Total Tumor Uptake and Absorbed Dose of ^{177}Lu-Lilotomab Satetraxetan in a First in Human Trial for Relapsed Non-Hodgkin Lymphoma - Are We Hitting the Target?

Ayca Løndalen (aycloe@ous-hf.no)
Oslo University Hospital
Johan Blakkisrud
Oslo University Hospital
Mona-Elisabeth Revheim
Oslo University Hospital
Jostein Dahle
Nordic Nanovector ASA
Arne Kolstad
Oslo University Hospital
Caroline Stokke
Oslo University Hospital

Research Article

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Abstract

Purpose: ^{177}Lu-lilotomab satetraxetan, a novel CD37 directed radioimmunotherapy (RIT), has been investigated in a first-in-human phase 1/2a study for relapsed non-Hodgkin lymphoma (NHL). Absorbed dose for all tumor tissue in the body is a crucial parameter in RIT which has traditionally been challenging to calculate. The aim of this study was to investigate the correlations between baseline FDG PET/CT and posttreatment SPECT/CT parameters, absorbed dose-response relationships and clinical responses.

Materials and methods: A total of 15 patients with different pre-treatment and pre-dosing regimens were included. ^{177}Lu-lilotomab satetraxetan was administered at dosage levels of 10, 15 or 20 MBq/kg. Total radioimmunoconjugate tumor volume (tRTV), total radioimmunoconjugate lesion uptake (tRLU) and total tumor absorbed dose (tTAD) were calculated from posttreatment SPECT/CT. The measured uptake values and absorbed doses were normalized for dosage when appropriate. For some of the analyses, the cohort was divided into low (arm 1) and high (arm 4+5) non-radioactive lilotomab pre-dosing groups. tMTV and tTLG were calculated from FDG PET/CT performed at baseline, 3 and 6 months after RIT, and the percent change for these parameters calculated ($\Delta tMTV_{3months}$, $\Delta tTLG_{3months}$ and $\Delta tMTV_{6months}$, $\Delta tTLG_{6months}$). Clinical responses were evaluated at 6 months.

Results: tTMV and tRTV were significantly correlated ($p<0.01$). A correlation was also found between tTLG and tRLU ($p<0.01$). Correlations were not observed between baseline tTMV and tTAD. Decreases in $\Delta tMTV$ and $\Delta tTLG$ were significantly higher at $PET_{3months}$ for patients receiving tTAD≥200cGy compared to patients receiving lower tumor absorbed doses (p=.03 for both). Also, significant decreases in $\Delta tMTV_{3months}$, $\Delta tTLG_{3months}$ and $\Delta tMTV_{6months}$, $\Delta tTLG_{6months}$ were observed with increasing tTAD in the high lilotomab patient group. Similarly, responders (patients with complete remission and partial remission) had higher mean tTAD compared to non-responders (stable disease and progressive disease). This was statistically significant in the high lilotomab group. Across the entire population, all non-responders had tTAD < 200cGy, and all patients with tTAD ≥ 200cGy were responders.

Conclusion: This work indicates that ^{177}Lu-lilotomab satetraxetan targets FDG avid lesions, and that increasing baseline (tMTV) does not have a decreasing effect on the total tumor absorbed dose (tTAD). The patient group receiving a higher amount of lilotomab pre-dosing demonstrated an absorbed dose–response relationship. Similar results were not observed in the low lilotomab group, which were expected since an overall very good response rate could mask such a relationship for this group. Regardless of pre-dosing, a mean absorbed dose to the total tumor tissue (tTAD) limit of 200cGy may prove valuable to separate clinical non-responders from responders.

Introduction

Individualized treatments in modern oncology demand accurate measurement of the amount of pharmaceutical reaching the target. Pharmacokinetic (PK) studies are often applied as indirect methods to theoretically determine the distribution of the pharmaceutical both in normal tissue and tumor. However, radiolabeled targeted therapies enable the direct measure of the amount of radiopharmaceutical accumulating in normal tissue and tumor. Such methods have become more precise with advances in imaging technologies and software solutions to calculate the information made available by imaging. Furthermore, accurate measuring of tumor burden

before treatment has also become more feasible with advances in imaging technologies and is proposed as part of individualized therapy strategies. In recent years, tumor volume measurement has gained increased interest as a parameter to guide individual dosage adjustments [1].

Targeted therapies like monoclonal antibodies (mAbs) administered as single agents or in combination with other treatments have changed the course of non-Hodgkin lymphoma (NHL). Clusters of differentiation (CD) 20 targeting mAb, rituximab, was the first of its kind to be approved and is still the most widely used. Variations in response were reported when rituximab was given as single agent since its introduction [2, 3]. Several studies in early 2000´s investigated if this variation may be explained by factors like tumor burden, antigen concentration in tumor, circulating antigens and genetic factors [4–6]. At first, tumor burden was measured by computer tomography (CT) and utilized methods like sum of perpendiculars of all lesions, sum of perpendiculars of target lesions or longest diameter of the largest involved node. With the introduction of metabolic tumor volume (MTV) and total metabolic tumor volume (tMTV) as ^{18}F-FDG PET/CT (FDG PET hereafter) parameters [7], measuring tumor volumes has become easier and more precise. Another FDG PET parameter, total lesion glycolysis (tTLG), helps characterize tumor biology as glucose consumption, but it is still a subject to debate on how it may be applied in treatment planning or evaluation.

Radioimmunotherapy (RIT) works both as targeted radiotherapy and immunotherapy, and this makes it possible to establish image proof of radioimmunoconjugates successfully targeting the viable tumor mass by measurements of the amount of uptake, volume of uptake, and tumor absorbed dose. Alongside with development of rituximab, mAbs with ß-emitting radionuclides have also been tested in clinical trials [8–11], Methods have been proposed to measure the patient mean tumor absorbed dose for ^{131}I-tositumomab [12–14]. However, to our knowledge, no studies have been conducted with RIT against lymphoma to investigate the impact of baseline tMTV/tTLG on total radioimmunoconjugate uptake in all tumor tissue and the patient mean tumor absorbed doses for the total tumor volume (from here on referred to as total tumor absorbed dose - tTAD). Furthermore, no previous studies have included absorbed dose versus treatment induced changes in tMTV / tTLG for this patient group.

^{177}Lu-lilotomab satetraxetan or Betalutin® (Nordic Nanovector ASA, Oslo, Norway) has been investigated in the first-in-human phase 1/2a study LYMRIT-37-01 for treatment of relapsed CD37 + indolent NHL [15]. Different combinations of non-radioactive pre-dosing and pre-treatments were explored in five different arms of the phase 1 dose escalation part of this study. In the current sub-study of LYMRIT-37-01 we aimed to investigate ^{177}Lu-lilotomab satetraxetan radioimmunoconjugate uptake parameters on the whole body level, and evaluate the impact of baseline tMTV / tTLG on total radioimmunoconjugate lesion uptake (tRLU) and total tumor absorbed dose (tTAD). Furthermore, the potential therapeutic effect of tTAD, measured as change in FDG PET parameters ($\Delta tMTV_{3months}$, $\Delta MTV_{6months}$ and $\Delta tTLG_{3months}$, $\Delta tTLG_{6months}$) and clinical response after 6 months, were then analyzed.

Materials And Method

Patient Characteristics and Treatment

Fifteen patients with relapsed B-cell indolent NHL from the multicenter phase 1/2a LYMRIT-37-01 trial led by Oslo University Hospital were included in this work. Table 1 shows patient characteristics. Only patients from our

center, eligible for dosimetry, were included to assure image standardization. CD37 status of patients were confirmed by immunohistochemistry. Histological subtypes were follicular lymphoma grade I-IIIA and mantle cell lymphoma. The LYMRIT-37-01 trial was approved by the regional ethics committee, and all patients had signed an informed consent form.

Table 1
Patient characteristics in the entire population. Median values (minimum to maximum) are indicated for continuous variables. Distributions of gender and type of lymphoma are given as number and as percentage.

Characteristic		Value
Age (y), median (range)		70 (38–78)
Gender, *n* (%)	Male	13 (87%)
	Female	2 (13%)
Body weight (kg), median (range)		85 (56–111)
Body surface area (m^2), median (range)		1,99 (1.54–2.35)
Histology, *n* (%)	Follicular lymphoma, grad I	5 (33%)
	Follicular lymphoma, grad II	8 (53%)
	Follicular lymphoma, grad III	1 (7%)
	Mantle cell lymphoma	1 (7%)

Arm 1, 4 and 5 patients at three different dosage levels were included. Patients received a single injection of ^{177}Lu-lilotomab satetraxetan; either 10, 15 or 20 MBq/kg body weight. All patients were pre-treated with rituximab, and non-radioactive lilotomab was injected as pre-dosing 1–3 hours before injection of ^{177}Lu-lilotomab satetraxetan (Table 2) (Fig. 1). Patients were also grouped further based on pre-dosing, defining arm 1 with 40 mg lilotomab as the “low lilotomab group” and arms 4 and 5 receiving 100mg/m2 or 60mg/m2 as the “high lilotomab group”, respectively (Fig. 1). We assumed that the modest difference between arm 4 and 5 regarding lilotomab pre-dosing would not significantly influence post-therapy SPECT and follow-up PET parameters.

