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Balancing Dose and Toxicity in Central NSCLC SBRT: Insights into Organ Motion and the IRV Framework

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ABSTRACT

Using an internal organ at risk volume (IRV) framework may offer a way to mitigate treatment-related injury during stereotactic body radiation therapy (SBRT) for non-small cell lung cancer (NSCLC). In this project, we examined: (1) distinctions in clinical presentation between tumors situated centrally and peripherally, (2) how the IRV strategy behaves in central disease, (3) the extent of positional and volumetric organ motion, and (4) the normal tissue complication probabilities (NTCPs) that arise from these factors. Two datasets were reviewed: patients treated with SBRT for localized NSCLC (n = 78), and a subgroup evaluated specifically for motion analysis (n = 35). When comparing tumor locations, central lesions required larger planning target margins, received lower biologically effective doses, delivered greater doses to lung tissue, and showed poorer locoregional tumor control. Motion of the bronchial structures was more pronounced in men and in taller individuals, while patients with elevated body mass index (BMI) demonstrated reduced esophageal volume variation. A retrospective, non-optimized application of the IRV method resulted in more than a 10% absolute NTCP increase for the bronchial tree in three patients. These observations reinforce the importance of improving planning techniques to balance effective dose intensification with acceptable toxicity in central tumors. Organ motion and shape changes may be more substantial in males and taller patients, and less evident in those with higher BMI. As emerging research further separates central tumor subtypes for tailored treatment, the IRV approach may be useful in refining risk estimation.

Keywords: NSCLC, SBRT, Central locations, Clinical endpoints, Patient factors, Respiratory motion

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Introduction

For individuals with early-stage non-small cell lung cancer (NSCLC) who cannot undergo surgery or decline operative management, stereotactic body radiation therapy (SBRT) serves as a highly effective alternative [1]. In stage I disease, SBRT routinely yields local control rates above 90% at 2 years [2]. Achieving these results depends heavily on delivering biologically effective doses of at least 100-125 Gy using an alpha/beta of 10 (BED10) [3, 4]. Roughly 44% of NSCLC tumors, however, arise in central locations [5], which carry elevated risks for events such as esophageal perforation and airway injury [6-9]. Timmermann and colleagues reported severe toxicity in 46% of such cases [10].

Maintaining safety in these situations requires meticulous planning and ongoing improvements in SBRT delivery techniques [4, 11]. Because lung tumors shift during breathing, accounting for motion is essential [11]. A four-dimensional CT (4D-CT)-based internal target volume (ITV) is commonly employed for this purpose [11, 12]. To reduce unintended dose to nearby organs at risk (OARs), the planning organ-at-risk volume (PRV) concept has been introduced, although evidence supporting its routine application remains sparse [13-15] and does not address intrafraction motion [15]. The internal organ at risk volume (IRV) principle has been suggested as a way to incorporate these additional variations [15, 16]. Nardone *et al*. demonstrated that using IRVs in SBRT planning for central NSCLC rendered 42% of plans unacceptable [15].

In summary, SBRT for centrally located NSCLC presents meaningful challenges for clinicians [17]. In this investigation, we contrasted clinical characteristics and outcomes for central versus peripheral tumors treated with SBRT in our department. We also quantified positional shifts between OARs and their corresponding IRVs, examined volume fluctuations in several serial organs (bronchial tree, trachea, esophagus, spinal canal) throughout respiration, and evaluated whether these movements relate to patient characteristics. Additionally, we tested whether applying the IRV concept retrospectively—without performing new treatment optimization—would produce notable increases in NTCPs.

Materials and Methods

Study design

We reviewed the records of all patients referred for SBRT directed at the lung or mediastinal regions, identifying 151 individuals. A prior component of the overarching research project examined diagnostic workflow patterns with an emphasis on the COVID-19 era [18]. The present analysis differs in terms of eligibility, objectives, and methodology **(Figure 1)**. For the comparison of clinical endpoints in central versus peripheral lesions, only patients with localized NSCLC were included (n = 78). For examinations involving organ motion and volume changes, we studied all cases receiving SBRT for NSCLC in a central anatomical position (n = 35). Following the criteria of Chang *et al*. a structure was classified as central when its distance from any key mediastinal organ was ≤2 cm [19]. Accordingly, this work focused on tumors situated within 2 cm of the central airway complex (bronchial tree plus trachea), the esophagus, or the spinal canal. Detailed selection criteria are illustrated in **Figure 1**. Ethical approval was granted by the University Medical Center Göttingen (application no. 3/10/20).

