Research Article

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"Evaluation of advanced Dosimetry in Transarterial Radioembolization of Hepatocellular Carcinoma with ^{90}Y microspheres"

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ABSTRACT

Objective : The aim of our study was to analyze the relationships between tumor (T) and normal tissue (N) absorbed dose in relation to the clinical outcomes in hepatocellular carcinoma (HCC) patients treated with ^{90}Y microspheres.

Materials and methods : After transarterial radioembolization of HCC with ^{90}Y microspheres, 62 patients (10 females: 52 males, mean age 68.2±8.2 years) were imaged using a four-ring, time-of-flight (TOF), PET/CT system. Low dose, non-diagnostic CT images from PET/CT were utilized for localization of the ^{90}Y microspheres and attenuation correction of PET images. Response assessment was conducted using mRECIST criteria on MRI one month post treatment and subsequently every three months after ^{90}Y treatment.

Results : Among 62 patients, mean liver, tumor, and normal tissue doses (mean ± SD) were 51.38±23.32 Gy, 682.60±785.19 Gy and 45.54±21.19 Gy, respectively. Out of these patients, 39 exhibited complete response (CR), 11 showed partial response (PR), 2 had stable disease (SD), and 10 showed progression of the disease (PD). For CR+PR patients the mean T was 824.63±833.10 Gy, whereas for PD patients, the mean T was significantly lower at 205.70±183.22 Gy. The mean liver and normal tissue doses were comparable; for CR+PR patients had liver and normal tissue doses of 51.01±22.55 Gy and 45.18±20.68 Gy, respectively, and for PD patients, these values were 54.34±26.73 Gy and 49.10±22.97 Gy, respectively.

Conclusion : Despite not considering the partial volume effect and having a limited number of PD cases, our data indicates a statistically significant lower (P = 0.0001) tumor dose in patients with disease progression compared to those with complete and partial response. These results suggest that post-therapy personalized, and image-based dosimetry provides promising predictive outcomes in ^{90}Y microsphere radiation therapy for liver cancers.

Keywords : ^{90}Y dosimetry; ^{90}Y microspheres; hepatocellular carcinoma

INTRODUCTION

Primary liver cancer is the sixth most common cancer worldwide[1] and hepatocellular carcinoma (HCC) accounts for approximately 90% of all liver cancers.[2] Considering the high incidence and poor prognosis of HCC, research on the epidemiology of HCC is an important public health issue. Unfortunately, due to extensive disease or other contraindications only about 20% of patients with HCC are candidates for surgical treatment in the form of resection or transplantation. For the remaining cases of unresectable HCC, there are many alternative treatment options, including thermal radiofrequency (RFA) or microwave ablation, external beam radiation, systematic chemotherapy (e.g., Sorafenib), alcohol injections, transarterial chemoembolization (TACE)[3,4], and yttrium-90 (^{90}Y) selective internal radiation therapy (SIRT).[5] SIRT with ^{90}Y microspheres is an effective and safe option for the treatment of HCC. Recently, there has been a growing interest in the use of SIRT, due to its favorable tumor response and safety profile.[6] This treatment is based on the fact that tumor vascularization is mainly arterial, as opposed to hepatic vascularization. In addition, the intraarterial injection of ^{90}Y microspheres, if properly performed, delivers high radiation absorbed doses to the tumor while sparing liver parenchyma. It has been shown that higher tumor doses usually achieve a better response.[7,8] However, using higher activities to increase the tumor-absorbed dose is limited by the increase in healthy liver or normal tissue absorbed dose. Our aim was to retrospectively study the relationships between tumor (T)

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and normal tissue (N) absorbed dose in relation to the clinical outcomes in HCC treated with 90Y microspheres.

MATERIALS AND METHODS

Patient selection and study design

Sixty-two patients (10 females: 52 males, mean age 68.2±8.2 years) with unresectable HCC who underwent SIRT with ^{90}Y microspheres at our institution from June 2013 to May 2019 were included in our study. Among them, fifty-three patients were treated with TheraSphere ® (glass microspheres; Boston Scientific, Marlborough, MA) and nine with SIR-Sphere ® (resin microspheres; Sirtex Medical, Sydney, Australia). All patients had lung absorbed doses under 30 Gy, negligible lung shunting, (i.e., less than 5%), and no extrahepatic leakage. All patients gave written informed consent for treatment, retrospective analysis of their clinical and imaging data for research purposes, and additional effective dose of 0.7 mSv due to the PET/CT study. The additional dose came from the low-dose CT portion in the PET/CT study used for attenuation correction and delineation of the region-of-interest (ROI). All procedures were performed in accordance with the ethical standards of the institutional and national research committee and the Declaration of Helsinki. Exclusion criteria included a small number of cases according to the mRECIST evaluation, which in this study excluded SD cases.

