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RESEARCH ARTICLE

Precision in Motion: The Dosimetric Edge of Adaptive Radiotherapy for Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Introduction: To evaluate the dosimetric advantages of adaptive radiotherapy (ART) in patients with inoperable Stage II–III non-small cell lung cancer (NSCLC), focusing on changes in target volumes and sparing of organs at risk (OARs) after mid-treatment re-planning. Settings and Design: This prospective, single-institution dosimetric study included patients treated with intensity-modulated radiotherapy (IMRT) between December 2023 and January 2025. **Materials and Methods:** Twenty-five patients with histologically confirmed NSCLC unsuitable for surgery underwent initial and mid-treatment planning using 4D-CT. IMRT plans were generated using Monaco® TPS, and re-planning was performed after 40 Gy based on updated tumor and OAR contours. Adaptive plans were implemented for treatment continuation. Paired t-tests evaluated changes in gross tumor volume (GTV) and planning target volume (PTV). Wilcoxon signed-rank tests assessed differences in dose–volume histogram (DVH) parameters between initial and adaptive plans. A p-value <0.05 was considered statistically significant. **Results:** Significant reductions in tumor volumes were observed post 40 Gy. Median primary GTV decreased by 40% (p = 0.001), nodal GTV by 52.3% (p = 0.001), and PTV by 36.2% (p = 0.001). ART led to substantial OAR sparing: ipsilateral lung V20 decreased by 49.6%, heart V5 by 45.5%, and mean esophageal dose by 24.5% (all p = 0.001). **Conclusion:** Adaptive radiotherapy offers significant dosimetric benefits in NSCLC by reducing radiation exposure to critical structures without compromising target coverage. These findings support broader clinical adoption of ART in medically inoperable NSCLC patients.

Keywords: Adaptive radiotherapy- non-small cell lung cancer- Intensity modulated radiotherapy

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Introduction

In 2022, lung cancer accounted for an incidence of 2.5 million, or one in 8 cancers worldwide (12.4%), making it the most commonly diagnosed disease as per GLOBOCAN 2022 [1]. Chemoradiotherapy is the treatment of choice in advanced stage and also early stage which is non operable due to medical reasons. In the majority of instances, the disease is unresectable at the time of diagnosis because it has either locally progressed or spread [2]. Numerous dosage intensification studies have documented improved local control along with greater survival and independence from recurrence [3, 4]. However, owing to increase normal tissue toxicity with increasing dose, RTOG 0617 differs in its opinion on dose escalation [5]. The 3-5 year survival rate increases by 1% and the risk of mortality decreases by 3% for every 1Gy increase in dosage as seen by Belderbos et al [4]. However, dose escalation comes with the risk of increased normal tissue toxicity. In an attempt to balance both, comes the concept of adaptive radiotherapy (ART) in carcinoma lung.

As it is known that tumour volumes diminish during radiotherapy [6, 7], so if the concept of ART is followed, this provides us with the window to balance dose escalation and achieve desirable organ at risk (OAR) doses. In patients in whom the tumor shrinkage was more than 30%, replanning improved the therapeutic ratio [8]. Also it has been seen that V20 and mean lung dose

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correspond with the occurrence of radiation pneumonitis [9], which is a major dose restricting toxicity in lung cancer patients. Advancements in radiotherapy techniques such as Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), and Stereotactic Body Radiotherapy (SBRT) have significantly improved the ability to deliver high radiation doses to tumor volumes while minimizing exposure to surrounding healthy tissues. Building upon these innovations, ART offers a dynamic treatment approach by enabling plan modifications in response to anatomical or physiological changes occurring during the course of treatment. The purpose of this study is to evaluate the dosimetric advantages of ART in lung cancer patients, with a specific focus on its impact on target volume coverage, sparing of OARs, and overall treatment plan quality in comparison to conventional non-adaptive radiotherapy techniques.

Materials and Methods

Between December 2023 and January 2025, a cohort of 25 patients with histologically confirmed non-small cell lung cancer (NSCLC), either inoperable early-stage (Stage II) or advanced-stage (Stage III), were enrolled in this study (Institutional Ethical Committee of Dr. RPGMC- No: IEC/108/2025). These patients were considered unsuitable for surgery due to comorbid conditions, making chemoradiotherapy the primary treatment approach.

