EUD based 90Y-TOF-PET post selective internal radionuclide therapy provides a similar TCP in HCC than observed in EBRT

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Abstract

Background: Tumor equivalent uniform dose (EUD) is a predictor of patient outcome after selective internal radionuclide therapy (SIRT) of hepatocellular carcinoma (HCC) and can be evaluated with ^{90}Y -TOF-PET. The aim is to evaluate the correlation between PET based tumors EUD and the clinical response evaluated with dual molecular tracer (^{11}C -acetate and ^{18}F -FDG) PET/CT post SIRT.

Methods: 34 HCC tumors in 22 patients were prospectively evaluated. The metabolic response was characterized by the Total Lesion Metabolism variation (ΔTLM) between baseline and follow up. This response allowed to compute a Tumor Control Probability (TCP) as a function of the tumor EUD.

Results: The dose response correlation was exponential-asymptotic shaped and highly significant ($R=0.72$, $P < 0.001$). With a cutoff of 40Gy, the metabolic response was strongly different in both groups (median response 35% versus 100%, $p < 0.001$). Moreover, the TCP (EUD) was very similar to that observed in External Beam Radiation Therapy (EBRT). Conclusions: EUD based ^{90}Y TOF-PET/CT predicts the metabolic response after SIRT of HCC assessed using dual molecular PET tracers and provides a similar TCP curve to that observed in EBRT. Both TCPs show that a EUD of 100 Gy is needed and sufficient to control a HCC.

Background

Liver selective internal radionuclide therapy (SIRT) is part of the treatment strategy of hepatocellular carcinoma (HCC) [1] and aims to deliver high efficient doses to tumors [2]. The tumor-absorbed dose is a predictive factor of the treatment's effectiveness [3]. Comparing the different types of radiation therapies, the absorbed dose efficacy cutoff for glass microspheres is twice that for resin microspheres and up to five times more than with external beam radiation therapy (EBRT)[4–7]. The heterogeneous dose distribution in SIRT explains these differences and can be accurately revealed with Time of Flight (TOF)-PET ^{90}Y imaging [8, 9] when taking into account the Equivalent Uniform dose (EUD)[10]. EUD reunifies the efficacy threshold doses in SIRT (performed with resin or glass microspheres) but also in EBRT [11]. Previous radiobiological models developed in SIRT for HCC demonstrated an exponential correlation between the tumor-absorbed dose and the clinical response assessed with conventional imaging [5, 12, 13]. In colorectal liver metastases, a similar correlation was demonstrated using the metabolic response assessed with ^{18}F -FDG PET/CT [14, 15].

Functional imaging (PET/CT) is currently not recommended for the management of HCC, especially because ^{18}F -FDG PET/CT has a low sensitivity, with a definite uptake in less than 50–65% of the cases[16]. ^{11}C -Acetate PET/CT is more sensitive for HCC detection, with an uptake reaching 85%[17].

^{11}C acetate enters the Krebs cycle as a substrate for β -oxidation in fatty acid and cholesterol synthesis which is likely the explanation of its uptake by differentiated HCC [17]. On the other hand, the high level of glucose-6-phosphatase in differentiated HCC leads to the release of ^{18}F FDG while poorly differentiated

HCC, which has a low abundance of this enzyme, tends accumulate ¹⁸F-FDG [16, 17]. As a result, performing a dual molecular tracer PET/CT acquisition (¹¹C- acetate and ¹⁸F- FDG) was able to improve this sensibility up to 98%[18].

This study aims to demonstrate a radiobiological model in HCC built on ⁹⁰Y TOF- PET/CT based EUD and the metabolic response assessed with dual molecular PET tracer.

Methods

Patients

23 HCC patients, referred to our department for SIRT, were prospectively enrolled in this study after their informed consent and approval by the local ethics committee (2015/01OCT/522).

Each patient was evaluated with dual isotope (¹¹C-acetate and ¹⁸F-FDG) PET/CT at baseline and at follow-up (FU) 2 and 4 months after SIRT. 4 patients received a second treatment after an interval of 5 months and were evaluated again. 4 patients had multifocal tumors (2 to 6) while the majority had only one tumor.

A total of 34 tumors demonstrated a metabolic uptake, 80% were positive with acetate PET/CT, 52% with FDG PET/CT and 40% with both imaging. In one patient, the tumor uptake was not significant with either PET tracers and the metabolic evaluation was not possible, resulting in 22 studied patients. No other exclusion factor was applied.

The patients characteristics are summarized in Table 1.

Table 1
Patients characteristics

Characteristics	Data
Age (Years)	73 (68–79)
Sex	Male: 14 (64%)
	Female: 8 (34%)
BCLC staging	A: 8 (36%)
	B: 8 (36%)
	C: 6 (28%)
Tumor volume (ml)	36 (11–97)

Continuous variables described with median and 95% confidence interval displayed between parentheses. BCLC: Barcelona Clinic Liver Cancer

Treatment

SIRT was performed according to standard recommendations [19]. Resin microspheres (Sir-Spheres®, Sirtex Medical Ltd., Sydney, Australia) and glass microspheres (Therasphere®, Boston Scientific, Boston, MA) were used in 17 and 9 treatments, respectively.