Table 2
Patient treatment. Median value (minimum to maximum) is given for the total injected activity in the entire population. Numbers of patients in each dosage level, stratified by arm, are also given.

Total injected activity (MBq), median (range)	1434 (746–2189)		
Injected activity/body weight, *n*	Arm 1 (lilotomab 40mg/m^2)	10 MBq/kg	2
		15 MBq/kg	2
		20 MBq/kg	2
	Arm 4 (lilotomab 100mg/m^2)	15 MBq/kg	1
		20 MBq/kg	7
	Arm 5 (lilotomab 60mg/m2)	20 MBq/kg	1

FDG PET/CT Imaging and quantification

FDG PET was performed at baseline ($PET_{baseline}$) and repeated 3 months ($PET_{3months}$) and 6 months ($PET_{6months}$) after ^{177}Lu-lilotomab satetraxetan treatment. PET/CT images were acquired using a Biograph 16 (Siemens Healthineers) and Discovery MI (GE Healthcare). According to the protocol, acquisition was performed from vertex to mid-thigh about 60 to 70 minutes (range in study 58–85 minutes) after intravenous administration of 185 to 370 MBq of FDG (range in study 267 to 405 MBq). All PET scans were reconstructed to comply with the EARL standard. tMTV and tTLG were measured at all three time-points according to EANM procedure guidelines for tumor imaging: version 2 [16]. Syngo.via software solution VB30 (Siemens Healthineers) was used, and a threshold of 41% of SUV_{max} applied. tMTV and tTLG were measured at $PET_{3months}$ and $PET_{6months}$ if uptakes were higher than liver uptake defined by PERCIST criteria [17]. Otherwise, they were registered as zero. Figure 2a illustrates the entire tumor uptake volume under the diaphragm at $PET_{baseline}$ in one of the patients. Changes in these parameters from baseline to $PET_{3months}$ and $PET_{6months}$ were calculated as percent reduction from baseline value, defined as $\Delta tMTV_{3months}$, $\Delta MTV_{6months}$ and $\Delta tTLG_{3months}$, $\Delta tTLG_{6months}$. Negative values represent increase in tMTV or tTLG. All measurements were performed by an experienced nuclear medicine physician. Two patients did not undergo $PET_{3months}$ and $PET_{6months}$ (one of these patients did not undergo contrast enhanced CT (CeCT) either) and one patient did not undergo $PET_{6months}$ because of progression.

SPECT/CT imaging and quantification

Patients underwent SPECT/CT at day 4 and day 7 post injection (p.i.) of ^{177}Lu-lilotomab satetraxetan in arm 1, and at day 1, 4 and 7 p.i. in arm 4 and arm 5 (Fig. 1). SPECT/CT scans were acquired with a dual-head Symbia T16 (Siemens Healthineers) camera. Scanner protocol and reconstruction parameters have been described previously [18]. SPECT/CT data were segmented using the software program PMOD (version 3.6; PMOD Industries) and later post-processed with in-house written python software (version 2.7). tRTVs representing tumor volumes with ^{177}Lu-lilotomab satetraxetan uptake were determined on the day 4 and 7 SPECT/CT scans by a semi-automatic approach. An initial manual segmentation was performed by a nuclear medicine specialist to exclude physiological uptake in normal tissue in close proximity to lesions. Then, a thresholding with a 26 % cut-off based on the voxel with the highest uptake in the initial segmentation was carried out. This threshold was chosen after a visual optimization. The segmentation was done individually for the day 4 and day 7 scan. The final segmentations were visually verified by side-by-side comparison with the FDG PET (Fig 2a-b). The tRLU was defined as the total activity inside the tRTV. Cumulative activity concentration was calculated by assuming a mono-exponential wash-out of the activity in the tumors and analytically integrates this curve. $tRLU_{Day0}$ was also calculated from this curve. Total tumor absorbed dose, defined as tTAD was calculated from the tRLU curve and the tRTV, by assuming a local dose deposition of all electron radiation particles, equating to 0.0853 Gy/(MBqhrs/ml) [19].

Day 4 tRLU was used as standard for further analyses, otherwise specified as $tRLU_{day7}$ or $tRLU_{day0}$. tRLU normalized by dosage level was defined as $tRLU_{dosage}$ (tRLU/dosage level)($^{MBq}/_{MBq/kg}$). Activity concentration (tRLU/volume) (MBq/cm^3), activity concentration normalized by dosage ($tRLU_{dosage}$/volume) (kg/cm^3) and percent of injected activity reaching the tumor (($tRLU_{day0}$/injected activity) x100) (%) was also calculated.

tTAD normalized by dosage level was defined as $tTAD_{dosage}$ (tTAD/dosage level) ($^{cGy}/_{MBq/kg}$).

Response assessment

Responses were assessed by FDG PET and CeCT at 3 and 6 months after treatment according to the Cheson criteria [20, 21] defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Bone marrow biopsy was performed to confirm CR if a bone marrow biopsy at baseline was positive. PD was confirmed by CT only.

Statistics

Spearman-rank correlation tests were performed to investigate relationships between PET and SPECT parameters and between SPECT parameters and changes in PET parameters. A significance level of 5% was used. Statistical analyses were carried out only for groups of more than two patients. The Mann-Whitney-U test was performed to test differences between groups. A null-hypothesis of equal populations with a rejection level of 5% was set. The boxplots show median values, interquartile ranges, and points lower or higher than 1.5 times the lower or upper quartile displayed as outliers. IBM SPSS version 27 (IBM SPSS Corp) was used for all statistical analysis. Graphpad Prizm 8 (GraphPad Software, LLC) and IBM SPSS version 27 (IBM SPSS Corp) was used to create graphs.

Results

Overall mean (range) imaging-based values were: $tMTV_{baseline}$ 212 cm^3 (44–585 cm^3), $tTLG_{baseline}$ 1427 g (275–4170 g), tRTV 236 cm^3 (39–531 cm^3), tRLU 18.2 MBq (1.1–56.6 MBq), tTAD 170 cGy (40–420 cGy), $\Delta tMTV_{3months}$ 69% (19–100%), $\Delta tTLG_{3months}$ 66% (8-100%), $\Delta MTV_{6months}$ 50% (-78-100%), and $\Delta tTLG_{6months}$ 46% (-134-100%) (negative values represent increase). These measures were also stratified by low- and high lilotomab groups, as presented in Table 3 and 4, and individual values are provided in supplementary table 1.

Table 3
FDG PET parameters stratified by low- and high lilotomab pre-dosing. Mean (range) values are given for each parameter. The Δ values are calculated from the change relative to baseline, and increases in FDG PET parameters are given as negative values.

	$tMTV_{baseline}$ (cm^3)	$tTLG_{baseline}$ (g)	$\Delta tMTV_{3months}$ (%)	$\Delta tTLG_{3months}$ (%)	$\Delta tMTV_{6months}$ (%)	$\Delta tTLG_{6months}$ (%)
Low lilotomab	138 (63–289)	735 (434–1540)	87 (44–100)	90 (53–100)	79 (7-100)	81 (15–100)
High lilotomab	261 (44–585)	1888 (275–4170)	58 (19–100)	52 (8-100)	30 (-78-100)	21 (-134-100)

Table 4
SPECT/CT parameters stratified by low and high lilotomab pre-dosing. Mean (range) values are given for each parameter.

	tRTV (cm^3)	tRLU (MBq)	$tRLU_{dosage}$ ($^{MBq}/_{MBq/kg}$)	tTAD (cGy)	$tTAD_{dosage}$ ($^{cGy}/_{MBq/kg}$)
Low lilotomab	141 (39–219)	6.2 (1.1–9.8)	0.4 (0.1–0.7)	142 (40–420)	8.6 (4.0–21.0)
High lilotomab	298 (114–531)	26.1 (6.4–56.6)	1.4 (0.3-3.0)	189 (60–380)	9.8 (3.0–19.0)

There were significant correlations between tumor volumes on $PET_{baseline}$ and SPECT day 4 and day 7, calculated as $tMTV_{baseline}$ and tRTV (Fig. 3a) and $tRTV_{day7}$ (both $p < .01$). We interpret this as a validation of our method of measuring tRTV. Significant correlations between glucose consumption, $tTLG_{baseline}$, and radioimmunoconjugate uptake normalized by dosage, $tRLU_{dosage}$ (Fig. 3b) and $tRLU_{dosage}$-day 7, were found (both, $p < .01$) indicating that ^{177}Lu-lilotomab satetraxetan successfully targets FDG avid tumor tissue. A significant correlation between $tRLU_{dosage}$ and tRTV ($p < .01$) indicates that the total tumor uptake of radioimmunconjugate increases with tumor volume (Fig. 3c). However, radioimmunconjugate activity concentration (expressed as $tRLU_{dosage}$/volume) did not correlate significantly with SUV_{mean} ($r = .48$ $p = .07$), indicating that consumption of glucose and CD37 expression on tumor cells does not correspond (Fig. 3d).