Additional inclusion criteria comprised an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, no prior treatment for NSCLC (including surgery, chemotherapy, radiotherapy, targeted therapy, or immunotherapy), adequate baseline organ function (hemoglobin ≥ 9.0 g/dL, absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, serum creatinine ≤ 1.5 × upper limit of normal [ULN] or creatinine clearance ≥ 50 mL/min, AST and ALT ≤ 2.5 × ULN, and total bilirubin ≤ 1.5 × ULN), and the ability to provide written informed consent. Patients were excluded if they had a history of another malignancy within the preceding five years, evidence of metastatic (Stage IV) disease at diagnosis, prior lung cancer–directed therapy, uncontrolled comorbid conditions (including unstable angina or myocardial infarction within six months, uncontrolled hypertension or diabetes, or severe chronic obstructive pulmonary disease not amenable to chemoradiotherapy), pregnancy or lactation, or any psychological, familial, sociological, or geographical factors that could potentially compromise adherence to the study protocol.

Each patient underwent a contrast-enhanced computed tomography (CECT) scan for radiotherapy planning, with a follow-up scan performed after receiving 40 Gy over 20 fractions. All scans were acquired using 4-dimensional computed tomography (4D-CT) and imported into the FOCAL® SIM v. 4.64 (Elekta) contouring system via DICOM protocol. Where available, staging PET-CECT images were fused with planning CTs to improve anatomical and metabolic delineation. Gross tumor volume (GTV) was defined as seen on the radiological images inclusive of the necrotic tumor areas. Lymph nodes were classified as involved based on a short-axis diameter >10 mm or significant FDG uptake. GTV was further classified as GTV-P (primary tumor) and GTV-N (nodal involvement). Clinical target volume (CTV) included a 6–8 mm expansion around the GTV in all directions. Internal Target Volume (ITV) was defined by contouring all images of the 4DCT scan, to account for respiratory motion. Planning target volume (PTV) was created with a uniform 5 mm margin around the CTV. Elective nodal irradiation was not performed. For the re-planning scan, both target and OAR structures were re-contoured to accommodate tumor response. OAR contoured included the lungs (ipsilateral and contralateral), heart, esophagus, and spinal cord.

Treatment planning was conducted using Monaco® v. 3.0 (Elekta, Crawley, UK) with IMRT plans consisting of 5-7 coplanar 6 MV photon beams. Beam orientations were selected to minimize normal tissue exposure while avoiding mechanical collisions. Monte Carlo-based optimization was used to achieve a plan where at least 95% of the prescribed dose covered the PTV, respecting dose constraints to normal tissues.

The dose constraints were defined for both Phase I and Phase II of treatment. In Phase I, the constraints were as follows: the ipsilateral lung (excluding the PTV) was limited to a V20 of less than 20% and a V15 of less than 30%; the contralateral lung had a V5 constraint of less than 20%; the mean dose to both lungs were restricted to under 9 Gy. Additionally, the heart was limited to a V15 of less than 20%, the maximum dose to the spinal cord was capped at 35 Gy, and the mean dose to the oesophagus was kept below 25 Gy. For Phase II, the dose constraints were further reduced to account for cumulative exposure: the ipsilateral lung (excluding the PTV) had V10 and V5 constraints of less than 20% and 30%, respectively; the contralateral lung V5 was limited to below 10%; the combined mean lung dose was restricted to under 4 Gy. The heart was limited to a V5 of less than 20%, the spinal cord maximum dose was limited to 10 Gy, and the mean oesophageal dose was kept below 10 Gy. For acceptance of the Phase II treatment plans, cumulative dose constraints were also considered: the lung outside the PTV was required to have a V20 of less than 35%, the heart V20 had to remain below 20%, and the maximum spinal cord dose at any point was not to exceed 45 Gy keeping in compliance with the QUANTEC dose constraints [10].

Initial IMRT plans for Phase I delivered 40 Gy to the initial PTV. Phase II plans were developed on both initial and mid-treatment scan datasets (Plan 1 and Plan 2, respectively), with patients ultimately treated according to Plan 2. The mid-treatment scan was co-registered with the initial scan in Monaco using multiple anatomical landmarks, including the lung apices, aortic arch, spine, heart, carina, sternum, diaphragm, and tumor. The FOCAL SIM platform's Auto Fusion algorithm, guided by mutual information within a region of interest, was used to ensure optimal alignment. All co-registrations were performed by a radiation oncologist, with verification by three experienced readers. Dosimetric comparisons focused

on reductions in radiation exposure to the ipsilateral lung PTV, lungs, heart (V5, V20, Dmean), esophagus (Dmean), and spinal cord (Dmax and D2%). For setup verification, X-ray volume imaging (XVI) was employed during the first three treatment sessions and subsequently on a weekly basis. All patient received concurrent chemotherapy with Paclitaxel 50mg/m^2 Carboplation at the rate of 2 AUC.

