^{18}F-NaF PET/CT-directed dose escalation in stereotactic body radiotherapy for spine oligometastases from prostate cancer

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Abstract— **Purpose: To investigate the technical feasibility of SBRT dose painting using ^{18}F-NaF positron emission tomography (PET) scans guidance in patients with spine oligometastases from prostate cancer.**

Materials/methods: Six patients with 15 spine oligometastatic lesions from prostate cancer who had ^{18}F-NaF PET/CT scan prior to treatment were retrospectively included. GTV_{reg} was delineated according to the regular tumor boundary shown on PET and/or CT images; and GTV_{MATV} was contoured based on a net metabolically active tumor volume (MATV) defined by 60% of the SUVmax values on ^{18}F-NaF PET images. The PTVs (PTV_{reg} and PTV_{MATV}) were defined as respective GTVs (plus involved entire vertebral body for PTV_{reg}) with a 3-mm isotropic expansion margin. Three 1-fraction SBRT plans using VMAT technique along with 10 MV flattened filter free (FFF) beams ($Plan_{24Gy}$, $Plan_{24\text{-}27Gy}$, and $Plan_{24\text{-}30Gy}$) were generated for each patient. All plans included a dose of 24 Gy prescribed to PTV_{reg}. The $Plan_{24\text{-}27Gy}$ and $Plan_{24\text{-}30Gy}$ also included a simultaneous boost dose of 27 Gy or 30 Gy prescribed to the PTV_{MATV}, respectively. The feasibility of ^{18}F-NaF PET-guided SBRT dose escalation was evaluated by its ability to achieve 100% of the prescription dose to cover at least 90% of the PTV volume while adhering to organ-at-risk (OAR) dose constraints.

Results: In all 33 SBRT plans generated, the planning objectives and dose constraints were met without exception. $Plan_{24\text{-}27Gy}$ and $Plan_{24\text{-}30Gy}$ had a significantly higher dose in PTV_{MATV} than $Plan_{24Gy}$ ($p < 0.05$), respectively, while maintaining a similar OAR sparing profile.

Conclusion: Using VMAT with FFF beams to incorporate a simultaneous ^{18}F-NaF PET-guided radiation boost dose up to 30 Gy into a SBRT plan is technically feasible without violating normal tissue tolerances. The relationship between local control and normal tissue toxicity during ^{18}F-NaF PET-guided dose escalation in SBRT should be validated in clinical trials.

Keywords— **^{18}F-NaF PET, Dose painting, SBRT, spine oligometastases, oligometastatic prostate cancer.**

I. Introduction

Aggressive stereotactic body radiotherapy (SBRT) using image guidance to locally deliver an ablative radiation dose for spine oligometastases may potentially impact local tumor control and/or possibly improve survival duration [1]. Recent clinical evidence has shown that SBRT using high dose with either a single fraction or a limited number of fractions can lead to excellent pain control as well as local tumor control in patients with spine oligometastases [2]. However, as a dose limiting factor, proximity to spinal cord often precludes SBRT delivering the full prescription dose (PD) and/or escalating dose to the planning target volume (PTV) of spine oligometastases, thus compromising the therapeutic ratio.

Advances in molecular imaging including positron emitting tomography (PET) allow us to selectively identify a metabolically active tumor volume (MATV) within the anatomical boundaries of a spine oligometastasis. PET/CT imaging using sodium fluoride labeled with fluoride-18 (^{18}F-NaF) as tracer has been applied to evaluate bone metastases in various malignancies including metastatic prostate cancer [3-4]. Skeletal MATVs defined by the increased uptake of ^{18}F-NaF reflect the areas of increased regional blood flow and mineral turnover characterizing these metastatic lesions [3-4]. Using SBRT with a simultaneous integrated dose boost (dose painting) to this higher risk volume might, on an individual basis, safely improve the local control without violating normal tissue tolerances.

Furthermore, it is postulated that the microenvironment of each bone metastasis from prostate cancer forms a tumor ecosystem containing host noncancer cells in addition to prostate cancer cells, in which tumor cells interact with both osteoclasts and osteoblasts to exacerbate bone destruction, alter the genotype and phenotype of the host facilitating cells, and increase cancer cell growth [5]. The strategy of delivering differential doses using SBRT with a simultaneous integrated dose boost to MATV offers the option of irradiating host facilitating cells simultaneously with the cancer cells in the tumor ecosystem.