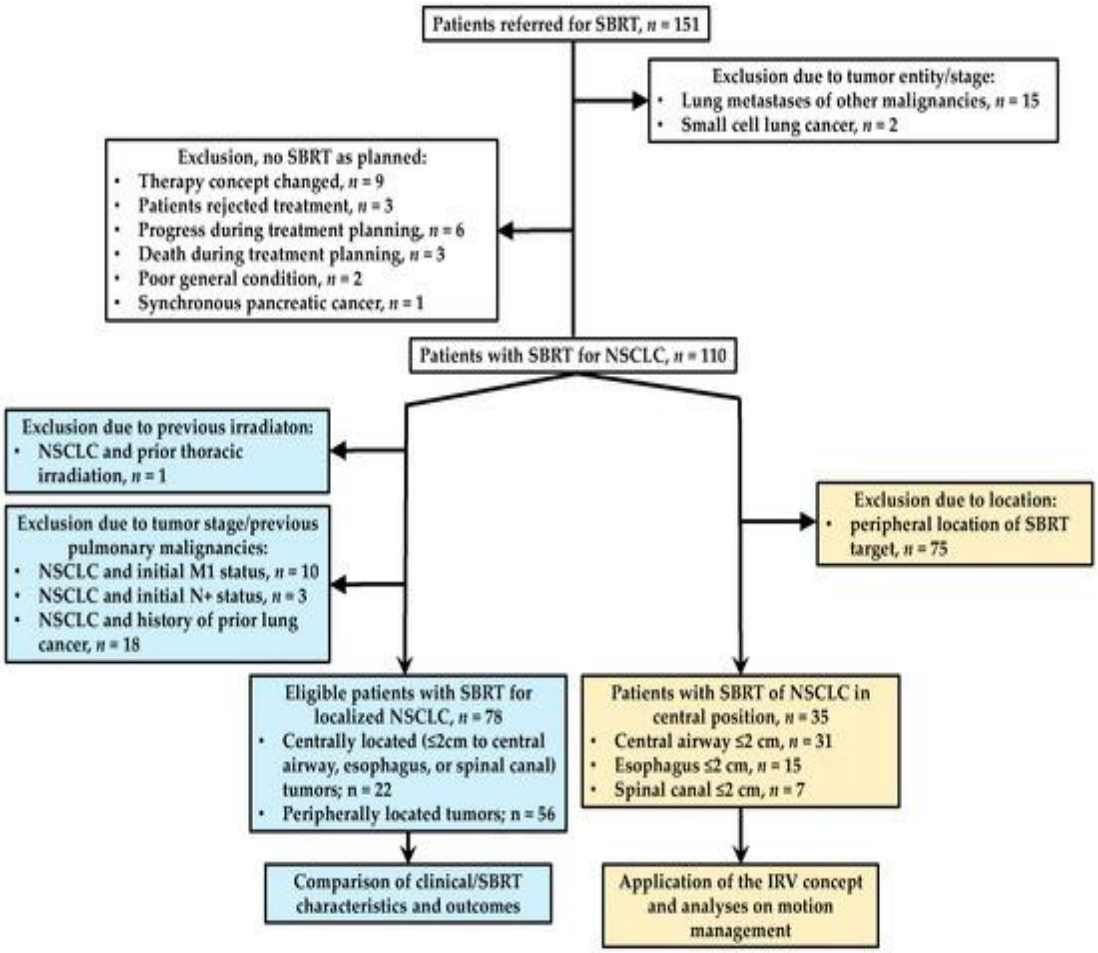


Figure 1. This diagram outlines how participants were sorted into two investigative paths: one examining clinical differences between central and peripheral tumors (left, blue) and another focusing on organ-at-risk motion (right, orange). SBRT = stereotactic body radiation therapy; OARs = organs at risk; IRV = internal organ at risk volume.

Radiotherapy, planning and delivery

A prior publication by Habermann *et al*. (2022) describes the general SBRT workflow used in this project [18]. Planning began with a 4D-CT acquired in the supine position using a respiratory belt, with individualized immobilization tools ensuring reproducible alignment. Tumor motion was addressed with the internal target volume (ITV) strategy [11, 12]: the gross tumor volume (GTV) was delineated on all 10 respiratory phases, and these were merged to form the ITV. The planning target volume (PTV) incorporated case-specific safety margins ranging from 3 mm to 10 mm, determined by the treating radiation oncologist.

Treatment planning used Eclipse (Varian Medical Systems, Palo Alto, CA, USA) in four software generations: version 10.0 (12/2012-09/2013), 11.1 (10/2013-09/2014), 13.5 (10/2014-05/2020), and 15.6 (from 06/2020 onward). SBRT delivery was performed with Varian Clinac 2300 CD linear accelerators. Daily cone-beam CT was employed for verification. Details for each patient group are outlined in Sections 2.2.1 and 2.2.2.

Patient Cohort: clinical/SBRT characteristics and outcomes

CT imaging for this analysis was carried out using Philips Gemini TF TOF 16 (n = 22), Philips Ingenuity Flex (n = 3), and Philips Brilliance Big Bore (n = 53) scanners (Philips Medical Systems, Fitchburg, WI, USA). Slice thicknesses included 2 mm (n = 4) and 3 mm (n = 72). In routine practice, two patients were scanned at 5 mm, and because technical factors were not endpoints for this arm of the research, they remained included. Dose calculations were performed using Acuros for 70 patients and AAA for 18. The prescription isodose level was 80% in 61 individuals, whereas homogeneous dose prescriptions were used in 17.

Patient cohort: motion-management evaluation

This subgroup included 35 centrally located NSCLC cases. CT scans were obtained with the Philips Gemini TF TOF 16 (n = 11), Philips Ingenuity Flex (n = 2), and Philips Brilliance Big Bore (n = 22) systems (Philips Medical Systems, Fitchburg, WI, USA). All datasets used a 3 mm slice thickness (n = 35). Dose computation relied exclusively on Acuros (n = 35). Twenty-six plans used an 80% isodose prescription, while nine were prescribed homogeneously.

Endpoints and statistical methods

Clinical/SBRT characteristics and outcomes

The analytic procedures followed those previously reported by Habermann *et al*. (2022) [18]. Clinical and treatment-related variables were compared between central and peripheral tumor groups. Pearson's Chi-square test and the Mann-Whitney U test were used for categorical and continuous variables, respectively (SPSS v. 27, IBM, Armonk, NY, USA).