Three different dosage levels of radioimmunoconjugate were tested in this study. We observed that the total tumor absorbed dose (tTAD) increased with increasing ^{177}Lu-lilotomab satetraxetan dosage levels. The differences in tTAD between patients treated with 15 MBq/kg and 20 MBq/kg were not significant ($p = .37$) (Fig. 4a). The 10 MBq/kg group was not included in this analysis because it only contained two patients. Significant correlations between tTAD and tRLU (Fig. 4b) and $tRLU_{day7}$, were found (both $p < .01$). This is expected as tTAD was calculated based on the uptake measured at day 4 and day 7 SPECT.

Although total tumor absorbed doses normalized by dosage levels ($tTAD_{dosage}$) increased slightly with larger tumor volumes ($tMTV_{baseline}$), this was not significant ($r = .30$ $p = .28$) (Fig. 5a). The same trend was seen between glucose consumption ($tTLG_{baseline}$) and $tTAD_{dosage}$ ($r = .42$ $p = .12$) (Fig. 5b).

The mean percent of injected activity accumulated in tumor volume calculated from the ^{177}Lu-lilotomab satetraxetan uptake at day 0 was 3.0% (range 0.18%-9.63%). Increasing percent of injected activity in tumor with increasing tumor volumes ($tMTV_{baseline}$) was observed but this was not significant ($r = .48$ $p = .07$).

Patient weight and BSA are parameters which may affect biodistribution of pharmaceuticals as proposed by PK studies [22–25]. Our analysis did not show any correlations between neither patient weight nor BSA versus $tTAD_{dosage}$ ($p = .34$ and $p = .50$ respectively), and activity concentration in tumor ($tRLU_{dosage}$/volume) ($p = .59$ and $p = .66$, respectively).

Total tumor absorbed doses normalized by ^{177}Lu-lilotomab satetraxetan dosage levels ($tTAD_{dosage}$) did not differ significantly across low and high lilotomab groups ($p = .61$) but was slightly higher in the high lilotomab group.

Changes in metabolic tumor volumes and glucose consumption at $PET_{3months}$, $\Delta tMTV_{3months}$ and $\Delta tTLG_{3months}$, were significantly higher for the tTAD ≥ 200cGy group compared to the patient group receiving less than 200cGy ($p = .03$ for both) (Fig. 6a-b). A similar correlation was shown at $PET_{6months}$, $\Delta tMTV_{6months}$ and $\Delta tTLG_{6months}$, but did not reach significance ($p = .07$ for both) (Fig. 6c-d).

Percent changes in $\Delta tMTV_{3months}$, $\Delta tMTV_{6months}$, and $\Delta tTLG_{3months}$ and $\Delta tTLG_{6months}$, were statistically significantly correlated with increasing tTAD in the high lilotomab group ($r = .85$ $p < .01$, $r = .82$ $p = .02$, $r = .87$ $p < .01$ and $r = .86$ $p = .01$, respectively), but not in the low lilotomab group ($r = .23$ $p = .70$, $r = .55$ $p = .33$, $r = .55$ $p = .33$ and $r = .55$ $p = .33$ respectively) (Fig. 7a-d; decrease illustrated as positive values and increase illustrated as negative values). The low lilotomab group had an overall better response that may contribute to this lack of correlation.

Five patients had CR, two had PR, five had SD and two had PD (Fig. 8a and supplementary table 1). tTAD was statistically significantly higher in responders (CR + PR) compared to non-responders (SD + PD) in the high lilotomab group ($p = .04$). This analysis was not carried out in in the low lilotomab group because only two patients in this group were non-responders (Fig. 8b). Large variations in tTAD were observed in responders in low lilotomab group (range 40–420 cGy) (Fig. 8b) (Supplementary table 1). Across the entire cohort, independent of amount of pre-dosing, all non-responders had tTAD < 200cGy (Fig. 8a and c) and all tTAD ≥ 200cGy were responders (Fig. 8a-c).

Discussion

In this era of precision medicine and personalized therapy it is imperative to explore the best way of delivering a treatment with precise dosing tailored for each individual patient. Although time-consuming, tumor and normal tissue dosimetry is a crucial part of targeted radiotherapies, and should be standard both in the clinical setting and in trials according to Council Directive 2013/59/EURATOM[26]. Radioimmunoconjugate uptake determined by post-therapy SPECT derived metrics is an accurate method of analyzing the amount of radioactivity accumulating in tumor; an option unavailable for non-radioactive mAb treatments. Hence, in this sub-study of LYMRIT-37-01, the total amount of ^{177}Lu-lilotomab satetraxetan accumulated in tumor (tRLU), total tumor uptake volume (tRTV) and total tumor absorbed doses (tTAD) were calculated from post-therapy SPECT/CT. We found that tRTV and $tRLU_{dosage}$ correlated significantly with tMTV and tTLG respectively, indicating that ^{177}Lu-lilotomab satetraxetan targets FDG avid tumor tissue without a reduction in tumor uptake in larger tumor volumes. Furthermore, especially for the high lilotomab group, tTAD showed an impact on both ΔtMTV and ΔtTLG, and on clinical response.

We interpret the strong correlation between baseline tMTV and both tRTV (Fig. 3a) and $tRTV_{day7}$ (data not shown) as a validation of our method of measuring tRTV. This correlation may be expected as we customized the SPECT threshold side-by-side with FDG PET images to determine a value for calculation of a final radioimmunoconjugate tumor volume. Still, anatomical agreement of uptake regions is required for such an approach to yield satisfactory results. While the fixed threshold of 26% of the maximum uptake for calculating tumor volumes on SPECT doesn't provide a regression slope of exactly one versus tMTV, it provided the best

visual agreement. Future studies are needed to investigate whether this threshold can be applied to other targeted radiotherapies.

Despite the strong correlation between tTLG and both $tRLU_{dosage}$ (Fig. 3b) and $tRLU_{dosage\ day7}$, no correlation between activity concentration defined by $tRLU_{dosage}$/volume and SUVmean (calculated across the total tumor tissue) was found ($r = .48$ $p = .07$) (Fig. 3d). Thus, the tTLG vs $tRLU_{dosage}$ correlation can possibly be attributed to the fact that these parameters were derived from their respective volumes rather than a similarity between consumption of glucose and CD37 expression on these cells. However, this still supports that ^{177}Lu-lilotomab satetraxetan successfully targets the viable tumor cells in the volume of interest determined from baseline FDG PET.