In this study, we investigated the technical feasibility of SBRT dose painting using ^{18}F-NaF PET scans guidance in patients with spine oligometastases from prostate cancer. The isodose distribution and dosimetric parameters in

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SBRT treatment plans with and without a simultaneous integrated boost in MATV using volumetric modulated arc therapy (VMAT) delivery technique with flattering-filter free (FFF) beams were statistically compared.

II. Materials and Methods

A. Patients and ^{18}F-NaF PET/CT imaging

As a proof-of-concept, six patients with 15 spine oligometastatic lesions from prostate cancer who had ^{18}F-NaF PET/CT scan prior to treatment were retrospectively included in this study from The Cancer Imaging Archive of NIH/NCI (delegated to Washington University in St. Louis). All ^{18}F-NaF PET/CT image collections in The Cancer Imaging Archive of NIH/NCI have been anonymized to remove all protected health information under a Washington University in St. Louis IRB protocol. The procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

The selection criteria were PET/CT findings consistent with spine metastases with 1 to 5 lesions. The prescribed injected ^{18}F-NaF dose was 3 mCi IV. Imaging was performed on a Phillips Gemini TF PET/CT scanner (Philips Medical Systems, Inc., Cleveland, OH) based on 4 × 4 × 22mm LYSO (lutetium yttrium orthosilicate) crystal detection elements covering 18 cm axial field of view (FOV) and 57 cm imaging transaxial FOV. The time of flight resolution is 585 ps. The scanner achieves a spatial resolution of 4.8mm at the center of the FOV. Data were reconstructed using the RAMLA iterative OSEM algorithm using 3 iterations and 33 subsets, along with CT based attenuation correction as well as randoms, normalization, dead time, and a model based scatter correction. The CT component of the scanner is a 16 slice helical CT. The CT images were generated using the 16 slice helical CT component of PET/CT scanner with 120 KV, 60 mAs setting.

B. Contouring

Coregistered PET/CT images were transferred to an image analysis workstation (MIM Maestro 6.2.7, MIM Software, Inc., Cleveland, OH) for contouring. Definitions of gross tumor volume (GTV), clinical target volume (CTV), and PTV as well as organs-at-risk (OARs) were based on RTOG protocol 0631 [6]. The detailed structure contouring was summarized at table 1.

C. SBRT planning

Final contour data was transferred to an Eclipse Treatment Planning System V11 workstation (Varian Medical Systems, Palo Alto, CA). The SBRT plans were designed using volumetric modulated arc therapy (VMAT) technique with flattering filter free beams (10 MV, 1400MU/min) in a Varian TrueBeam Linear Accelerator (Varian Medical Systems, Inc. Palo Alto, CA).

Three plans ($Plan_{24Gy}$, $Plan_{24\text{-}27Gy}$, and $Plan_{24\text{-}30Gy}$) were created. All plans were scheduled for 1 fraction. In all plans, PTV_{reg} was prescribed with a dose of 24 Gy. For $Plan_{24\text{-}27Gy}$ and $Plan_{24\text{-}30Gy}$, a simultaneous MATV boost dose of 27 Gy or 30 Gy was also prescribed to PTV_{MATV}, respectively. Coverage for PTV_{reg} and PTV_{MATV} was based on at least 90% of the structure receiving at minimum 100% of the prescription dose (i.e., D90% ≥ 100% of prescription dose). Dose constraints for OARs were based on previous study [2]. Planning objectives and OARs' constraints for the plans are listed in Table 1.