Survival endpoints included overall survival (OS: death from any cause), progression-free survival (PFS: relapse at any site or death), local progression-free survival (LPFS: local recurrence or death), and locoregional control (LRC: relapse within local or regional boundaries). Time-to-event analyses were calculated from the first SBRT session. Cox proportional hazards models were computed in SPSS (v. 27), and Kaplan-Meier estimates with log-rank tests were produced using KMWin v. 1.53 [20]. Significance was set at $p < 0.05$.

Motion-management cohort

For the 35 centrally located NSCLC patients receiving SBRT, the IRV framework was retrospectively applied to the existing plans without modifying optimization steps. Structures—including the bronchial tree, trachea, esophagus, and spinal canal—were contoured on all 10 respiratory phases of the 4D-CT and on the average intensity projection (AIP). Delineation followed Radiation Therapy Oncology Group conventions [21].

The bronchial tree definition incorporated the distal 2 cm of the trachea, the carina, major bronchi, upper-lobe bronchi, bronchus intermedius, middle-lobe bronchus, lingular bronchus, and lower-lobe bronchi [21]. The trachea was segmented from the inferior laryngeal margin to its junction with the bronchial tree. The esophagus was drawn from the region beneath the cricoid ring to the gastroesophageal junction [21]. The spinal canal contours were based on adjacent osseous structures and spanned thoracic vertebrae 1 through 12. Contours from all respiratory phases were transferred to the AIP dataset to generate the IRV for each organ.

Our objective was to determine which patients experienced a clinically important rise in NTCP values once the IRV methodology was applied retrospectively (i.e., without performing a new treatment optimization). The initial

step involved identifying cases in which D1%, D2%, or the maximum dose (Dmax) to an OAR exceeded that of its IRV on the AIP CT scan by more than 5 Gy for the bronchial tree, trachea, or esophagus, or by more than 0.5 Gy for the spinal canal. For individuals exceeding these thresholds, NTCPs were determined for each OAR alongside its IRV. Computations for the spinal canal and esophagus were carried out with the Lyman-Kutcher-Burman model implemented in RADBIOMOD (version 0.3b) [22]. Because NTCP information for the trachea and bronchial tree is scarce, risk estimates were taken from the probability models of Dujim *et al*. [23]. These structures required calculating the maximal EQD2 (normalized to 2-Gy fractions, $\alpha/\beta = 3$) and mapping this to the reported NTCP values for any radiographic toxicity grade in the lobar bronchi [23]. Prior publications dealing with proximal bronchial tree injury used a nearly identical strategy [24].

For evaluating motion-related effects, we compared OAR volumes on the AIP CT with the IRVs created from the same dataset. We also assessed positional displacement. The geometric centers (x, y, z) for each OAR were recorded across all respiratory phases as well as for the AIP dataset; the offsets between these centers and the IRV center on the AIP CT were computed. The largest center-to-center deviation per OAR was used for statistical analysis. Possible links between patient characteristics (such as height) and either volume changes or centroid distances were tested with the Mann-Whitney U method and Spearman's rank correlation (SPSS v27, IBM, Armonk, NY, USA). A p-value < 0.05 signified statistical significance.

Results and Discussion

Clinical and SBRT parameters in central vs. peripheral lesions

We examined differences between tumors close to major OARs (defined as ≤2 cm from the central airways, spinal canal, or esophagus) and those located farther away (>2 cm). Patients with peripheral tumors received substantially higher biologically effective doses (BED, $\alpha/\beta = 10$ Gy), with a median of 115.5 Gy versus 105 Gy in the central-tumor group ($p = 0.001$). BED values below 100 Gy were delivered more often in central cases (27.3%) than peripheral ones (5.4%) ($p = 0.006$). Planning target volumes were larger for central tumors ($p = 0.046$). All lung-GTV dose metrics (mean lung dose, V5Gy, V20Gy) were increased in individuals with centrally situated tumors (each $p < 0.05$). Two patients did not finish SBRT (central: 7.5/60 Gy; peripheral: 52.5/60 Gy). Details are summarized in **Table 1**.

Table 1. Comparison of SBRT and clinical variables for centrally and peripherally positioned tumors (distance to OARs ≤2 cm vs. >2 cm). ECOG = Eastern Cooperative Oncology Group; UICC = Union Internationale Contre le Cancer, 8th edition; VMAT = volumetric modulated arc therapy; IMRT = intensity-modulated radiotherapy; 3DCRT = 3D conformal radiotherapy; GTV = gross tumor volume. Unless indicated otherwise, values represent patient counts and percentages.

Parameter	Central Tumors (n = 22 Patients)	Peripheral Tumors (n = 56 Patients)	p-Value
Gender			0.32[4]
Male	16 (72.7)	34 (60.7)	
Female	6 (27.3)	22 (39.3)	
ECOG (median, min-max)	1 (0-2)	1 (0-4)	0.3[5]
UICC stages[1]			0.96[4]
I	17 (77.3)	43 (76.8)	
II-III	5 (22.7)	13 (23.2)	
Planned dose[1] [Gy, median, min-max]	60 (44-60)	55 (54-60)	0.28[5]
Planned fractions[1, 2] (median, min-max)	8 (3-18)	5 (3-18)	0.002[5]
Planned dose[1] [BED, α/β = 10 Gy, median, min-max]	105 (68.2-151.2)	115.5 (70.2-151.2)	0.001[5]
Applied dose[1] [BED, α/β = 10 Gy, median, min-max]	105 (13.13-151.2)	115.5 (70.2-151.2)	0.001[5]
Applied dose < 100 Gy[1] [BED, α/β = 10 Gy]	6 (27.3)	3 (5.4)	0.006[4]
Radiotherapy technique[1]			0.83[4]
VMAT/IMRT	20 (90.9)	50 (89.3)	
3DCRT	2 (9.1)	6 (10.7)	