A 40-min 2-bed positions ^{90}Y TOF-PET scan (Gemini TF64 Philips Medical Systems, Cleveland, OH) was acquired within 4 h following the SIRT. Reconstruction was performed with the 3D line of response (LOR)–TOF blob-based OSEM algorithm from Philips with 2 iterations times 33 subsets and a 4x4 mm³ voxel size. ^{90}Y activity distribution was transformed into a 3D-map of absorbed doses using a previously validated method [20]. In summary, voxel counts were converted to absorbed dose distribution by convolving the ^{90}Y activity distribution with a dose point kernel, after spatial resolution recovery.

Tumor response assessment

Whole body TOF-PET/CT acquisition (Gemini TF 64, Philips Medical Systems, Cleveland, OH) was acquired 20 minutes after intravenous injection of ^{11}C -acetate (370–540 MBq, half-life: 20 minutes). 30 minutes after this first acquisition, ^{18}F -FDG was injected (280–310 MBq) and images were acquired after an incorporation of 60 minutes. Acquisitions were performed at baseline and during FU at 2 and 4 months after treatment.

Tumor contours were automatically defined with acetate or FDG PET/CT using an isocontour method (41% SUVmax threshold) performed with the MIM software (V7.1, MIM Software Inc., Cleveland, OH).

For each patient, the tracer, i.e., ^{11}C -acetate or ^{18}F -FDG, giving the highest normal liver to tumor tissue ratio on the baseline PET imaging was selected to assess the tumor response metabolism.

For each tumor and each time point, the total lesion metabolism (TLM) was defined as:

$$\text{TLM} = \text{SUV}_{\text{mean}} \times \text{Volume}$$

1

The ΔTLM between baseline (B) and FU defined the metabolic response:

$$\Delta\text{TLM}(\%) = \frac{\text{TLM}_B - \text{TLM}_{\text{FU}}}{\text{TLM}_B} \cdot 100 \quad (2)$$

The best metabolic response between the baseline and either 2- or 4-month was considered (corresponding to the maximal effects of radiations).

No TLM cutoffs are established to classify the metabolic response of tumors. However, regarding EUD, a threshold of 40 Gy was previously defined as an efficacy cutoff in HCC [11] and corresponded also to the efficacy cutoff in EBRT [7]. Therefore, this cutoff was applied for comparing the metabolic responses.

Tumor dosimetry

Tumor contours were matched with the 3D map of absorbed doses, as previously defined, using a rigid co-registration with the MIM software.

Equivalent uniform dose (EUD) was calculated according to the Jones and Hoban formalism [21]:

$$\text{EUD} = -\frac{1}{\alpha} \ln \left(\frac{\sum_i e^{-\alpha D_i}}{N} \right)$$

3

where α is the apparent HCC radiosensitivity, N the number of voxels in the tumor and D_i the absorbed dose in tumor voxel i . The terminology apparent radiosensitivity was introduced by Chiesa et al. [13] in order to take into account that this value depends on the spatial resolution of the imaging system as shown in [22]. In a previous ^{90}Y TOF-PET based EUD analyses, the apparent α coefficient was estimated to be 0.038 Gy^{-1} [11], i.e., about tenfold lower than the intrinsic in vitro HCC 0.40 Gy^{-1} radiosensitivity [23].

The Tumor Control Probability (TCP) was determined in consecutive EUD bins of 20 Gy. Tumor control was defined as a metabolic response with $\Delta\text{TLM} \geq 0.80$, the value giving the best sigmoid shaped curve.

Statistical analysis

Wilcoxon signed rank test was used to compare groups. The correlation was analyzed using a Spearman coefficient (R).

Analyses were conducted with Prism software (version 7.0, GraphPad Software, La Jolla, Ca).

Results

The metabolic response correlated well with EUD (Fig. 1): the larger the EUD the higher the metabolic response. This dose response correlation was linear-exponential and highly significant according to the Spearman coefficient ($R = 0.72$, $P < 0.001$). Moreover, the metabolic response to radiations was very similar for tumors positive with FDG PET/CT and with acetate PET/CT (Fig. 1). The metabolic response was significantly higher in tumors receiving more than 40 Gy (median ΔTLM : 1.0) compared to tumors receiving a lower dose (median ΔTLM : 0.35, $P < 0.001$).

Discussion

This study confirms the strong correlation already observed between reduction of tumor metabolism and EUD [13, 14], as well as between the TCP and the tumor EUD [12, 13]. A novelty of the present observation is that this correlation holds true when mixing acetate and FDG data for the tumor metabolism

assessment. This makes sense considering the fact that reduction of acetate or FDG uptake mainly results from the reduction of tumor living cells number. Indeed, proteins which constitute the metabolic engines are hugely radioresistant. For instance, a dose of 100 Gy damages less than 5% of albumin (Figure. 1a in [25]) whereas 40 Gy, assuming a radiosensitivity $\alpha = 0.4 \text{ Gy}^{-1}$ [23], kills $1 - e^{-0.4 \times 40} \approx 99.99999\%$ of HCC cells [23]. Finally, the use of ^{90}Y TOF-PET to compute the dose, rather than MAA or bremsstrahlung SPECT used in previous studies [12–14], improved the correlation.