Standard PK methods without molecular imaging based support assessed to theoretically calculate the amount of a pharmaceutical reaching the tumor volumes is not straight forward, mainly because of changes in biodistribution outside blood compartment as shown by Stokke et al.[27]. Direct image-based measurement of the amounts accumulating in the tumor mass would be preferable for all treatments. However, while this is feasible for targeted radiotherapies where it also enables the calculation of tTAD, it is still a grossly underutilized method. From such measurements, several interesting findings were derived for ^{177}Lu-lilotomab satetraxetan in this work. A strong correlation between $tRLU_{dosage}$ and tRTV ($r = .75$, $p < .01$) implicates that increasing tumor volumes do not reduce ^{177}Lu-lilotomab satetraxetan accumulation in tumor (Fig. 3c). This was also demonstrated by increase in mean percentage of injected activity reaching the tumor volumes with increasing tMTV, although this was not significant (r = .48, p = .07). In addition, lack of correlation between tMTV and $tTAD_{dosage}$ (Fig. 5a, r = .30 $p = .28$), supports the same assumption; that increasing volumes do not reduce absorbed doses. It is therefore fair to assume that the injected amount of radioimmunoconjugate was sufficient for all tumor volumes studied. Recent PK studies have reported that tumor burden influences availability of two different CD20 mAbs, rituximab and obinutuzumab, in NHL patients. It was proposed that the standard dose given may not reach sufficient therapeutic levels of mAbs in cases with high tumor burden [23, 1, 25]. Reduction of tRLU or tTAD with increasing tumor burden were not demonstrated in our study. However, a lower mean tumor volume (212 cm^3) in our population compared to Tout et al (313cm^3) [1] and Ternant et al (600cm^3) [25] might explain why we did not observe such effects. Unfortunately, Ternant et al. used different methodology to assess tMTV; thus, a direct comparison with our study is not possible. Also, different levels of CD20 and CD37 expressed by cells, and different injected amounts and pharmacological properties of rituximab (also given in multiple injections) versus ^{177}Lu-lilotomab satetraxetan hinder direct comparisons. By another approach, whole body (WB) absorbed doses were for ^{131}I-tositumomab used to demonstrate availability of radioimmunoconjugate to evaluate dosing and pre-dosing regimens and the possibility of fractionation to reach high WB absorbed doses and longer half-life of radioimmunoconjugate [6]. Changes in biodistribution after different pre-dosing regimens have previously been demonstrated for ^{177}Lu-lilotomab satetraxetan [27]. Thus, the approach using WB absorbed doses is probably not precise enough to reflect the amount reaching the tumor and organs at risk for ^{177}Lu-lilotomab satetraxetan.

Application of tTLG baseline in treatment planning or changes in this parameter to evaluate response during and after treatment in lymphoma has been proven useful [28, 29]. In our study, lack of correlation between baseline tTLG and $tTAD_{dosage}$ indicates that absorbed dose cannot be predicted by FDG uptake intensity at baseline FDG

PET (Fig. 5b). ^{177}Lu-lilotomab satetraxetan activity concentration in tumor ($tRLU_{dosage}$/volume) did not correlate with SUV_{mean} neither, as discussed above, and in support of the assumption that FDG uptake intensity does not necessarily correlate with CD37 expression in tumor. Further studies are needed to assess the role of heterogeneity in tumors in regard to both FDG and radioimmunoconjugate uptake and how they overlap.

We have previously investigated lesion-based tumor absorbed doses and dose-response relationships, with analyses including 1–5 lesions per patient [30]. The criteria for lesion inclusion were then strictly defined to allow for precise individual dosimetry of each tumor. Significant intra-patient variations were observed and absorbed dose-response relationship at lesion level could not be demonstrated based on changes in FDG PET parameters and Deauville 5-point-scale [30]. By measuring tTAD we here averaged out intra-patient variations and most importantly avoided possible selection bias. While it can be argued that mean absorbed dose is not an adequate metric, and that local low-dose areas are relevant for the overall response, this parameter has been demonstrated as a significant predictor for ^{131}I-tositumomab treatment [13, 12]. Mean tTAD in our study was 170 cGy (median 130cGy). This is lower than the median value of between 341 and 275 cGy reported with ^{131}I-tositumomab (Bexxar) by Dewaraja et al. [13, 12]. Methodologies applied in these two studies are partly comparable to ours, although the CT-driven approach for tumor delineation, performed for ^{131}I-tositumomab, can potentially result in a lower mean tumor absorbed dose (i.e. tTAD) compared to our current method which may exclude tumor tissue with very low uptake.

Based on the proposal by Dewaraja et al [13], we decided to pursue a 200cGy tTAD threshold by investigating the changes in FDG PET parameters and response status stratified by this limit in our population. $\Delta tMTV_{3months}$, $\Delta tTLG_{3months}$, $\Delta tMTV_{6months}$ and $\Delta tTLG_{6months}$ were higher in tTAD ≥ 200cGy group and this difference was significant for $\Delta tMTV_{3months}$ and $\Delta tTLG_{3months}$ (Fig. 6a-b), indicating that there is indeed an absorbed dose response correlation also for ^{177}Lu-lilotomab satetraxetan and that the same threshold can be applied. All four patients with tTAD ≥ 200cGy had $\Delta MTV_{3months} \geq 90\%$. Variations in response in the lower tTAD (< 200cGy) group was larger. While the patient with lowest tTAD (37cGy) had $\Delta MTV_{3months} = 96\%$ and $\Delta MTV_{6months} = 89\%$, a patient with progression ($\Delta MTV_{6months} = -77\%$) had tTAD = 100cGy. One of the patients with progressive disease was the only mantle cell lymphoma in our study with tTAD = 77 cGy. Even though mantle cell lymphomas have been characterized as radiosensitive [31], like follicular lymphomas, this patient unfortunately did not respond to ^{177}Lu-lilotomab satetraxetan treatment. There are few patients in our study and these dissident findings may be random, but it is likely that absorbed doses ≥ 200cGy gives a more predictable effect, whereas the response to lower absorbed doses (< 200cGy) may be more dependent on individual radiosensitivity.

When analyzing the effect of pre-dosing on absorbed doses we observed a slight but not significantly higher $tTAD_{dosage}$ in high lilotomab group. Interestingly, mean $\Delta tMTV_{3months}$, $\Delta MTV_{6months}$, $\Delta tTLG_{3months}$ and $\Delta tTLG_{6months}$ were lower in this group despite slightly higher tTAD (Table 3). A clear dose-response relationship was illustrated for this group, with higher tTAD inducing statistically significant metabolic tumor volume shrinkage and reduction in lesion glycolysis (Fig. 7a-d). On the contrary, the low lilotomab group with slightly lower $tTAD_{dosage}$, had higher mean $\Delta tMTV_{3months}$, $\Delta MTV_{6months}$, $\Delta tTLG_{3months}$ and $\Delta tTLG_{6months}$ (Table 3). Dose-response relationships could not be demonstrated in this group (Fig. 7a-d). This is expected since the overall very good response rate could mask a possible dose-response relationship. Why such a difference in response as

higher mean $\Delta tMTV_{3months}$, $\Delta tTLG_{3months}$, $\Delta tMTV_{6months}$ and $\Delta tTLG_{6months}$ was observed in low lilotomab group and whether other factors that may influence the response are still open questions.

The LYMRIT 37 – 01 PK study demonstrated an increase in blood activity adjusted exposure (area under the curve) with higher lilotomab pre-dosing levels. According to this analysis, arm 4 (high lilotomab) demonstrated highest exposure, lowest clearance and longest biological half-life of ^{177}Lu-lilotomab satetraxetan, slightly higher than arm 1 (low lilotomab) [15]. Furthermore, lower bone marrow and spleen absorbed doses in arm 4 [27] in addition to higher blood exposure shown by PK [15] indicates that more ^{177}Lu-lilotomab satetraxetan is available for tumor uptake. This proposed effect was supported in this study by slightly higher $tTAD_{dosage}$ in the high lilotomab group, even though this was not significant. Larger $tTAD_{dosage}$ variations were also observed in the high lilotomab group, in line with our previous lesion based tumor absorbed dose analysis [30].

Evaluation of response versus tTAD also supports the assumption of absorbed dose-response relationships and a 200 cGy threshold. Patients with CR had large variations in tTAD (range 69.5–418.3 cGy) (supplementary table 1), while all patients with SD or PD had tTAD < 200cGy (Fig. 8a and c). Only two patients had PR; one just above a tTAD of 200 cGy and one below. Notably, all patients with tTAD ≥ 200 were responders, whereas all non-responders had tTAD < 200cGy (Fig. 8c). Based on this analysis, we propose that above a threshold of 200cGy CR is probable, while for < 200cGy large variations in response should be expected. Our methodology for tTAD can exclude tumor volumes with low uptake (as discussed above), however, it ensures that we never overestimate the patients' mean tumor absorbed doses. This means that our conclusions with respect to the 200 cGy limit are conservative and can be safely employed regardless of methodology. If we were to apply a different approach, resulting in lower tTADs, this would not misplace any < 200 cGy patients in the ≥ 200 cGy group (only CR). Hence, the observation that all non-responders had tTAD < 200cGy would also hold true using a different approach. When comparing responders and non-responders in low- and high lilotomab groups, a similar pattern as for the PET response evaluation was revealed. tTAD was statistically significantly higher in responders (CR + PR) compared to non-responders (SD + PD) in the high lilotomab group ($p = .04$). In the low lilotomab group the response rates were higher, and there were only two patients with SD + PD (Fig. 8b). The reason for the difference between the high and low lilotomab groups is not clear, as discussed above, but regardless of pre-dosing all non-responders had tTAD < 200cGy.