GTV volume[1] [cm³, median, min-max]	32.55 (2.7-141.9)	14.8 (1.4-119.4)	0.17[5]
PTV volume[1] [cm³, median, min-max]	90.26 (11.9-244.9)	45.0 (12.8-329.8)	0.046[5]
Lungs-GTV[1], Dmean [Gy]	5.8 (1.24-11.3)	3.7 (1.7-10.5)	0.009[5]
Lungs-GTV[1], V5Gy [%]	26.9 (4.9-56.2)	17.3 (5.9-49.9)	0.003[5]
Lungs-GTV[1], V20Gy [%]	8.0 (0-15.6)	5.5 (2.0-18.7)	0.02[5]
Pneumonitis[3]	5 (22.7)	12 (21.4)	0.90[4]

1. One individual underwent SBRT for two tumors at the same time—44 Gy in 8 fractions for a central lesion and 55 Gy in 5 fractions for a peripheral one—and was categorized in the central group [18]. Tumor stages were cT1a and cT1b (both listed as UICC stage I). Dosimetry and GTV/PTV data from the central lesion were used for analysis. Both tumors were treated with VMAT, and lung-GTV assessment used the composite dose of both plans.
2. Because this part of the research dealt primarily with clinical outcomes, three patients treated in 18 fractions were retained [18], even though current definitions cap SBRT at 12 fractions [11, 18].
3. Pneumonitis grading: 9 cases of grade 1, 6 cases of grade 2, and 2 cases of grade 3.
4. Pearson's χ^2 test.
5. Mann-Whitney U test.

Across all 78 participants, the 2-year overall survival rate was 56.8%. Local recurrence occurred in four patients, regional relapse in five, and distant progression in ten. Median follow-up measured 18.5 months (range 0.6-65.5 months). At the last observation, 36 of 78 individuals (46.2%) remained alive. Death was recorded in 42 of 78 (53.8%), although the cause was unknown in 35 of those 42 (83.3%). Among the seven cases with an identified cause (16.7%), two were attributed to tumor progression, one to pneumonitis, one to a pulmonary infection, one to exacerbated COPD, one to a hemorrhagic intracranial mass (possible metastasis or vascular/ischemic origin), and one to pancreatitis.

Outcome comparisons showed inferior local-regional control for central tumors (2-year LRC: 64.8% vs. 94.4%; log-rank p = 0.0051; **(Figure 2)**). Analyzing the relevant OAR-specific endpoints revealed that the central airways demonstrated worse PFS, LPFS **(Figure 3)**, and LRC, and the esophagus showed poorer OS, PFS, LPFS, and LRC. No significant differences were seen for the spinal canal.

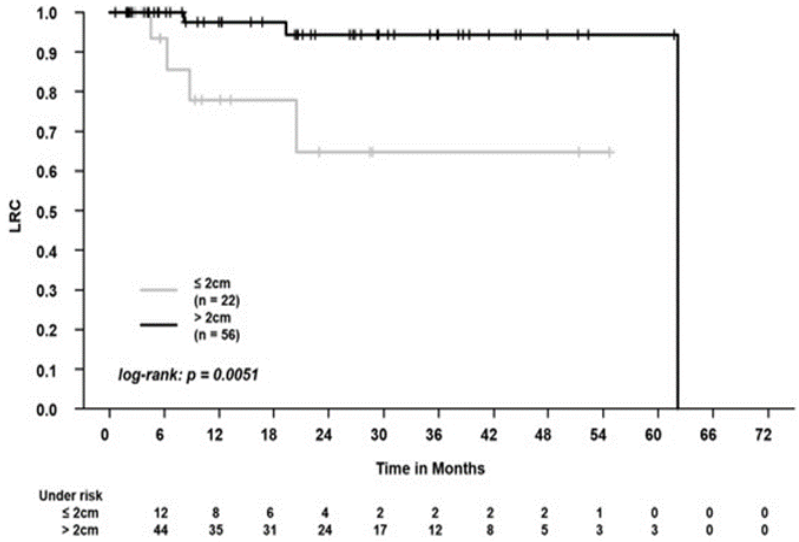


Figure 2. Locoregional control (LRC) outcomes for tumors situated ≤2 cm vs. >2 cm from major thoracic OARs (central airways, spinal canal, esophagus). At 2 years, LRC measured 64.8% for centrally located lesions and 94.4% **for peripheral ones.**