Table 1 Dose coverage requirements and organs-at-risk constraints

Structure	Contouring	$Plan_{24Gy}$	$Plan_{24\text{-}27Gy}$	$Plan_{24\text{-}30Gy}$
GTV_{reg}	Gross disease visualized on ^{18}F-NaF PET and/or CT			
GTV_{MATV}	60% SUVmax of ^{18}F-NaF PET within GTV with clinician's adjustment			
CTV_{reg}	GTV plus involved entire vertebral body			
CTV_{MATV}	Same as GTV_{MATV}			
PTV_{reg}	CTV_{reg} plus 3 mm isotropic expansion margin. Exclusion from spinal cord by 3mm and direct exclusion from esophagus	D90% ≥ 24 Gy To ensure the sparing of spinal cord, there is no limits on dose heterogeneity	D90% ≥ 24 Gy	D90% ≥ 24 Gy
PTV_{MATV}	CTV_{MATV} plus 3 mm isotropic expansion margin. Exclusion from spinal cord by 3mm and direct exclusion from esophagus	Not applicable	D90% ≥ 27 Gy To allow gradients for MATV boosting and to spare the dose to spinal cord, there is no limits on dose heterogeneity	D90% ≥ 30 Gy To allow gradients for MATV boosting and to spare the dose to spinal cord, there is no limits on dose heterogeneity
Spinal Cord	10 cm above the superior extent of the PTV_{reg} and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV_{reg}	$D_{max,0.03cc}$ < 14 Gy	Same as $Plan_{24Gy}$	Same as $Plan_{24Gy}$
Partial spinal cord	5-6 mm above the superior extent of the PTV_{reg} to 5-6 mm below the inferior extent of the PTV_{reg}	$D_{max,0.03cc}$ < 14 Gy; V10Gy < 10%	Same as $Plan_{24Gy}$	Same as $Plan_{24Gy}$
Esophagus	10 cm above and below the extent of PTV_{reg}	V14.5 Gy < 2.5 cc; V15 Gy < 2 cc	Same as $Plan_{24Gy}$	Same as $Plan_{24Gy}$
Bowl		V16Gy < 5cc	Same as $Plan_{24Gy}$	Same as $Plan_{24Gy}$

Abbreviations: Dx%: dose received by at least x% of the volume; VxGy: volume receiving at least x Gy; Dmean: the mean dose received within the designated volume; Dmax,0.03cc: the maximum point dose (size: 0.03 cc) received within the designated volume; Dmin: the minimum dose received within the designated volume; Dmax: the maximum dose received within the designated volume.

Plans were optimized for the RapidArc technique (Varian Medical Systems, Inc. Palo Alto, CA) with 2 fully rotational arcs with the collimator angle set to ±20°. The addi-

tional partial arc and avoidance sectors were used if needed to help reduce anterior and posterior doses to the spinal cord. Dose calculations were carried out using the anisotropic analytical algorithm (AAA_10028) with a grid resolution of 2 mm and heterogeneity correction in the Eclipse treatment planning system (Varian Medical Systems, Inc. Palo Alto, CA).

D. Plan evaluation

Isodose distribution and dose-volume histograms (DVHs) were evaluated for all plans and clinically used dosimetric measures were analyzed. The conformity index (CI) was calculated to evaluate the quality of each SBRT plan [7].

E. Statistical methods

The Page's test was used to detect the ordered alternative of the plan parameters among three plans for each patient [8]. If the overall test were significant ($p < 0.05$), the Wilcoxon signed rank test would be performed for pair-wise comparisons in the plan parameters between each two plans for each patient. Median values and the ranges were reported. Statistical analysis was performed in SAS 10.0/JMP 11 (SAS Institute, Cary, NC). A p-value < 0.0017 was taken as statistically significant.

III. Results and Discussion

Table 2 summarizes the positions of spine oligometastases in patients. Fig. 1 shows an example of the delineation of targets and OARs. All planning objectives and dose constraints were met (Table 3). Fig. 2 compares isodose distributions for $Plan_{24Gy}$, $Plan_{24\text{-}27Gy}$, and $Plan_{24\text{-}30Gy}$ from one patient. Fig. 3 shows the corresponding cumulative DVH results.

For target coverage, all plans reached that at least 90% of the PTV volume received 100% of the prescription dose while adhering to spinal cord and partial spinal cord dose constraints.

Singh et al. reported that patients with oligometastatic prostate cancer had a 5-year overall survival similar to metastases-free patients and significantly better than patients with more than five metastases (73 % versus 45 %) [9]. The authors suggested that oligometastatic patients may harbor biologically less aggressive cancers with weaker metastatic potential. Such metastases might be suitable for more aggressive treatment approaches.

Table 2 Patient target characteristics

Patient (n = 6)	GTV_{MATV} (lesions n = 15)	Tumor position
1	1	T10
	2	T1
2	1	L2
	2	T6
3	1 plus 2	T1 plus T2
4	1	L5 plus S
	2	C4
5	1	L2
6	1	L5
	2 plus 3	T4 plus T2
	4 plus 5	C5 plus C6