We observed increasing tTAD with increasing ^{177}Lu-lilotomab satetraxetan dosage levels in this study (Fig. 4a), however, the differences were not significant between 15 MBq/kg and 20 MBq/kg groups (p = .37) (the 10MBq/kg group was not included in this analysis because the group consisted of only two patients). This illustrates that increasing the amount of activity administrated will not necessarily increase the absorbed dose significantly as this value will also depend on patient-specific uptake and kinetics. While $\Delta tMTV_{3months}$, $\Delta MTV_{6months}$, $\Delta tTLG_{3months}$ and $\Delta tTLG_{6months}$ did not vary between the two dosage levels ($p = 1$, $p = .71$, $p = 1$ and $p = .71$ respectively), there was a difference for these parameters according to tTAD (threshold 200cGy, as discussed above, p = .03 for both $\Delta tMTV_{3months}$ and $\Delta tTLG_{3months}$, and p = .07 for both $\Delta MTV_{6months}$ and $\Delta tTLG_{6months}$) (Fig. 6a-d). This finding indicates that response does not necessarily directly rely on dosage levels, and that absorbed dose can be further investigated as a solitary predictor.

Conclusion

In this study ^{177}Lu-lilotomab satetraxetan total tumor absorbed doses were calculated and a rarely seen absorbed-dose-response relationship was revealed in the high lilotomab pre-dosing group. While similar results were not observed for the patients receiving lower amounts of lilotomab, this was probably since this group had an overall very good response rate. Increasing tumor burden did not have a decreasing effect of on availability of mAbs, indicating that the amount of ^{177}Lu-lilotomab satetraxetan given was sufficient for all tumor volumes studied. However, further studies are needed to establish this in a patient population with a larger range of volumes. Prediction of CR with tumor absorbed doses ≥ 200cGy is reasonable, while large variations of response should be expected with tumor absorbed doses < 200cGy.

We argue that well-designed dosimetric studies are largely underutilized as the most direct method to measure the uptake of targeted therapies. This provides valuable information to determine the optimal radioimmunoconjugate dosage levels and pre-dosing regimens to attain the highest possible absorbed dose to tumor while maintaining acceptable absorbed doses to normal tissues.

Declarations

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Authors' contributions All authors contributed to design and draft of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Arne Kolstad were both in part supported by grants from the Norwegian Cancer Society. Arne Kolstad is member of the Scientific Advisory Board of Nordic Nanovector ASA. Jostein Dahle is an employee and shareholder of Nordic Nanovector ASA. Ayca Løndalen has no conflict of interest. Johan Blakkisrud has no conflict of interest. Mona-Elisabeth Revheim has no conflict of interest. Caroline Stokke has no conflict of interest.

Ethical approval and informed consent All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Figures

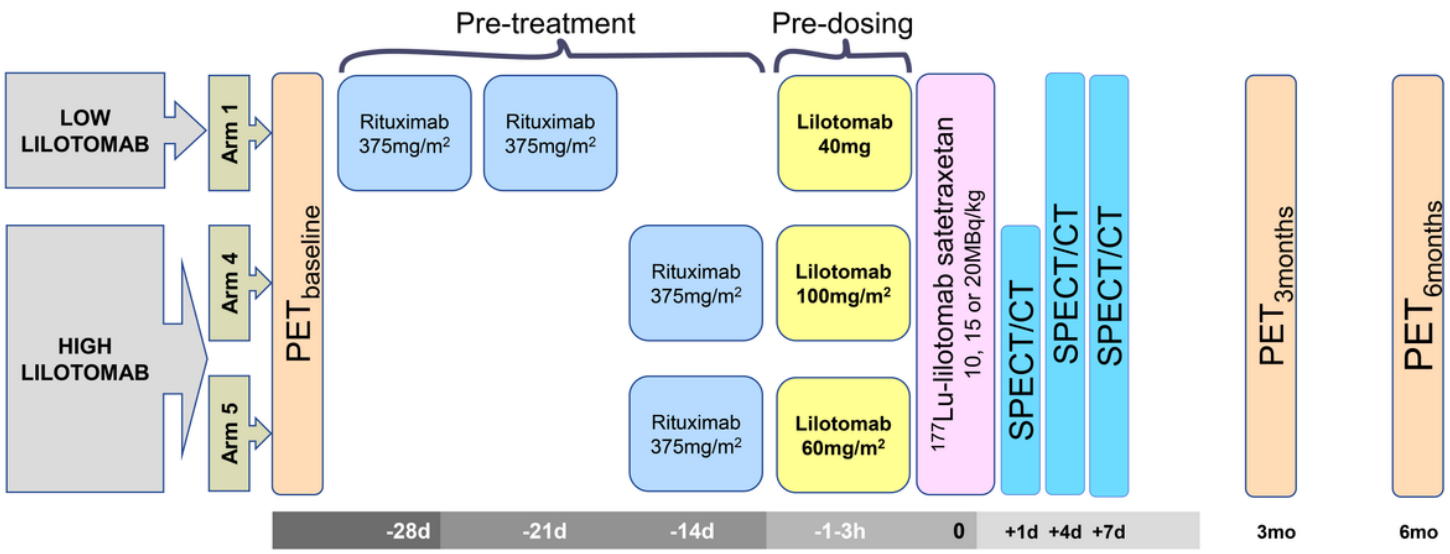


Figure 1

Study design: Three different dosage levels, 10, 15 or 20 MBq/kg, were investigated in the LYMRIT-37-01 study. The zero-hour time point on the grey time line indicates administration of 177Lu-lilotomab satetraxetan. The current study included arms with three different pre-dosing regimens given 1-3 hours before 177Lu-lilotomab satetraxetan injection. Based on pre-dosing, patients were here divided into two groups as indicated; low and high lilotomab. Pre-treatment regimens were given 28 and 21 days before or 14 days before the radioimmunoconjugate. FDG PET was performed as baseline investigation and at 3 and 6 months

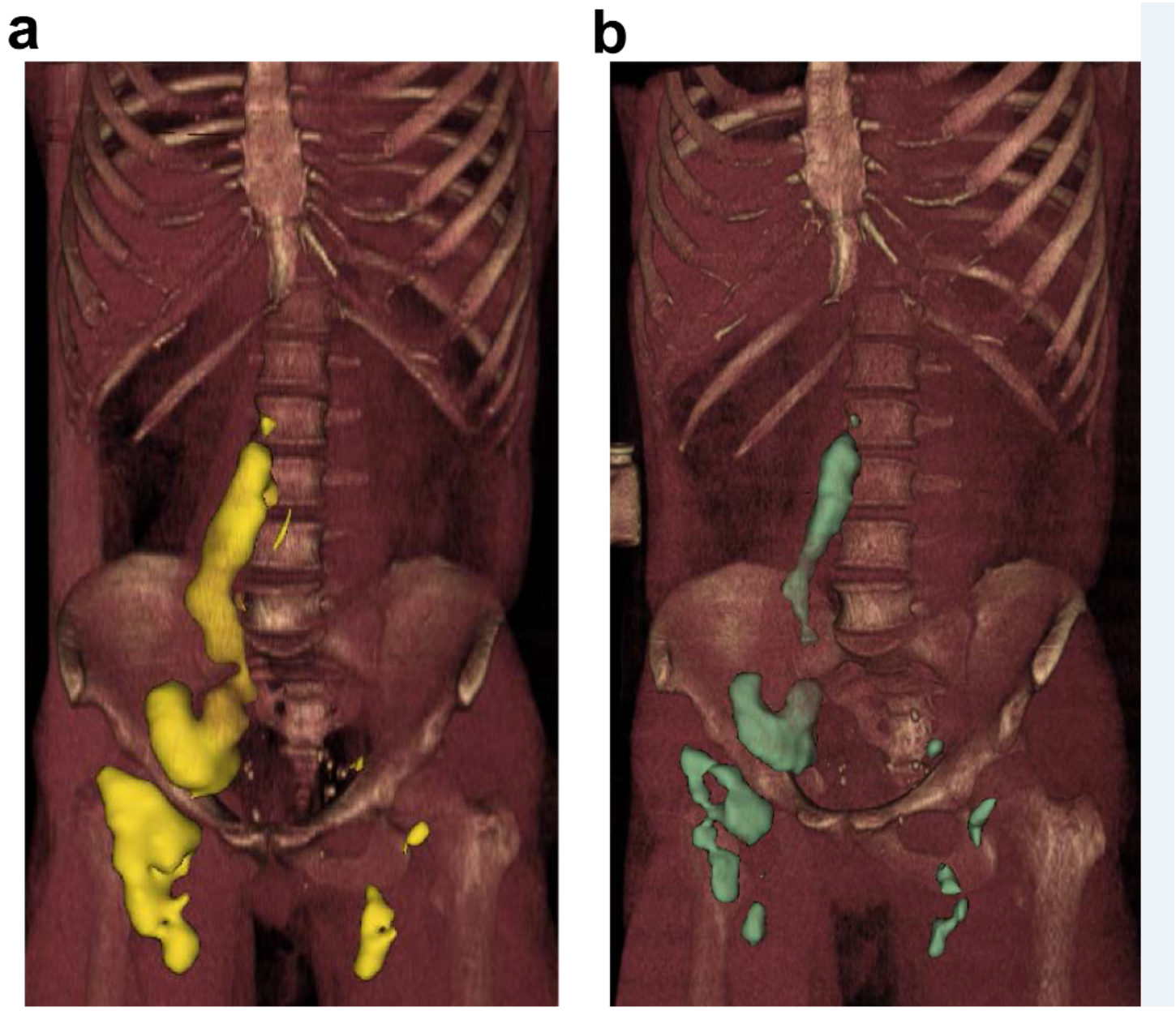


Figure 2

Illustration of FDG PET/CT and 177Lu-lilotomab satetraxetan SPECT/CT images and uptake agreement for tumors. a PETbaseline with all tumor volumes with uptake higher than liver uptake segmented. b All tumor volumes at day 4 SPECT after a 26% of the maximum uptake threshold was applied. Physiological uptake was removed from both PET and SPECT