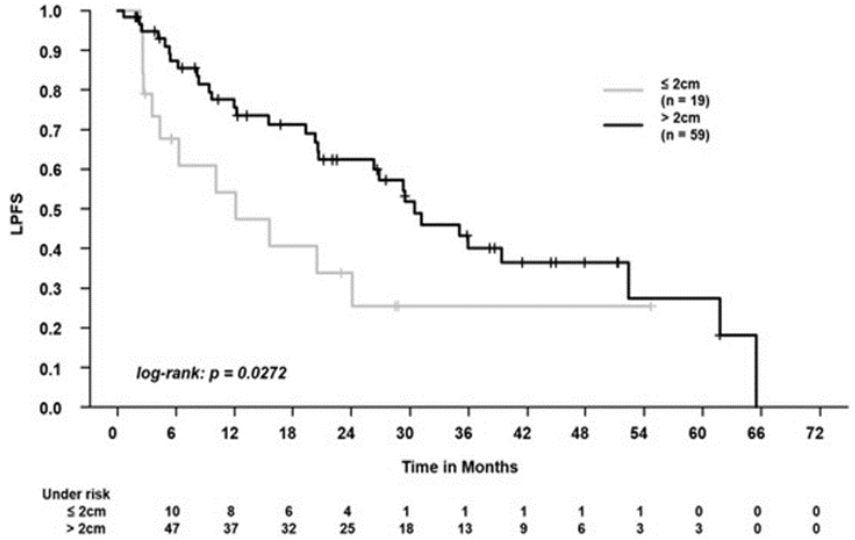


Figure 3. Locoregional progression-free survival (LPFS) for tumors positioned ≤2 cm vs. >2 cm relative to the central airways. The corresponding 2-year LPFS rates were 33.8% and 62.4%.

Magnitude of organ motion and associated volume findings

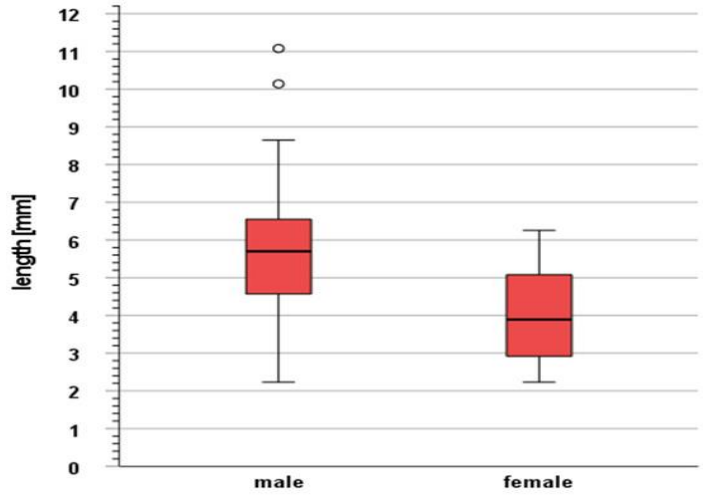
Motion-related assessments were carried out in a cohort of 35 patients with centrally positioned tumors. Mean values for the group are reported. The largest deviations between the centroid of each OAR across respiratory phases and its IRV centroid on the AIP CT were 5.2 mm (bronchial tree), 4.2 mm (trachea), 5.5 mm (esophagus), and 4.3 mm (spinal canal). Corresponding absolute OAR-IRV volume discrepancies were 22.0 cm^3, 7.8 cm^3, 19.6 cm^3, and 8.2 cm^3, respectively. Full metrics are provided in **Table 2**.

Table 2. Amplitudes of movement and volume shifts: comparison of OAR volumes across all respiratory phases with the IRV volumes derived from the AIP CT. Data are presented as mean values along with minimum and maximum observations.

Parameter	Bronchial Tree	Trachea	Esophagus	Spinal Canal
Maximum difference in geometric centers, OAR (each respiratory phase), and IRV on AIP CT scan [mm]	5.2 (2.2-11.1)	4.2 (1.4-14.6)	5.5 (2.0-13.2)	4.3 (1.5-9.7)
OAR volumes on AIP CT scan [cm^3]	54.4 (34.7-85.4)	40.5 (22.3-57.2)	42.0 (25.7-74.2)	57.2 (33.5-90.0)
IRV volumes on AIP CT scan [cm^3]	76.4 (46.8-116.1)	48.3 (27.2-75.7)	61.5 (37.4-103.9)	65.4 (48.9-88.7)
Absolute difference, IRV-OAR volume [cm^3]	22.0 (10.5-35.5)	7.8 (2.7-18.8)	19.6 (11.4-33.7)	8.2 (−1.3-20.2)
Relative difference, IRV-OAR volume [%]	40.9 (26.9-60.4)	19.4 (6.6-53.5)	47.5 (25.4-91.4)	16.1 (−1.4-57.4)

Effect of patient-specific variables on motion and volume alterations

We further explored whether characteristics such as age, sex, stature, weight, and BMI influenced motion amplitudes or volume changes in the same 35-patient group. Only parameters showing statistically significant associations are illustrated in **Figures 4a-4c**. Male individuals exhibited larger displacement magnitudes of the bronchial tree **(Figure 4a)**. Increased height (cut-off at the median of 1.68 m) was also linked to greater movement **(Figure 4b)**. In contrast, patients with higher BMI (>25 kg/m^2) demonstrated smaller esophageal volume differences **(Figure 4c)**.



