3 mCi (range, 6.4–37.7 mCi) or 0.91 GBq (range, 0.24–1.34 GBq).

Immediately after radioembolization, ^{90}Y SPECT/CT was performed using Siemens Symbia T6 SPECT/CT (Siemens Corporation, Concord, California) with medium-energy general purpose collimation. SPECT acquisition was a 128 × 128 matrix with a pixel size of 4.5 mm, 30 stops (60 total projections) at 40 s/stop, and a 75-keV 54% energy window. SPECT was reconstructed on an imaging workstation using the manufacturer's modified ordered subset expectation maximization algorithm (Flash 3D [Siemens Medical Solutions USA Inc., Hoffman Estates, Illinois], 30 iterations and 2 subsets, 12.0-mm gaussian post-filter).