Image acquisition and reconstruction protocols

After SIRT with ^{90}Y microspheres, patients were imaged on a four-ring, time-of-flight (TOF) PET/CT system Biograph mCT (Siemens Medical Systems, Erlangen, Germany). Only one-bed position acquisitions were used, due to the axial FOV of 216 mm. The acquisition time was 15 min. The reconstruction matrix size was 200 × 200 × 75, and the voxel size was 4.07 × 4.07 × 3.00 mm. Model-based scatter correction method and delayed event subtraction method for randoms correction were used. The low-dose CT, with 120 kV, automatic tube current modulation and slice thickness of 3 mm, was used for PET attenuation correction and localization of the ^{90}Y microspheres. The iterative 3D Poisson-OSEM algorithm with point spread function and TOF correction was used for the reconstruction of PET data with 2 iterations, 21 subsets (2i21s), and a 5 mm Gaussian post-reconstruction filter.[9]

Dosimetry calculation

A personalized, voxel-based dosimetry method was used to calculate tumor (T), normal tissue (NT), and total liver absorbed doses. The commercially available software package, MIM 7.1 (MIM Software Inc., Cleveland, Ohio), was utilized to calculate post-treatment ^{90}Y dosimetry from the PET/CT images. For each patient using CT images, volume-of-interest (VOI) for the whole liver and tumor(s) was manually created and a program automatically created a normal tissue VOI. Since, ^{90}Y decays almost entirely with β- emission (0.93 MeV mean energy, half-life 64.1 h, 2.5 mm mean tissue penetration), the local deposition method, which is a practical alternative to a more complicated dose-point-kernel convolution approach, was used for dosimetry calculations.[10] **Figure 1** shows a "miss" situation with a low T of 15.77 Gy and N of 43.90 Gy, where the tumor ROI and high ^{90}Y activity area do not overlap. This was a PD case. On the contrary, in **Figure 2**, a combined PET/CT image shows a "good hit" situation with a high T of 1296.38 Gy and N of 28.58 Gy. The tumor area and relatively high ^{90}Y activity are nicely correlated. This was a CR case.

Figure 1

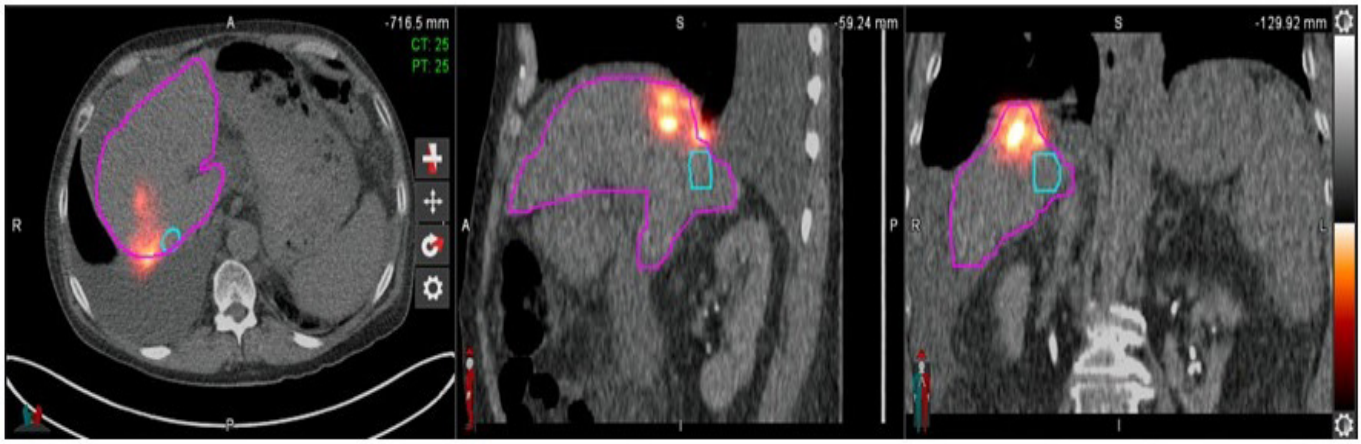

Figure 1. Progression of disease (PD) case. A "miss" situation with a low T of 15.77 Gy and N of 43.90 Gy, where the tumor ROI and high ^{90}Y activity area do not overlap.