Table 3 Summary of the DVH analysis for the PTVs and OARs

Parameter	$Plan_{24Gy}$ Median (Range)	$Plan_{24\text{-}27Gy}$ Median (Range)	$Plan_{24\text{-}30Gy}$ Median (Range)
CTV_{reg}: Volume 39.4 cm^3 (11.0 – 83.1 cm^3)			
D80% (cGy)	2535.0 (2485.0 –2616.0)	2586.0 (2507.0 – 2622.0)	2593.0 (2505.0 – 2668.0) †
D90% (cGy)	2463.0 (2348.0 – 2554.0)	2495.0 (2400.0 – 2543.0)	2492.0 (2446.0 – 2578.0)
V80% PD (%)	99.4 (98.4 – 100.0)	99.5 (98.3 – 100.0)	99.6 (97.4 – 100.0)
V90% PD (%)	97.2 (95.3 – 100.0)	97.8 (95.6 – 100.0)	98.4 (95.7 – 99.7)
PTV_{reg}: Volume 79.0 cm^3 (22.1 – 126.6 cm^3)			
D80% (cGy)	2501.0 (2475.0 – 2609.0)	2508.0 (2472.0 – 2573.0)	2515.0 (2475.0 – 2569.0)
D90%(cGy)	2425.0 (2400.0 – 2550.0)	2426.0 (2400.0 – 2513.0)	2430.0 (2400.0 – 2499.0)
V80% PD (%)	99.2 (98.6 – 100.0)	99.2 (98.4 – 100.0)	99.2 (98.2 – 100.0)
V90% PD (%)	97.5 (95.7 – 99.8)	97.5 (95.6 – 99.7)	97.7 (95.4 – 99.7)
V100% PD (%)	92.0 (90.0 – 95.0)	92.0 (90.0 – 95.0)	92.0 (90.0 – 95.0)
CI	0.9 (0.8 – 0.9)	0.9 (0.8 – 0.9)	0.9 (0.8 – 0.9)
MATV: Volume 2.8 cm^3 (0.5 – 19.0 cm^3)			
Dmax (cGy)	2743.0 (2632.0 --2880.0)	3075.0 (2835.0 - 3119.0))*	3365.0 (3260.0 - 3427.0) *, ††
Dmean (cGy)	2626.0 (2501.0 - 2697.0)	2934.0 (2778.0 - 3029.0) *	3243.0 (3129.0 - 3284.0) *, ††
D80% (cGy)	2574.0 (2449.0 - 2664.0)	2871.0 (2752.0 - 2992.0) *	3182.0 (3071.0 - 3237.0) *, ††
D90% (cGy)	2538.0 (2430.0 - 2634.0)	2835.0 (2744.0 - 2967.0) *	3139.0 (3083.0 - 3214.0) *, ††
V80% PD (%)	100.0 (100.0 – 100.0)	100.0 (99.5 - 100.0)	100.0 (99.3 - 100.0)
V90% PD (%)	100.0 (99.5 - 100.0)	100.0 (98.1 - 100.0)	100.0 (97.4 - 100.0)
PTV_{MATV}: Volume 10.7 cm^3 (2.7 – 36.9 cm^3)			
Dmax (cGy)	2767.0 (2694.0 - 2879.0)	3093.0 (2865.0 - 3119.0) *	3370.0 (3279.0 - 3433.0) *, ††
Dmean (cGy)	2589.0 (2542.0 - 2669.0)	2871.0 (2769.0 - 2969.0) *	3178.0 (3102.0 - 3210.0) *, ††
Dmin (cGy)	1849.0 (1337.0 - 2515.0)	2316.0 (1699.0 - 2630.0) *	2557.0 (1698.0 - 2898.0) *, ††
D80% (cGy)	2537.0 (2469.0 - 2632.0)	2791.0 (2727.0 - 2906.0) *	3099.0 (3037.0 - 3138.0) *, ††
D90% (cGy)	2457.0 (2400.0 - 2803.0)	2731.0 (2450.0 - 2849.0) *	3032.0 (2997.0 - 3076.0) *, ††
V80% PD (%)	99.8 (99.2 - 100.0)	100.0 (98.6 - 100.0)	100.0 (98.8 - 100.0)
