Radiation Oncology

BRIEF REPORT Open Access

Feasibility of Biology-guided Radiotherapy (BgRT) Targeting Fluorodeoxyglucose (FDG) avid liver metastases

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Abstract

Introduction Biology-guided radiotherapy (BgRT) is a novel radiation delivery approach utilizing fluorodeoxyglucose (FDG) activity on positron emission tomography (PET) imaging performed in real-time to track and direct RT. Our institution recently acquired the RefleXion X1 BgRT system and sought to assess the feasibility of targeting metastatic sites in various organs, including the liver. However, in order for BgRT to function appropriate, adequate contrast in FDG activity between the tumor and the background tissue, referred to as the normalized SUV (NSUV), is necessary for optimal functioning of BgRT.

Methods We reviewed the charts of 50 lung adenocarcinoma patients with liver metastases. The following variables were collected: SUVmax and SUVmean for each liver metastasis, SUVmean and SUVmax at 5 and 10 mm radially from the lesion, and NSUV at 5 mm and 10 mm (SUVmax of the liver metastasis divided by SUV mean at 5 mm at 10 mm respectively).

Results 82 measurable liver metastases were included in the final analysis. The average SUVbackground of liver was 2.26 (95% confidence interval [CI] 2.17–2.35); average SUVmean for liver metastases was 5.31 (95% CI 4.87–5.75), and average SUVmax of liver metastases was 9.19 (95% CI 7.59–10.78). The average SUVmean at 5 mm and 10 mm radially from each lesion were 3.08 (95% CI 3.00-2.16) and 2.60 (95% CI 2.52–2.68), respectively. The mean NSUV at 5 mm and 10 mm were 3.13 (95% CI 2.53–3.73) and 3.69 (95% CI 3.00-4.41) respectively. Furthermore, 90% of lesions had NSUV greater than 1.45 at 5 mm and greater than 1.77 at 10 mm.

Conclusions This is the first study to comprehensively characterize FDG contrast between the liver tumor and background, referred to as NSUV. Due to the high background SUV normally found in the liver, this work will be valuable for guiding optimization of BgRT for treating liver metastases in the future using the RefleXion® X1 and potentially other similar BgRT platforms.

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Introduction

Biology-guided radiotherapy (BgRT) is a novel radiation therapy (RT) modality that combines the biological imaging information from positron emission tomography/computed tomography (PET/CT) with a 6 MV linear accelerator. BgRT utilizes fluorodeoxyglucose (FDG) activity in real-time to track and direct RT at sub-second latency. This differs from typical radiation treatments which use a fully formed image as the target for radiation [1]. This also potentially allows for delivery of tracked radiation to multiple tumors in the same treatment session, since the tumors are continuously signaling their location. In addition, BgRT reduces treatment margins which compensate for tumor motion, and therefore can potentially reduce toxicity by decreasing the RT dose delivered to healthy tissue [2]. Further, BgRT could eventually be used to target tumor sub-volumes, individually adapt treatment strategies based on recurrence risk, and adapt RT according to treatment response [3].

RefleXion® X1 is a novel radiotherapy delivery system that delivers BgRT using a ring gantry equipped with kV-FBCT and PET imaging subsystems. Our institution is currently one of three sites in the United States with the delivery system. For BgRT to be successful and function optimally, there must be adequate contrast in FDG activity between the tumor and background tissue. This is especially important for tissues with background FDG avidity, such as the liver. The background FDG avidity of the liver may pose potential challenges for BgRT if there is not enough difference in the FDG uptake of the tumor to differentiate between tumor and normal tissue. In addition, the liver is a common metastatic site for various cancers such as lung and colorectal cancer, so the differences in FDG avidity of normal liver tissue and liver metastases must be measured and deemed sufficient for BgRT to target these metastases. Adequate contrast in FDG activity between the tumor and the background tissue, referred to as the normalized standardized uptake value SUV (NSUV), is necessary for optimal functioning of BgRT.

The purpose of this study is to characterize the NSUV of liver metastases by comparing background liver SUV to tumor SUV in order to evaluate the future feasibility of BgRT to liver lesions.

Materials and methods

We performed a retrospective analysis of 50 consecutive patients with metastatic lung adenocarcinoma to the liver diagnosed and treated at our center between 2016 and 2018. Patients were identified from an institutional database. Included patients had PET/CT scans at baseline prior to starting systemic therapy which confirmed FDG avid liver metastases. Patients who did not have a PET/CT prior to starting systemic therapy or who did not have liver metastases identified on PET/CT prior to starting systemic therapy were excluded ($n=23$). Lesions within 10 mm of an adjacent avid metastases were not analyzed to avoid inaccurate calculations due to FDG falloff of adjacent metastases. The study was approved by the institutional review board at our institution.