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Figure 2

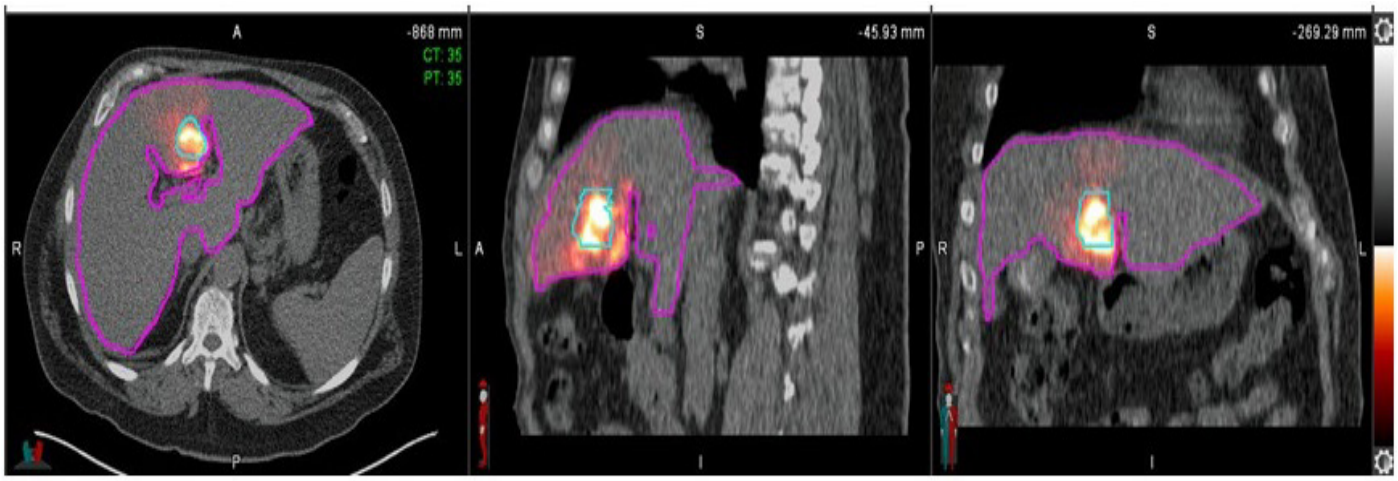

Figure 2 : Complete response (CR) case. A "good hit" situation with a high T of 1296.38 Gy and N of 28.58 Gy. The tumor area and relatively high ^{90}Y activity are nicely correlated.

Statistical analyses

Variables were reported as mean ± SD and/or as percentages. Statistical analysis was performed using MedCalc Software, 22.009–64 bit version.[11] Welch's t-test, or unequal variances t-test was used for statistical analysis due to the unequal sample size of variables and unequal sample distribution variance. p-values less than 0.05 were considered significant.

Dose–Response Evaluation

One month post treatment and subsequently every three months after ^{90}Y treatment, mRECIST criteria done on MRI were used to assess response.

RESULTS

For 62 patients, the mean liver, tumor and normal tissue doses (mean ± SD) were 51.38±23.32 Gy, 682.60±785.19 Gy and 45.54±21.19 Gy respectively. Among these patients, 39 showed complete response (CR), 11 showed partial response (PR), 2 showed stable disease (SD), and 10 showed progression of the disease (PD). The overall response rate (ORR), defined as the proportion of patients who have a complete or partial response (CR+PR) to therapy, was 81%. For these patients the mean T was 824.63±833.10 Gy, and for patients with PD, the mean T was significantly lower at 205.70±183.22 Gy. The mean liver and normal tissue doses were similar; for CR+PR patients, liver and normal tissue doses were 51.01±22.55 Gy and 45.18±20.68 Gy, respectively, and for PD patients, the same values were 54.34±26.73 Gy and 49.10±22.97 Gy, respectively. Because we had only two SD cases, they were not considered in this comparison. In **Figure 3**, average tumor doses for CR+PR patients and for PD patients are shown. Welch's t-test, assuming unequal variances, demonstrated that patients with complete and partial response (CR+PR) had a statistically higher (P = 0.0001) tumor dose than those with progression of the disease.