Beyond this dose-response confirmation, the main finding of the study is that the observed TCP as a function of the EUD in SIRT is very similar to that of EBRT. We already demonstrated [26] that ^{90}Y TOF-PET based EUD provided the same threshold to discriminate “responding” and “non-responding” patients in glass SIRT, resin SIRT and EBRT, i.e., 40Gy. These results proved that ^{90}Y TOF-PET based EUD rightly takes into account the impact of the heterogeneity of the dose distribution. In addition, the similarity of the SIRT and EBRT TCPs consolidates that to surely control a tumor, i.e., $\text{TCP} \approx 1$, the needed and sufficient EUD is 100 Gy. The sigmoid shape of the TCP curve enlightens the importance to reach at least a EUD of 100 Gy in each tumor and emphasize the necessity to optimize the treatment planning liver to reach this goal [3, 27, 28]. Note that the absorbed dose D needed to achieve this EUD can vary from 190 to 1800 Gy depending on the dose distribution heterogeneity (supplementary material, appendix A).

The observed SIRT TCP also explains why the EUD = 40 Gy threshold well split the patient survival curves into 2 clear different groups [26]. Indeed, this threshold correspond to the EUD50, as a result one group contains a majority of responding patients and the other one a majority of non-responding patients.

The optimal ΔTLM 80% threshold, and not 100%, used to obtain a well-shaped TCP sigmoid curve results from different effects: errors in the TLM assessment, FU delay too short to allow all the tumor cells to die or in contrary FU delay sufficiently long enough to allow a repopulation of the tumor site by healthy liver tissue which also takes up ^{11}C -acetate or ^{18}F -FDG.

This study has some limitations. First, analyses were performed in a limited number of patients and tumors compared to previous reported studies [12–14]. However, the better accuracy of ^{90}Y TOF-PET in dose distribution assessment, versus MAA or bremsstrahlung SPECT, reduces the statistical blurring, allowing to get a good correlation with a reduced number of patients. Only few tumors received low absorbed doses and demonstrated a poor metabolic response, limiting the accuracy of our radiobiological model for low doses. Second, the follow up was 4 months at maximum but some tumors could respond later to radiations and hence the effects of radiations could be sometimes underestimated, justifying the choice of the threshold $\Delta\text{TLM} = 80\%$ rather than 100% in the TCP derivation [2]. EUD is based on a single alpha value and it is likely that the radiosensitivity may vary between HCC occurring within different clinical entities. Accordingly, this delayed response may explain why some tumors did not disclose complete metabolic response 4 months after therapy despite a very efficient EUD.

Conclusions

^{90}Y -TOF-PET based EUD is strongly correlated with the metabolic response in HCC assessed by dual molecular tracer PET imaging and is associated with a TCP close to that in EBRT. ^{90}Y -TOF-PET based EUD reconciles dose levels in SIRT and EBRT. The use of this parameter must be encouraged in future dosimetry studies for a better understanding of the toxicity and efficacy threshold doses in SIRT.

Abbreviations

EBRT: External beam radiation therapy

EUD: Equivalent Uniform dose

FU: Follow-up

HCC: Hepatocellular carcinoma

RE: Radioembolization

TCP: Tumor control probability

TLM: Total lesion metabolism

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Université Catholique de Louvain (2015/01OCT/522). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable

Availability of data and materials

Data generated in the study can be found at the Mendeley repository website at:

<https://doi.org/10.17632/x68ys6nz5d.1>

Competing interests

The Authors, PdA, SW, MH, IB, RL and FJ, declare no financial or non-financial competing interests.

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Authors' contributions

Conceptualization, PdA, SW and FJ.; methodology, PdA, SW and MH.; software, MH; validation, PdA, SW. and FJ.; formal analysis, PdA and FJ.; investigation, IB and RL.; resources, RL, IB; data curation, PdA.; writing—original draft preparation, PdA.; writing—review and editing, SW and FJ.; visualization, FJ.; supervision, FJ.; project administration, FJ.; funding acquisition, none. All authors have read and agreed to the final manuscript.

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Figures

Figure 1

ΔTLM as a function of the EUD obtained from post-SIRT ^{90}Y TOF-PET. Blue circles: measured on ^{11}C -acetate PET. Red diamonds: measured on ^{18}F -FDG PET. Dashed line: EUD threshold used to discriminate responding and not responding tumor in the TCP computation.

Figure 2

TCP as a function of the EUD. Blues circles: this SIRT study. Red bullets: External Beam Radiation Therapy (EBRT) derived from Lausch et al.[24]. Red solid line: EBRT TCP fitted with a logistic function.

Supplementary Files

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