Velocity™ 4.0 oncology imaging informatics system, developed by Varian, was utilized to capture standardized uptake value (SUV) values. A threshold SUV of 4 was selected a priori to auto contour each liver metastasis. Radial expansions of 5 and 10 mm were performed off of each liver metastasis auto contour. The following variables were collected: SUVmax and SUVmean for each liver metastasis, SUVmean and SUVmax 5 mm radially from the lesion, and SUVmean and SUVmax 10 mm radially from the lesion. SUVbackground of liver was captured, NSUV at 5 mm (SUVmax of liver metastasis divided by SUVmean at 5 mm), and NSUV at 10 mm (SUVmax of liver metastasis divided by SUV mean at 10 mm) were calculated for each metastasis. Expansions of 5 and 10 mm were off of the gross tumor volume with SUV of ≥4 (Fig. 1).

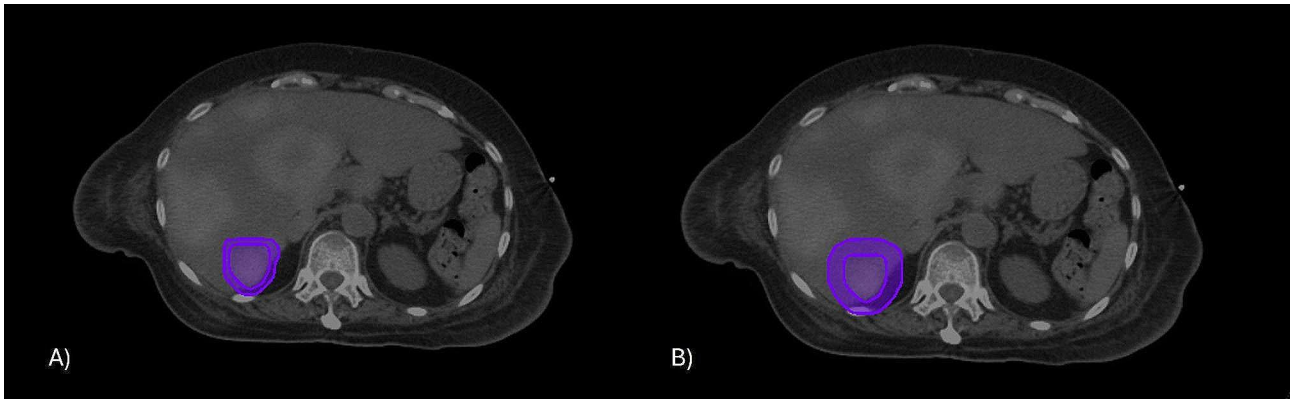

Fig. 1 Positron emission tomography/computerized tomography (PET/CT) images of a patient with liver metastases with auto contouring of a single liver metastases and associated 5 and 10 mm expansions demonstrated

$$NSUV\ at\ 5\,mm = \frac{SUV\,max\ in\ 5\,mm\ radial\ expansion\ of\ lesion}{SUV\,mean\ of\ 5\,mm\ radial\ expansion\ of\ lesion}$$

$$NSUV\ at\ 10\,mm = \frac{SUV\,max\ in\ 10\,mm\ radial\ expansion\ of\ lesion}{SUV\,mean\ of\ 10\,mm\ radial\ expansion\ of\ lesion}$$

Statistical analysis was performed with SPSS version 27.0 (SPSS Inc, Chicago, IL). One-sided t-test was used to calculate 95% confidence interval (CI) for variables included in the analysis.

Results

A total of 27 patients were included in the final analysis, with 82 measurable liver metastases. 16 patients (59%) were females and the median age was 64 (range, 40–87). Median SUVbackground of normal liver was 2.20 (range, 1.22–3.11). Median SUVmax of liver metastases was 7.14 (range, 4.06–47.35) and median SUVmean of liver metastases was 4.93 (range, 1.22–15.84). Median distance between analyzed liver metastases was 53 mm (range, 11–110 mm). Figure 2 represents one patient included with autocontours of PET avid disease.

The average SUVbackground of the normal liver was 2.26 (95% CI 2.17–2.35). The average SUVmean for all liver metastases was 5.31 (95% CI 4.87–5.75) and the average of SUVmax of liver metastases was 9.19 (95% CI 7.59–10.78). The mean ratio of SUVmean for liver metastases to SUVbackground of the normal liver was 2.44 (95% CI 2.21–2.66). The mean ratio of SUVmax of liver metastases to SUVbackground of the normal liver was 4.17 (95% 3.45–4.91).