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Figure 3

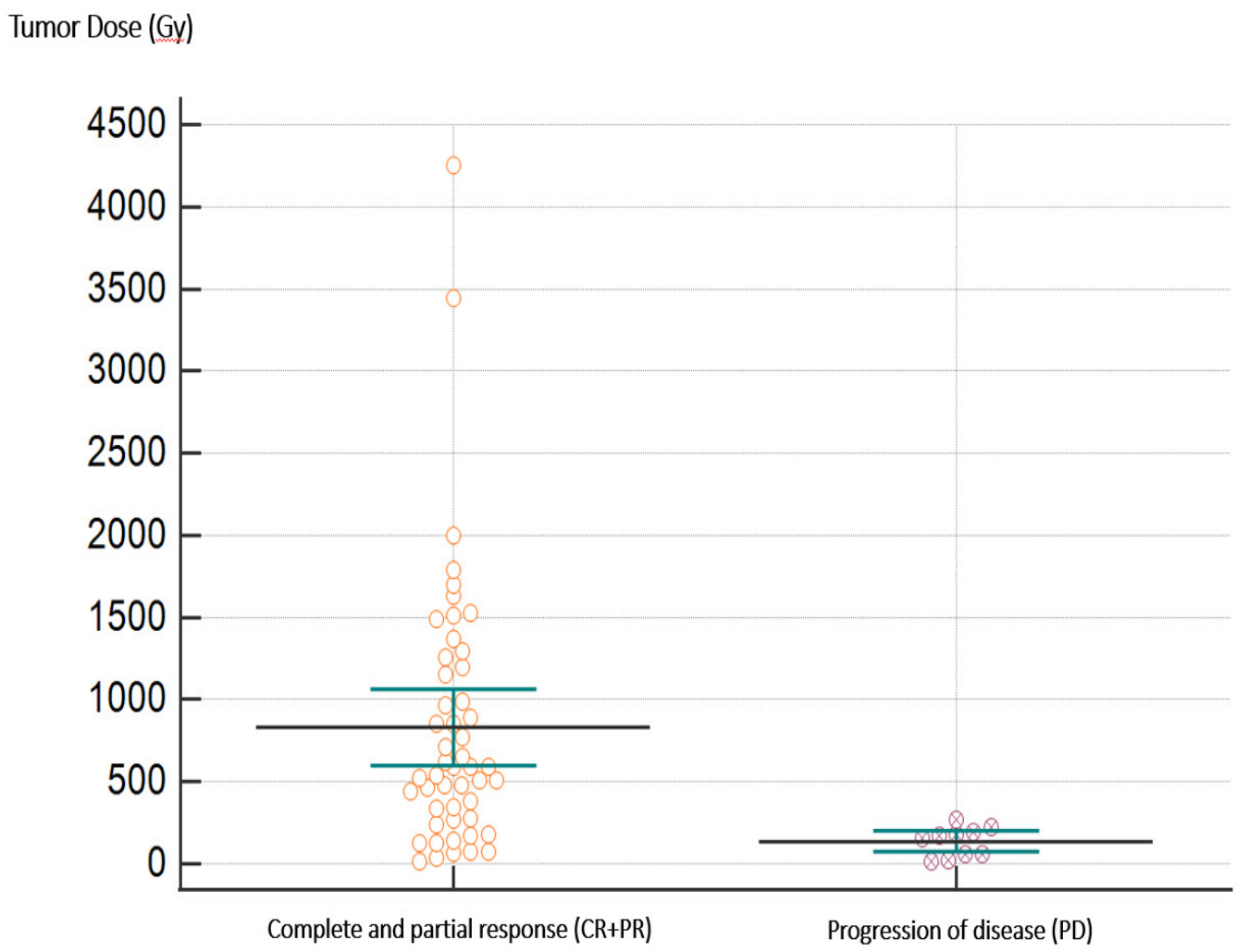

Figure 3. Tumor doses for complete and partial response (CR+PR) patients and for progression of disease (PD) patients. Data shows that patients with complete and partial response (CR+PR) have a statistically higher (P = 0.0001) tumor dose than those with progression of disease.

DISCUSSION

Rather than using semi-quantitative, vendor-designed dosimetry methods, we utilized a personalized dosimetry approach based on quantifiable PET/CT imaging. This method allows for more accurate calculations of liver, tumor, and normal tissue dosimetry than those obtained using predictive ^{99m}Tc-MAA studies[7] and/or semi-quantitative dosimetry approaches. Post-therapy quantitative PET/CT images show true ^{90}Y distribution and provide accurate dosimetry values.

In any radiotherapy treatment, including ^{90}Y SIRT of unresectable HCC, one of the main goals is to maximize tumor dose and preserve normal tissue by minimizing its dose. Additionally, in this process, one must deliver at least the recommended tumor mean absorbed dose and keep normal liver tissue below or equal to the safety threshold of the absorbed dose of 40 Gy.[12] A recent study recommended a 200 Gy threshold for tumor mean absorbed dose[13], but higher values would be even more desirable.[14] The limitation of our approach includes the exclusion of respiratory motion corrections for lesions in the superior hepatic lobes[15] and the exclusion of partial volume corrections for lesions smaller than 2.5 cm

CONCLUSIONS

Despite the limited number of PD cases and the exclusion of partial volume effect considerations, our data indicates that patients with complete and partial responses (CR+PR) have a statistically higher (P = 0.0001) tumor dose than those with

progression of disease. Further investigation is warranted because we omitted SD cases due to the limited number of cases, preventing any meaningful statistical analysis. Additionally, the total number of all cases should be increased to provide more meaningful results. However, according to our results, we concluded that patients with CR and PR have statistically higher tumor mean absorbed doses than those with progression of disease.

Conflict of interest

None.

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