V90% PD (%)	98.8 (97.0 - 100.0)	99.3 (96.1 - 100.0)	99.9 (93.2 - 100.0)
V100% PD (%)	96.1 (90.0 - 100.0)	96.1 (90.0 - 98.9)	95.0 (90.8 - 98.9)
CI	0.1 (0.0 - 0.3)	0.6 (0.4 - 0.8)	0.8 (0.7 - 1.0)
Spinal Cord: Volume 38.5 cm^3 (13.1 – 50.8 cm^3)			
Dmax (cGy)	1185.0 (1091.0 - 1257.0)	1188.0 (1080.0 - 1254.0)	1180.0 (1100.0 - 1254.0)
Dmean (cGy)	131.0 (70.0 - 302.0)	132.0 (71.0 - 299.0)	135.0 (8.0 - 295.0)
D50% (cGy)	6.0 (1.0 - 103.0)	6.0 (1.0 - 105.0)	6.0 (1.0 - 107.0)
Partial Spinal Cord: Volume 5.3 cm^3 (2.7 – 8.1 cm^3)			
Dmax (cGy)	1187.0 (1087.0 - 1257.0)	1190.0 (1077.0 - 1247.0)	1202.0 (1100.0 - 1247.0)
Dmean (cGy)	741.0 (668.0 - 841.0)	758.0 (681.0 - 834.0)	752.0 (681.0 - 837.0)
D50% (cGy)	711.0 (661.0 - 848.0)	728.0 (665.0 - 842.0)	724.0 (679.0 - 847.0)
V14Gy (%)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
V12Gy (%)	0.7 (0.0 - 1.1)	0.5 (0.0 - 1.1)	0.6 (0.0 - 1.2)
V10Gy (%)	7.4 (4.1 - 9.9)	7.2 (3.4 - 9.6)	7.3 (5.4 - 10.0)
V8Gy (%)	29.8 (22.8 - 66.5)	33.4 (22.7 - 63.4)	33.2 (24.7 - 66.3)
V6Gy (%)	88.1 (65.7 - 94.8)	87.1 (64.1 - 94.0)	87.6 (71.7 - 93.4)
Esophagus Volume 40.6 cm^3 (32.4 – 46.0 cm^3)			
Dmax (cGy)	2042.0 (1697.0 – 2490.0)	2013.0 (1673.0 – 2486.0)	1971.0 (1734.0 – 2481.0)
Dmean (cGy)	67.0 (3.0 – 391.0)	70.0 (3.0 – 391.0)	73.0 (3.0 – 391.0)
D50% (cGy)	27.0 (4.0 – 51.0)	27.0 (4.0 – 51.0)	27.0 (4.0 – 51.0)
V15Gy (cm^3)	0.4 (0.1 – 1.7)	0.4 (0.1 – 1.5)	0.5 (0.5 – 1.7)
V14.5Gy (cm^3)	0.6 (0.1 – 2.0)	0.7 (0.2 – 1.8)	0.7 (0.5 – 1.5)
Trachea: Volume 42.0 cm^3 (30.8 – 48.4 cm^3)			
Dmax (cGy)	1211.5 (962.0 – 1542.0)	1231.0 (943.0 – 1477.0)	1196.0 (936.0 – 1514.0)
Dmean (cGy)	135.9 (7.0 – 526.0)	135.5 (7.0 – 523.0)	132.5 (7.0 – 535.0)
D50% (cGy)	60.7 (27.0 – 606.0)	63.5 (28.0 – 604.0)	65.0 (29.0 – 620.0)
V10.5Gy (cm^3)	0.6 (0.0 – 1.1)	0.6 (0.0 – 1.0)	0.7 (0.0 -1.1)
Bowel: Volume 1475.0 cm^3 (51.7 – 5073.8 cm^3)			
Dmax (cGy)	1170.5 (1000.0 – 1436.0)	1182.5 (1028.0 – 1483.0)	1174.0 (1053.0 – 1544.0)
Dmean (cGy)	125.5 (78.0 – 137.1)	127.5 (78.0 – 136.0)	127.0 (78.0 – 146.0)
D50% (cGy)	20.9 (11.0 -23.4)	21.5 (11.0 -23.0)	21.5 (11.0 – 23.0)
V10.5Gy (cm^3)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)