The average SUVmean at 5 mm and 10 mm radially from each lesion were 3.08 (95% CI 3.00-2.16) and 2.60 (95% CI 2.52–2.68) respectively. The mean NSUV at 5 mm and 10 mm were 3.13 (95% CI 2.53–3.73) and 3.69 (95% CI 3.00-4.41) respectively. Furthermore, 90% of lesions had NSUV greater than 1.45 at 5 mm and 1.77 at 10 mm. 50% of lesions had NSUV greater than 2.32 at 5 mm and 2.91 at 10 mm. In total, 27 patients were included in the final analysis, with 82 measurable lesions (Table 1).

Discussion

Stereotactic body radiation therapy (SBRT) is a safe and effective method of treatment of liver metastases, as it provides a focused, high dose of RT to a small target volume, sparing the majority of normal liver tissue [4, 5]. SBRT for liver metastases is more effective in oligometastatic patients with good performance status, limited extra-hepatic disease, and smaller and fewer liver metastases [5]. Given randomized data supporting the role of SBRT in oligometastatic lung cancer, it is important that we continue to improve RT delivery for liver metastases [6–8]. Furthermore, BgRT potentially obviates the need

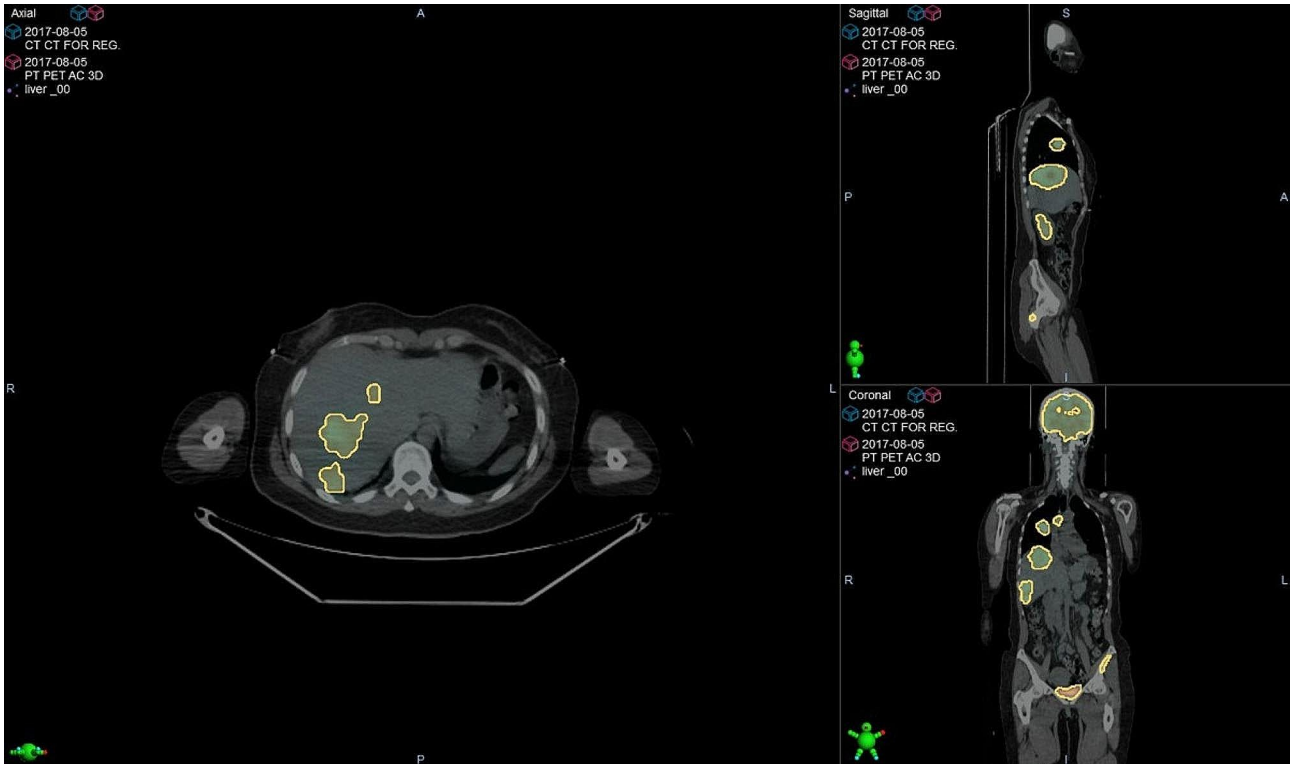

Fig. 2 Positron emission tomography/computerized tomography (PET/CT) images of a patient with liver metastases with auto contouring of all FDG avid lesions with an SUV ≥ 4

Table 1 Summary of results

Variable	Mean	(95% CI)
SUV background	2.26	2.17–2.35
SUV liver met	5.31	4.87–5.75
SUV max liver met	9.19	7.59–10.78
SUV mean liver met/SUV background	2.44	2.21–2.66
SUV max liver met/SUV background	4.17	3.45–4.91
SUV at 5 mm	3.08	3.00-2.16
SUV at 10 mm	2.60	2.52–2.68
NSUV at 5 mm	3.13	2.53–3.73
NSUV at 10 mm	3.69	3.00-4.41