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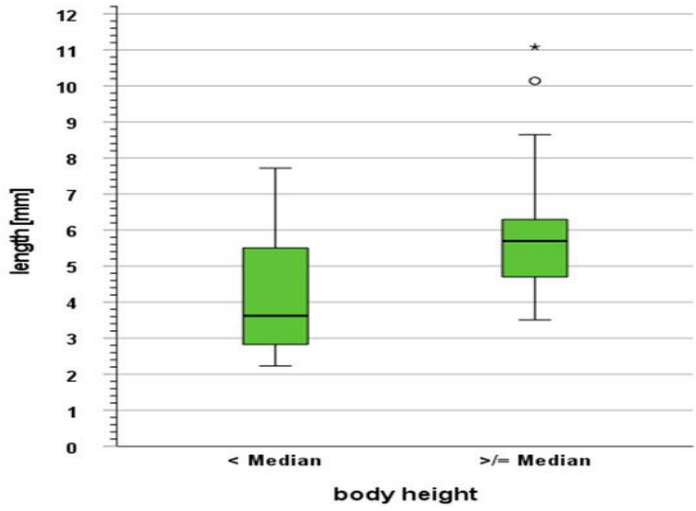

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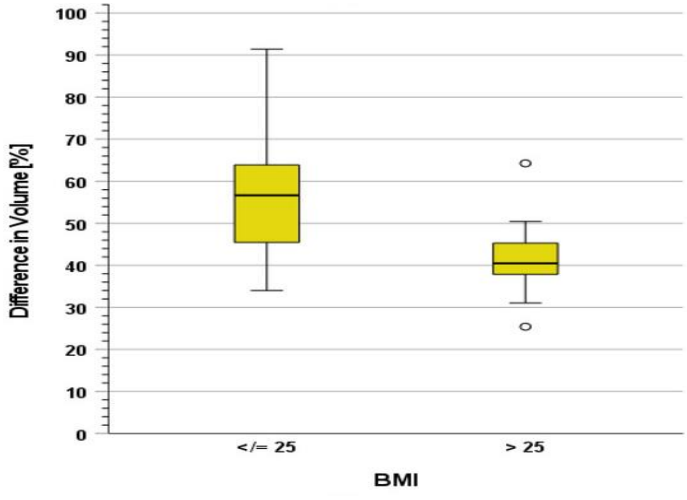

c)

Figure 4. (a) Gender-related differences in bronchial tree motion (median: 5.7 mm in men vs. 3.9 mm in women; $p < 0.05$; 21 males, 14 females). (b) Height-related effect on bronchial tree displacement (median: 5.7 mm vs. 3.6 mm; $p < 0.05$; 16 shorter vs. 19 taller patients based on the 1.68 m median). Values >3× IQR outside quartiles are marked. (c) BMI influence on esophageal volume differences, comparing OAR with IRV. Higher BMI was associated with reduced volume variation (56.7% vs. 40.5%; $p < 0.05$; 13 patients with BMI ≤25 kg/m² vs. 22 with BMI >25 kg/m²).

Impact of the IRV method on NTCP estimates

Our goal in this section was to identify, among the 35 centrally located tumor cases, those with a clinically meaningful rise in NTCP values when the IRV approach was used retroactively (without altering the original plan). Twelve patients met the predefined thresholds for dose escalation between OAR and IRV (see Section 2.3.2 and). NTCPs were then derived for both sets of structures **(Table 3)**. Across these individuals, the mean absolute NTCP increase was 5.5% (range 0-22.5%), while the mean relative increase reached 54.78% (range 0-181%). An example illustrating respiratory-driven positional shifts and dose changes is shown in **Figure 5**.

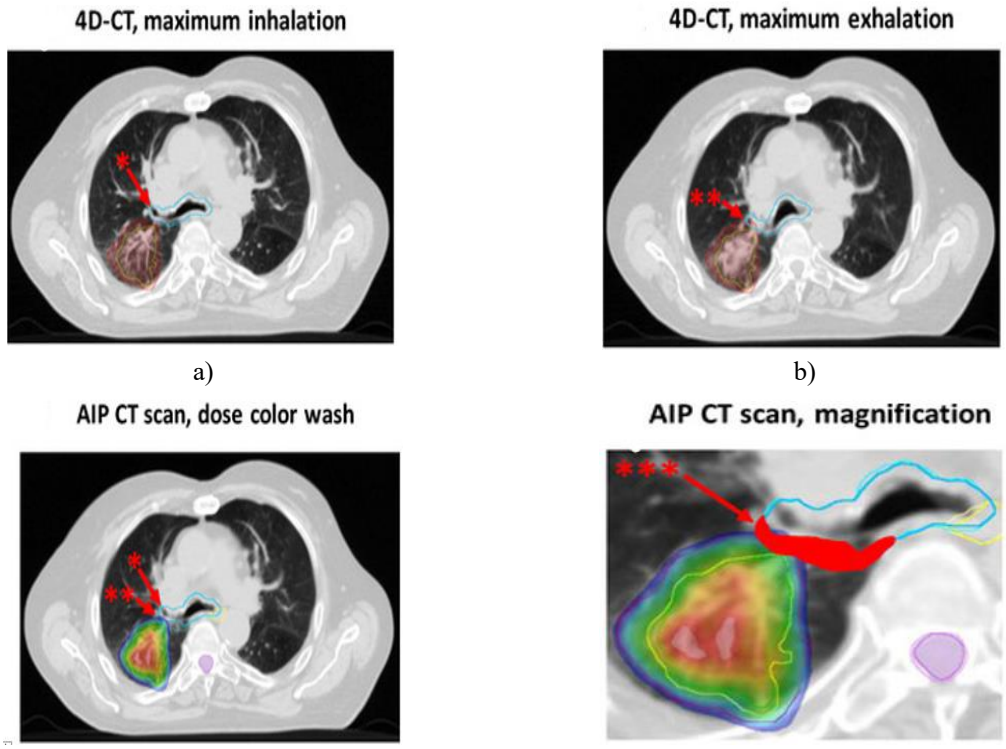

Figure 5. Visualization of breathing-related bronchial tree motion for a patient with stage IIA right-upper-lobe adenocarcinoma. SBRT was delivered as 60 Gy in 8 fractions to the 80% isodose using VMAT. Panels A and B show the 4D-CT slices at maximal inspiration and expiration. Panel C (AIP CT) displays the 60-75 Gy dose region (blue to red) along with bronchial tree contours (turquoise). Panel D magnifies the OAR-IRV volume difference. The GTV lay 3 mm from the bronchial tree. The bronchial tree volume measured 59.0 cm^3, compared with an IRV of 94.4 cm^3 (a 35.5 cm^3 increase; +60%). The maximum centroid shift between the two structures was 10.1 mm. Dmax increased by 8.4 Gy (62.9 Gy for the OAR vs. 71.2 Gy for the IRV). The rise in NTCP was 11.5% (relative increase 44.2%).