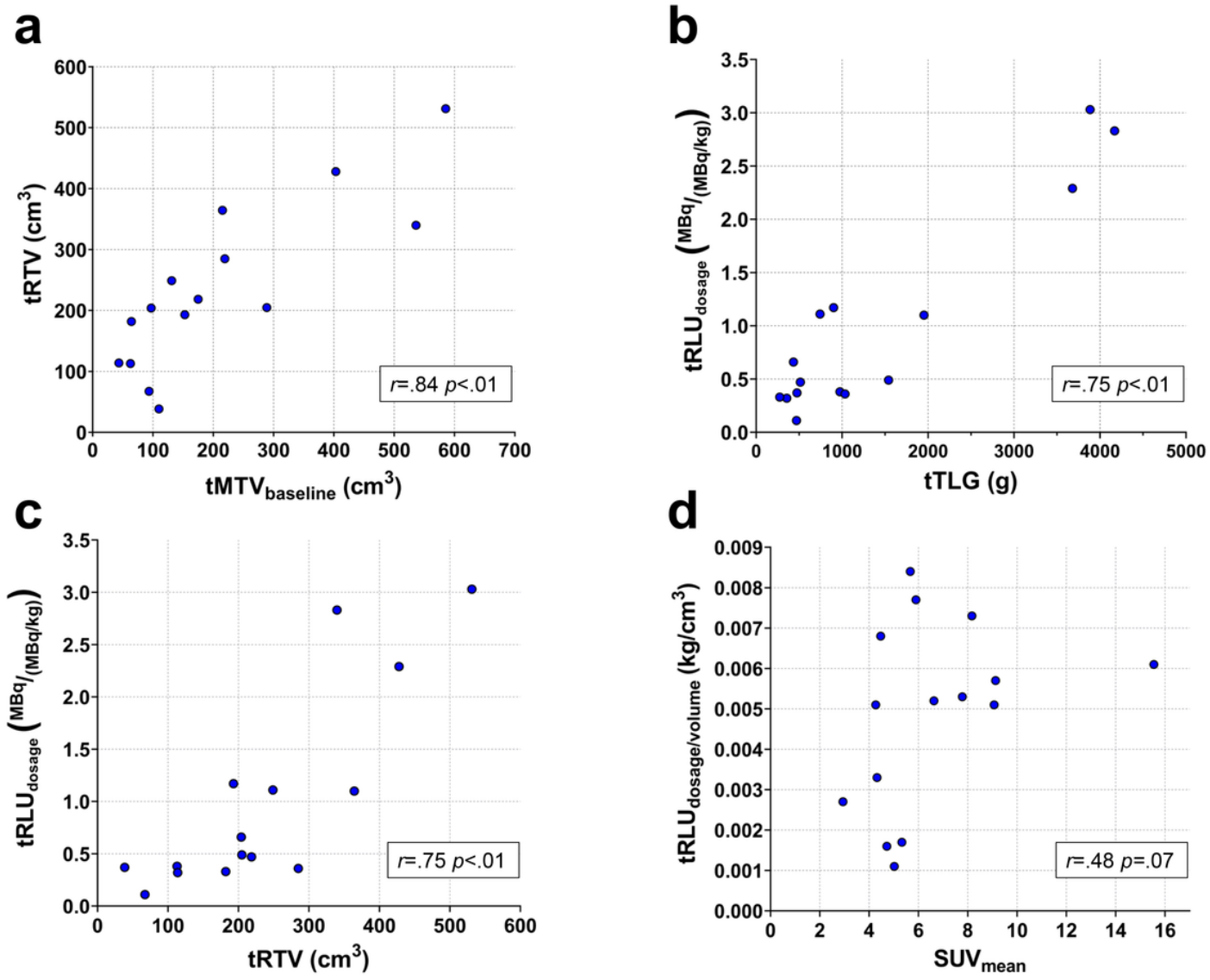


Figure 3

a 177Lu-lilotomab satetraxetan uptake volume tRTV plotted against tMTVbaseline. A statistically significant correlation between the volumes tMTVbaseline and tRTV supports the validity of our method to measure tRTV. b 177Lu-lilotomab satetraxetan uptake tRLUdosage plotted against tTLGbaseline. A significant correlation between tTLG and tRLUdosage demonstrates that 177Lu-lilotomab satetraxetan targets FDG avid viable tumor cells as visualized by FDG PET. c tRLUdosage plotted against tRTV shows that increasing tumor volume does not have a reducing effect on 177Lu-lilotomab satetraxetan uptake. d 177Lu-lilotomab satetraxetan activity concentration tRLUdosage/cm3 plotted against SUVmean. Lacking correlation between tRLUdosage/cm3 and SUVmean can be interpreted as that glucose metabolism not necessarily agrees with CD37 expression. For all panels; blue dots represent data for individual patients and results from the Spearman-rank correlation tests are indicated in each panel

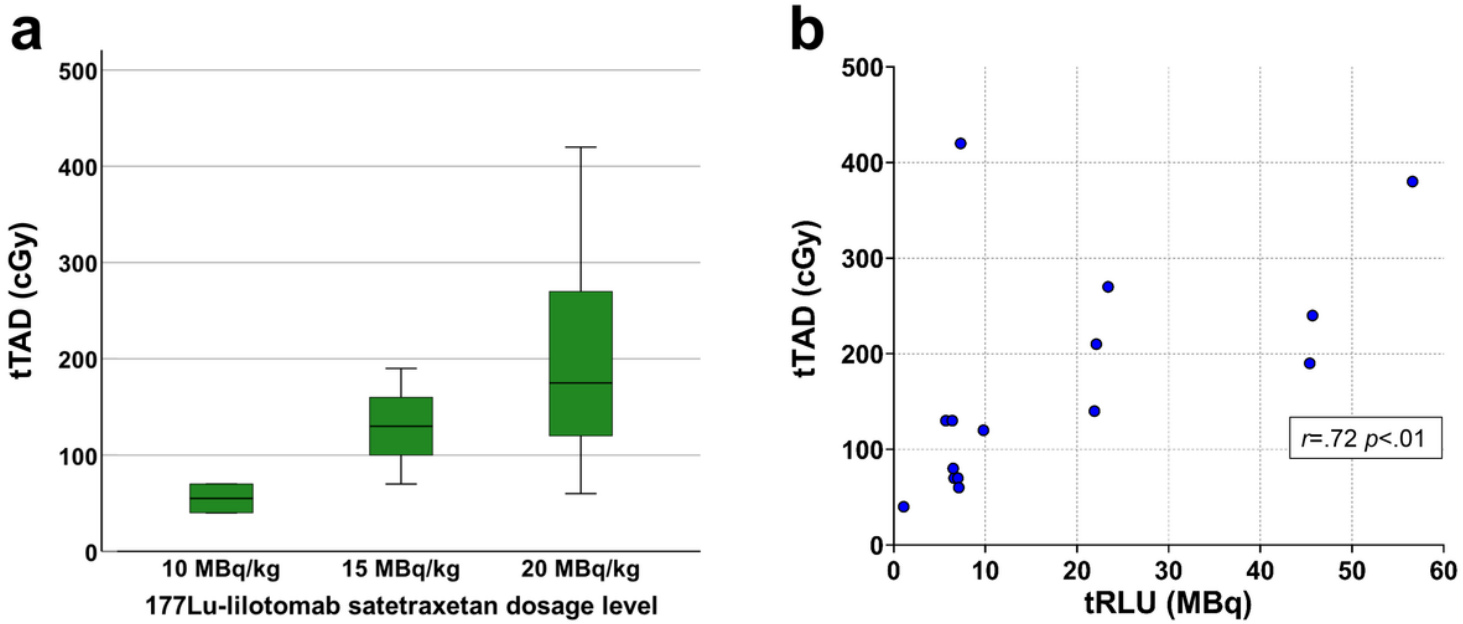


Figure 4

a Increasing absorbed dose to the total tumor volume, tTAD, was observed with increasing 177Lu-lilotomab satetraxetan dosage levels. However, the differences in tTAD were not significant between the groups (15 MBq/kg vs 20 MBq/kg; p=.37, 10 MBq/kg group excluded because of few patients). b tTAD plotted against tRLU. As expected, there was a significant correlation between these parameters Fig. 5 a tTADdosage plotted against tMTVbaseline. There was no significant correlation between baseline tMTV and tTADdosage (r=.30, p=.28), implicating that increasing tMTV did not have a reducing effect on tTAD. b tTADdosage plotted against tTLG. tTLG did not correlate with tTADdosage (r=.42, p=.12). This indicates that absorbed dose cannot be predicted by the FDG uptake at baseline FDG PET