Abbreviations: CI, confidence interval; SUV, standardized uptake value; met, metastasis; max, maximum; NSUV, normalized standardized uptake value

for larger margins and could therefore lead to the use of higher biologically effective dose (BED) and ultimately better local disease control [9, 10]. One of the challenges of BgRT includes differentiating between the SUV of tumor and normal physiologic uptake of FDG in organs including the liver, heart, brain, mediastinum, bowel and bladder. The RefleXion X1 platform is only capable of proceeding with BgRT if it is able to lock on the biology tracking zone (BTZ) of the tumor, which incorporates the targets activity, motion, with some margin. If the BTZ overlaps with FDG uptake from an adjacent normal organ, the BgRT is unable to proceed. Therefore, understanding the threshold between background SUV and tumor SUV is critical to broaden the use of BgRT in our field.

Our study evaluated the threshold SUV uptake between liver metastases and background liver noise. Mean, median, and maximum values of the SUV in the liver background and tumor were obtained and NSUV was calculated at 5 and 10 mm (selected a priori) in order to assess the degree of SUV falloff from the metastatic lesion and differentiation between normal liver. NSUV was the primary measurement used as the endpoint of our study as it was felt to be the simplest and most reproducible way to differentiate between SUV tumor and SUV background at various distances from the target site. The values identified in this current study are presently incorporated in ongoing work on the RefleXion machine in order to successfully enable BgRT for liver metastases. Other similar work will be needed in various clinical scenarios where primary or metastatic lesions are adjacent to other organs, which also have normal physiologic uptake after a FDG injection. For example, a lung lesion by the left ventricle, mediastinal node adjacent to the pulmonary artery, or pelvic node adjacent to the bladder may pose similar challenges where BgRT is unable to localize to the tumor and therefore "a no go" approach is taken. Overcoming these potential obstacles is therefore critical to expanding BgRT across all tumor sites.

Currently, RefleXion guidelines incorporate net activity concentration (AC) and normalized target signal (NTS) for proper patient selection for BgRT in cases of lung and bone, which are the current disease sites approved for BgRT by the Food and Drug Administration (FDA). These values were not the primary focus of this manuscript and not included, as the purpose of our study was to define the threshold between the SUV of metastatic disease compared to background liver which can be reproducible on either a diagnostic PET detector or RefleXion detector. Indirectly however, the higher NSUV is, the higher AC and NTS should be. Additionally, AC and NTS are not the only metrics important in verifying whether a lesion is amenable to BgRT. Background noise in the liver or physiologic uptake of FDG in normal organs such as the bladder or heart, may also play a role in whether BgRT is an option or not. Lastly, based on our present clinical experience, we know there is a clear difference between diagnostic PET data and RefleXion X1. Diagnostic PET detectors appear to have a better signal to noise ratio due to a larger PET detector size and angle coverage and difference in image reconstruction algorithm [11]. Additionally, the X1 system uses a filtered back projection algorithm for PET imaging reconstruction to gather linear and unbiased PET image data, while diagnostic PET images are often reconstructed with an iterative reconstruction algorithm with scatter correction [12]. Because of these reasons, there is no simple technique to evaluate whether a patient is currently a candidate for BgRT unless they are assessed on the machine itself. Currently, we have an ongoing trial evaluating SUV uptake of liver metastases on the X1 PET. Patients are injected with FDG and are scanned on the RefleXion X1 within 1 h to evaluate uptake on tits detectors. Data from this ongoing trial will provide more insight on the feasibility of BgRT for liver primaries and metastases on the machine itself.

There is currently no literature on using BgRT specifically to treat liver metastases. Our study is the first study to delineate tumor-to-background SUV contrast of liver metastases and demonstrated that a threshold between the background SUV of the liver and liver metastases does exists and should therefore provide an opportunity to target liver metastases by discounting background noise. This work is guiding ongoing trials including the one described earlier in order to better optimize BgRT to active disease in the setting of background FDG uptake. Future work will also evaluate other radiotracers that can be used for the same purpose and may in fact have more disease-specific uptake and less background noise due to specificity and therefore obviate any potential hurdles BgRT currently may have due to normal FDG physiologic uptake in organs such as the liver.

Acknowledgements
Not applicable.

Author contributions
BC, TA, SH, CH, AL and AA gathered the data. AA, AL analyzed the data. BC, AA wrote the manuscript. All authors reviewed the manuscript.

Funding
The study was funded by a grant provided by RefleXion.

Data availability
All data generated and analyzed during this study are included in this published article.

Availability of supporting data
Not applicable.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
Not applicable.

Received: 14 September 2023 / Accepted: 2 August 2024
Published online: 18 September 2024

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