$P < 0.0017$: *: $Plan_{24Gy}$ vs $Plan_{24\text{-}27Gy}$; ↑: $Plan_{24Gy}$ vs $Plan_{24\text{–}30Gy}$; ††: $Plan_{24\text{–}27Gy}$ vs $Plan_{24\text{–}30Gy}$

Abbreviations: Dx%: dose received by at least x% of the volume; VxGy: volume receiving at least x Gy; Dmean: the mean dose received within the designated volume; Dmax,0.03cc: the maximum point dose (size: 0.03 cc) received within the designated volume; Dmin: the minimum dose received within the designated volume; Dmax: the maximum dose received within the designated volume; PD: prescription dose; CI: conformity index.

Recent studies have confirmed that SBRT with high-dose, single-fraction, image-guided IMRT could achieve higher local control rates for spinal metastases with minimal toxicity [2]. The current study follows these previous technical and clinical accomplishments with results supporting

even more aggressive dose escalation in the context of VMAT with FFF beams. This study estimates the advantage of selective dose escalation through analyzing the dosimetric parameters. These results require validation in a prospective trial that will be susceptible to many of the common radiation therapy clinical uncertainties.

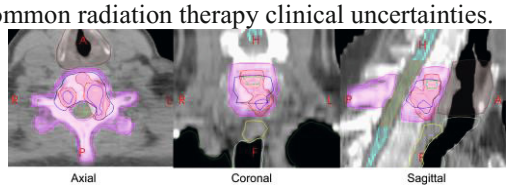

Fig. 1. An example of the delineation of targets and OARs defined on ^{18}F-NaF PET/CT image. MATV1: blue; MATV2: green; GTV_{reg}: dark blue; CTV_{reg}: light green; PTV_{reg}: magent; PTV_{MATV}: red; Spinal cord: cyan; Partial spinal cord: orange; Esophagus: yellow; Trachea: light green; Larynx: brown; Lung: dark green. Abbreviation: A: anterior; P: posterior; L: left; R: right; H: head; F: feet.

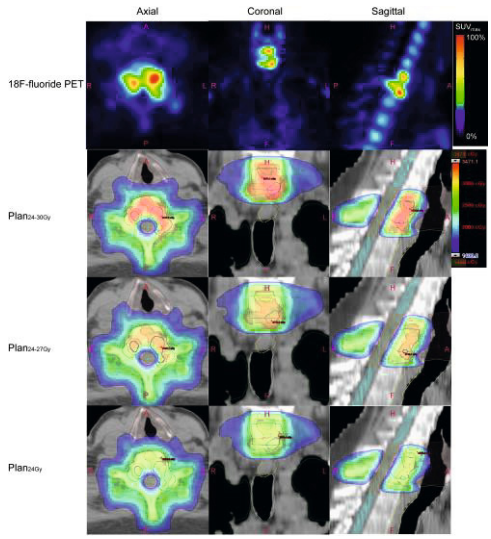

Fig. 2. PET/CT images and corresponding treatment plan dose distribution images from a patient with spine oligometastaese. The dose distribution is shown in axial, coronal and sagittal projections; with color scale of red representing high doses and blue representing low doses. $Plan_{24\text{-}30Gy}$ shows a stratified dose distribution with a dose hot spot occupying the PTV_{MATV} (red) contour, with dose dropping in the "non-boost" region (i.e., PTV_{reg}). The color wash for dose scaling was set in the range of 1400 – 3471 cGy. The maximum point dose (0.03cc) in the $Plan_{24\text{-}30Gy}$ is confined within the PTV_{MATV}. In contrast, the maximum point dose (0.03cc) in the $Plan_{24Gy}$ is located outside the PTV_{MATV}. Anchoring the "hot spot" as close as to the SUVmax was accomplished by defining MATV in the $Plan_{24\text{-}30Gy}$. This could have a radiobiological advantage as the most biologically active tumor volume would then receive the highest radiation dose. Abbreviation: A: anterior; P: posterior; L: left; R: right; H: head; F: feet.

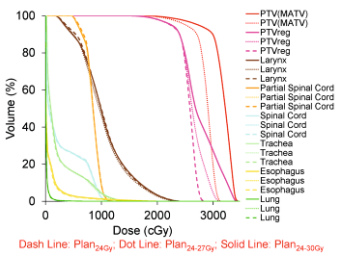

Fig. 3 Dose volume histogram corresponding to the case shown in Fig. 2 demonstrates significant differences in dose coverage of of PTVs and comparable doses to the surrounding OARs in $Plan_{24Gy}$, $Plan_{24\text{-}27Gy}$, and $Plan_{24\text{-}30Gy}$.

IV. Conclusions

Using ^{18}F-NaF PET-guided dose escalation in SBRT for spine oligometastases from prostate cancer is technically feasible without violating normal tissue tolerances. It could achieve a high differential boost dose between PTV_{MATV} and PTV_{reg}. The relationship between tumor response and normal tissue toxicity in ^{18}F-NaF PET-guided dose escalation should be validated in clinical trials.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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