Table 3. NTCP differences for OARs versus IRVs. NTCPs for the bronchial tree and trachea were derived from EQD2-based maximum dose curves reported by Dujim *et al*. [23]. NTCP estimates for the esophagus and spinal canal were obtained via RADBIOMOD using the Lyman-Kutcher-Burman formulation (see Section 2.3.2).

Patient No.	Distance between Tumor and Structure [cm]	NTCP of OAR [%]	NTCP of IRV [%]	NTCP, Absolute Increase [%]	NTCP, Relative Increase [%]
Bronchial Tree					
1	1.4	17.0	34.0	17.0	100.0
2	0.0	63.0	66.0	3.0	4.8
3	0.3	26.0	37.5	11.5	44.2
4	0.0	23.0	32.0	9.0	39.1
5	0.0	45.0	48.0	3.0	6.7
6	1.1	35.5	58.0	22.5	63.4
Esophagus					

3	2.4	2.1	5.9	3.8	181.0
7	0.3	1.5	4.0	2.5	166.7
Spinal Canal					
1	2.2	0.0	0.0	0.0	0.0
8	1.8	<0.01	<0.01	0.0	0.0
9	4.1	<0.01	<0.01	0.0	0.0
Trachea					
6	4.1	4.0	5.0	1.0	25.0
10	1.2	4.0	10.5	6.5	162.5
11	3.5	4.5	5.5	1.0	22.2
12	1.0	24.5	26.0	1.5	6.1

SBRT is known to achieve strong local disease control for early-stage NSCLC, particularly in individuals who are elderly or decline operative management [2]. However, notable toxicities may arise, especially when tumors lie close to central thoracic structures [10, 25]. Earlier investigations proposed that incorporating PRV/IRV-based approaches could help reduce adverse effects [13-15]. In the study by Nardone *et al*. use of the IRV methodology in SBRT for NSCLC revealed that 42% of treatment plans became unacceptable once motion was integrated into the evaluation [15]. The objectives of the present analysis were: (1) to contrast clinical features between central and peripheral lesions, (2) to test the IRV method retrospectively in centrally located cases without reoptimization, (3) to quantify organ displacement, and (4) to investigate the related NTCP outcomes.

Our findings demonstrated that patients with centrally situated tumors received substantially lower median BED values (105 Gy for central vs. 115.5 Gy for peripheral). BED <100 Gy was delivered in 27.3% of central cases compared with 5.4% of peripheral cases. Central tumors were linked to larger PTVs as well as increased pulmonary exposure around the GTV (higher mean dose, V5Gy, and V20Gy). Moreover, LRC was inferior for centrally located disease, with a 2-year LRC of 64.8% compared with 94.4% in peripheral tumors. When evaluating outcomes for individual OARs, poorer control was apparent for the central airways and esophagus, while the spinal canal exhibited no such decline.

These observations align with earlier reports comparing central and peripheral lesions treated with SBRT for early-stage NSCLC. Prior work has described reduced BED (e.g., mean 120.2 vs. 143.5 Gy [5]), increased lesion size (parallel to our findings of greater PTVs, with tumor diameters of mean 1.9 vs. 2.5 cm and medians of 2.6 vs. 3.1 cm in peripheral vs. central tumors [5, 26]), higher pulmonary dose metrics (V5Gy, V20Gy [27]), and diminished local control (freedom from progression 52% for central vs. 84% for peripheral [26]). Additionally, other researchers showed that achieving a BED10Gy ≥100 Gy correlates with better local control, while dose escalation enhances both tumor control/overall survival and complication risks [28]. Consistent with this, the present cohort with central tumors more often received BED10Gy <100 Gy and consequently demonstrated poorer LRC.

Overall, the tendency in routine practice to anticipate higher complication rates in central tumors often results in suboptimal dose levels and compromised outcomes [26]. Despite these concerns, earlier studies have reported relatively low frequencies of ≥grade 3 or higher acute toxicity [5] and limited overall adverse event rates [26] in central lesions. Determining how to optimize tumor dose while avoiding injury—especially to the central airway structures [25]—continues to be a complex and debated topic [29]. In this context, motion-management techniques remain crucial [11]. When dedicated motion-control options are unavailable or unsuitable, reliance on 4D-CT, internal motion assessment, and safety margins becomes necessary [11]. Nonetheless, information describing the internal displacement of central thoracic OARs during SBRT for early-stage NSCLC is sparse (e.g., [15]).

Using the IRV framework retrospectively (without re-planning), we identified mean maximum shifts of the geometric center of 4.2 mm (trachea), 4.3 mm (spinal canal), 5.2 mm (bronchial tree), and 5.5 mm (esophagus). Mean relative volume increases (IRV-OAR) amounted to 16.1% for the spinal canal, 19.4% for the trachea, 40.9% for the bronchial tree, and 47.5% for the esophagus. Bronchial tree displacement was more pronounced in male and taller patients, whereas esophageal volume differences (IRV-OAR) were smaller in those with elevated BMI.