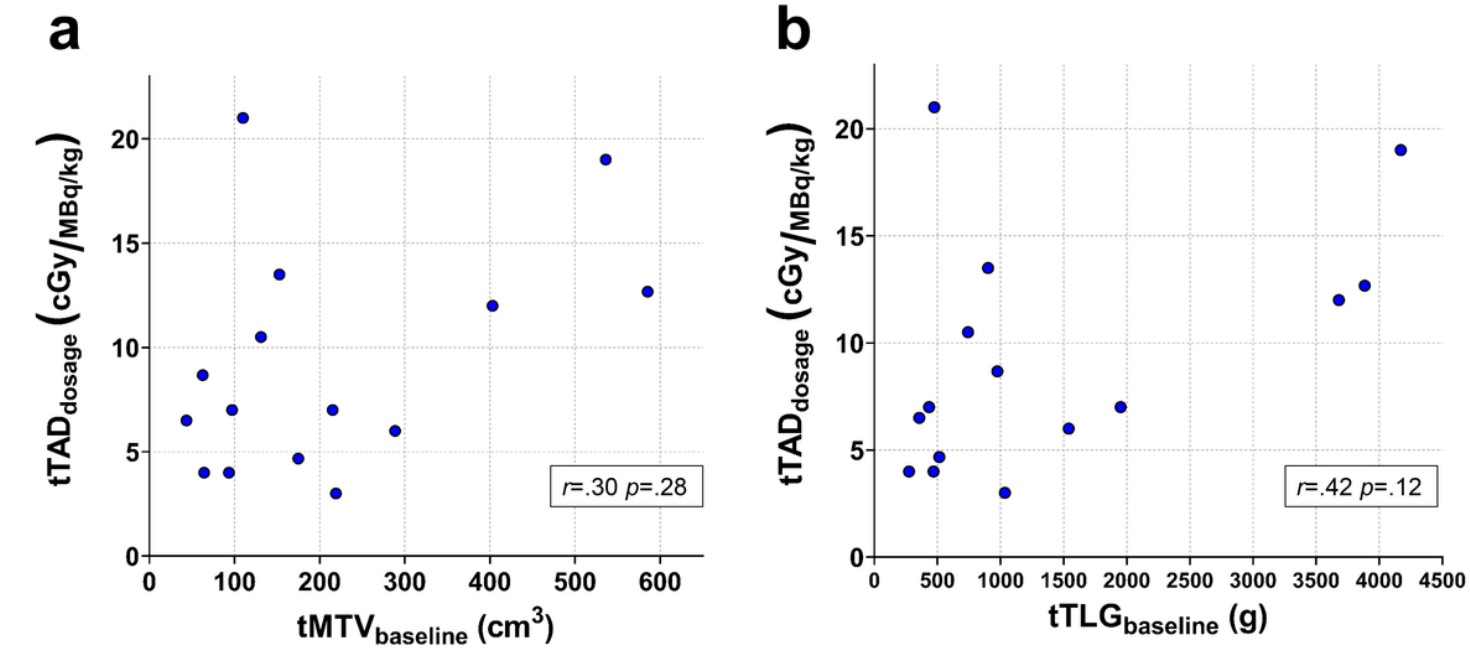


Figure 5

a tTADdosage plotted against tMTVbaseline. There was no significant correlation between baseline tMTV and tTADdosage (r=.30, p=.28), implicating that increasing tMTV did not have a reducing effect on tTAD. b tTADdosage plotted against tTLG. tTLG did not correlate with tTADdosage (r=.42, p=.12). This indicates that absorbed dose cannot be predicted by the FDG uptake at baseline FDG PET

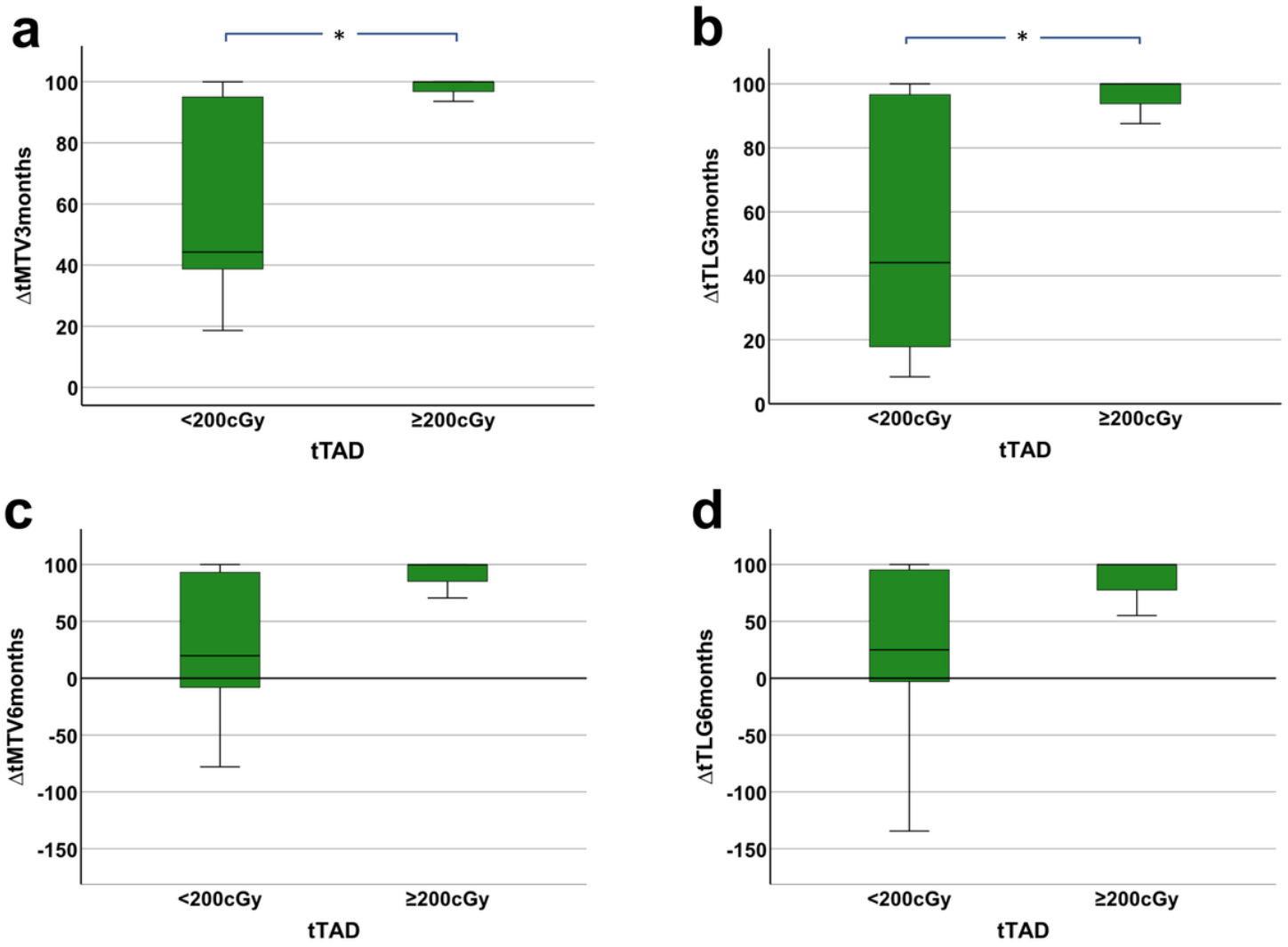


Figure 6

a ΔtMTV3months, b ΔtTLG3months, c ΔtMTV6months and d ΔtTLG6months were higher for patients with absorbed doses of over 200 cGy to the total tumor volume (tTAD). This difference was significant for ΔtMTV3months and ΔtTLG3months (both p=.03) but not for ΔtMTV6months and ΔtTLG6months (both p=.07). Large variations in these parameters were observed for tTAD< 200cGy, while a more predictable response was observed for tTAD ≥200cGy. Note that negative values represent an increase in ΔtMTV and ΔtTLG. Significant differences annotated by asterisks

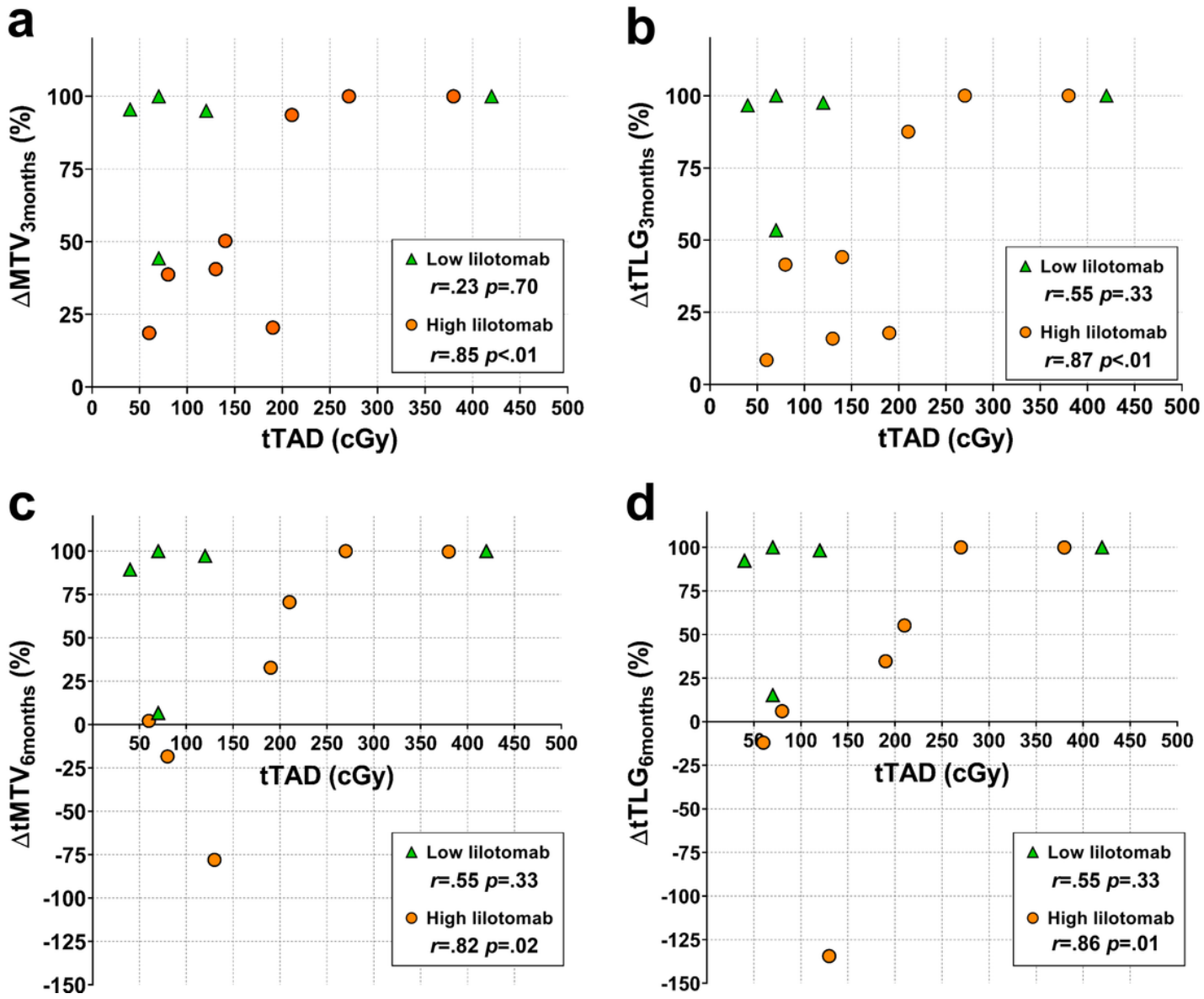
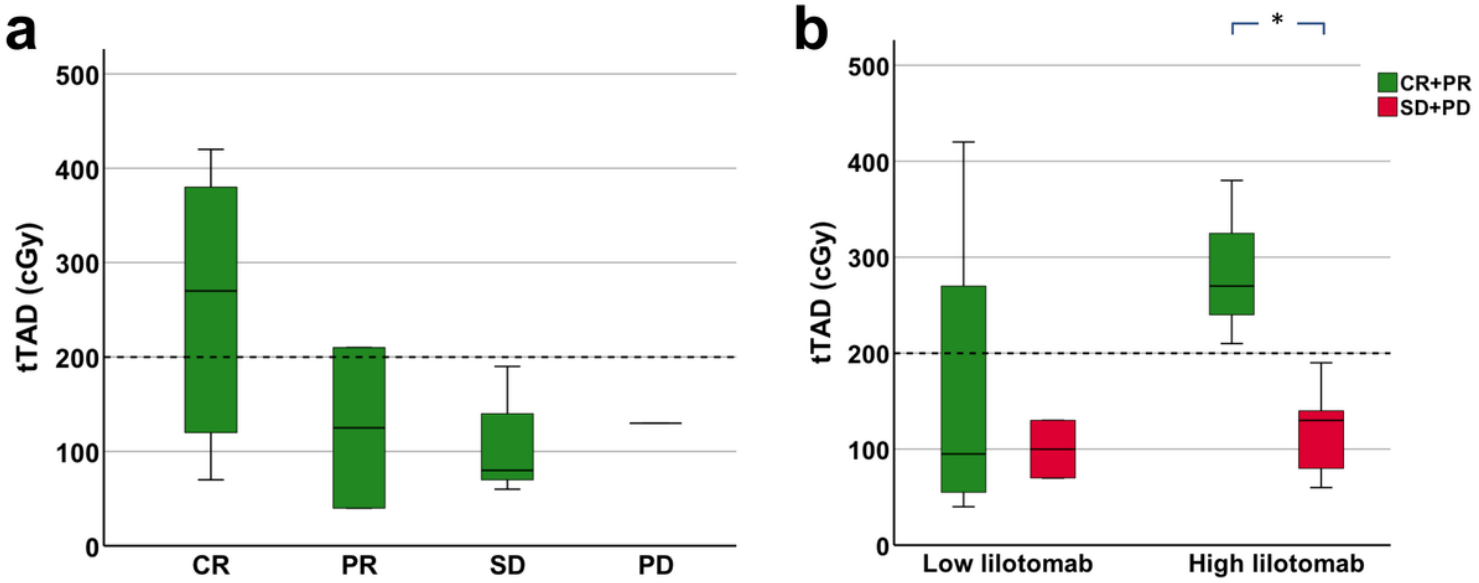


Figure 7

a ΔtMTV3months b ΔtMTV6months c ΔtTLG3months and d ΔtTLG6months plotted against tTAD for the high- and low lilotomab groups. A decrease in ΔtMTV or ΔtTLG is here shown as a positive percentage, and an increase correspondingly as a negative percentage. Statistically significant decreases in PET parameters were observed with increasing tTAD after 3 and 6 months in the high lilotomab group, but not in the low lilotomab group. It may be that the overall good response for low lilotomab group masks such a correlation. The results from the Spearman rank correlation tests are indicated for each group. Each symbol represents an individual patient



c

	CR+PR	SD+PD	Total
≥200cGy	4	0	4
<200cGy	3	7	10
	7	7	

Figure 8

a Absorbed dose to the total tumor volume, tTAD, in the four clinical response categories. Higher tTAD was observed in patients with CR, compared to SD and PD. b tTAD for response categories grouped as responders (CR+PR; in green) and non-responders (SD+PD; in red), and further stratified by low and high lilotomab. Responders had a significantly higher tTAD than non-responders in the high lilotomab group. In the low lilotomab group only two patients were non-responders, and variations in tTAD were large for responders. Significant difference annotated by asterisks. c Responders and non-responders stratified by a 200cGy threshold. All non-responders had tTAD <200cGy, while all with tTAD≥200 were responders

Supplementary Files

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- supplementarytable.docx