Only limited published work has quantified the movement of these thoracic structures. When juxtaposing our findings with Nardone *et al*. [15], both datasets suggest meaningful IRV-OAR discrepancies. Their reported differences were 4% (spinal cord), 23% (trachea), and 25% (esophagus); for the proximal bronchial tree, the absolute disparity was 18 cm^3 vs. 26 cm^3 (relative difference not listed but likely ~44%) [15]. Zhang *et al*. also

employed an IRV approach for thoracic and abdominal regions, but the central OARs evaluated in our study (bronchial tree, trachea, esophagus, spinal canal) were not assessed in that work [16]. To our knowledge, potential associations between patient-specific factors and thoracic organ movement or volume variation have not been documented previously. Such investigations appear relevant, considering studies linking greater toxicity risks in SBRT-treated NSCLC to variables such as female sex (higher pneumonitis risk [30]) or obesity (greater likelihood of chest wall pain [31]). Taken together, our results suggest that organ mobility may be accentuated in taller or male individuals and attenuated in patients with higher BMI. These patterns could influence how risk-adapted motion strategies or toxicity surveillance are implemented.

In the comparison of OARs with their corresponding IRVs, a noticeable rise in key dose metrics (D1%, D2%, Dmax) was identified in 12 of the 35 centrally located tumor cases (34.3%). In the work of Nardone *et al*. 42% of treatment plans were deemed unsuitable, and in that cohort, 63% of the tumors were situated centrally [15]. Taken together, these observations show that incorporating the IRV method can substantially alter dosimetric values and may reshape radiotherapy plans. Within the subgroup of 12 affected patients in our analysis, the mean absolute increase in NTCP was 5.5% (ranging from 0 to 22.5%), while the average proportional increase reached 54.78% (0-181%). An absolute rise in NTCP of 10% or greater is likely to be of clinical significance. This threshold was exceeded in three individuals, all of whom had tumors located 0.3-1.4 cm from the bronchial tree.

Regarding complications in SBRT for centrally positioned disease, larger prospective investigations have repeatedly highlighted the bronchial tree as a critical risk region (e.g., in the report by Lindberg *et al*. 8 of 10 treatment-related fatalities were attributed to bronchopulmonary hemorrhage [25]). The zone within approximately 2 cm of the proximal bronchial tree is widely considered a high-risk area ("no-fly zone") because of the elevated probability of severe toxicity [10, 32]. Some studies have subdivided this region further by looking at tumors situated very near the bronchial tree (≤1 cm) [33]. More recently, Lindberg *et al*. refined toxicity-related predictors by evaluating dose exposure to individual airway components such as mainstem, intermediate, and lobar bronchi [34]. In our cohort, applying the IRV approach revealed NTCP increases ≥10% in three patients whose tumors were only 0.3-1.4 cm from the bronchial tree. This suggests that when working with extremely small margins or sub-segmental structures, motion-related considerations—potentially via the IRV framework—should be prioritized. Nevertheless, as noted by Noël *et al*. (2022), although the PRV methodology has existed since 2006, there remains no standardized definition, rationale, or dose-constraint consensus [14, 35]. Research specifically examining IRV use for thoracic OARs is scarce but may contribute to better awareness of OAR movement in SBRT, echoing Galileo's remark, "and yet it moves" [15, 16, 36]. A notable recent advancement is the adoption of MRI-guided linear accelerators, enabling real-time motion visualization (four-dimensional MRI, 4D-MRI) [37]. Evidence indicates that 4D-MRI may enhance lung tumor contouring and motion estimation and may be more stable across treatment sessions than 4D-CT-based methods [37]. While prior studies have presented findings on 4D-MRI for targets [37], far fewer have examined thoracic OARs [38]. Consequently, for central lung tumors requiring motion-sensitive SBRT, 4D-MRI represents a promising tool for achieving a safer balance between toxicity avoidance and tumor dose coverage [39].

Conclusion

The IRV methodology has been proposed as a means to improve toxicity outcomes in SBRT for NSCLC [13-15]. In this project, we evaluated (1) clinical distinctions between central and peripheral lesions, (2) the feasibility of applying the IRV approach in centrally located tumors, (3) movement patterns of thoracic organs, and (4) the resulting NTCP implications. Centrally located disease was associated with lower biologically effective doses, larger PTVs, increased pulmonary exposure, and inferior locoregional control. These results underscore the challenge of achieving effective dose escalation in central tumors while limiting toxicity. Organ displacement was more pronounced in male and taller individuals (specifically involving the bronchial tree), whereas volume alterations were smaller in patients with higher BMI (notably for the esophagus). Such differences may support personalized motion-management strategies or more tailored toxicity monitoring. Applying the IRV technique retrospectively (without plan re-optimization) revealed NTCP increases exceeding 10% for the bronchial tree in three patients whose tumors lay 0.3-1.4 cm from that structure. Recent literature has attempted to subdivide the central "no-fly zone" using exact distances or by analyzing specific airway subunits (e.g., mainstem, intermediate, and lobar bronchi) [33, 34]. Based on our observed NTCP elevations, the introduction of motion-management

considerations—potentially through IRV analysis—may be particularly relevant when dealing with such narrowly defined or highly localized anatomical regions.

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