Data collection and statistical analysis

GTV and PTV volumes were quantified before and after 40 Gy using FOCAL SIM. Statistical analysis was conducted with SPSS® v. 20.0 (SPSS Inc., Chicago, IL). Paired t-tests evaluated changes in target volumes, while Wilcoxon signed-rank tests were applied to dose–volume histogram (DVH) parameters comparing Phase II plans (Plan 1 vs. Plan 2). A p-value of less than 0.05 was considered statistically significant.

Results

Patient Demographics and Baseline Characteristics

A total of 25 patients with histologically confirmed NSCLC were enrolled between December 2023 and January 2025. The median age was 66 years (range: 51–75), with a male predominance (92%). Squamous cell carcinoma was the most common histology (72%), followed by adenocarcinoma (28%), likely reflecting the older age profile. Most patients (76%) had Stage III disease, while 24% had Stage II; all were medically inoperable and treated with definitive chemoradiotherapy as shown in Table 1. Nodal involvement was present in 68% of patients. Tumor laterality was nearly equal, with 52% right-sided and 48% left-sided tumors. This cohort reflects a typical population considered for adaptive radiotherapy in advanced, unresectable NSCLC.

Tumor Volume Changes During Treatment

Significant reductions in tumor volumes were observed following mid-treatment re-evaluation after 40 Gy as shown in Figure 1 and 2. The mean GTV of the primary lesion decreased from 183.30 cm³ (min-max: 55.72–384.0 cm³) at baseline to 107.84cm³ (min-max: 33–225.86 cm³) mid-treatment, representing a mean reduction of 42.22% (min-max: 2.42–81.40%; p = 0.001). Similarly, the nodal GTV demonstrated a substantial decline from a pre-treatment mean of 14.01cm³ (min-max: 0.00–31.34 cm³) to 6.57 cm³ (min-max: 0.00–13.23 cm³), yielding a mean reduction of 50.74% (min-max: 33.33–70.22%; p = 0.001). The PTV also showed a statistically significant decrease, from a mean of 390.22 cm³ (min-max: 160.23–700.34 cm³) before treatment to 264.15 cm³ (min-max: 97.45–510.67 cm³) after 20 fractions. This corresponds to a mean reduction of 36.20% (min-max: 17.33–45.34%; p = 0.001) as shown in Table 2.

Dose Variation Between Pre-treatment and Mid-treatment Plans of OARs

Ipsilateral Lung

The V20 (volume of lung receiving ≥20 Gy) showed a substantial decline, with the pre-treatment mean of 204.23 ± 52.22 cm³ (range: 90.0–290.67 cm³) reduced to 102.50 ± 28.40 cm³ (range: 40.0–151.43 cm³) at mid-treatment. This represented a mean reduction of 49.58% (p = 0.001). Similarly, the V5 (volume receiving ≥5 Gy) decreased from 466.86 ± 51.9 cm³ to 348.52 ± 56.06 cm³, a 25.56% reduction (p = 0.001). The mean dose to the ipsilateral lung also dropped significantly from 12.15 ± 1.23 Gy to 8.35 ± 1.53 Gy, accounting for a 31.52% decrease (p = 0.001) as depicted in Table 3.

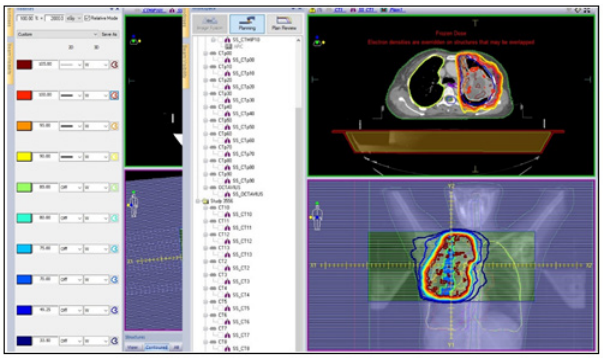

Figure 1. Pre-treatment Dose Distribution

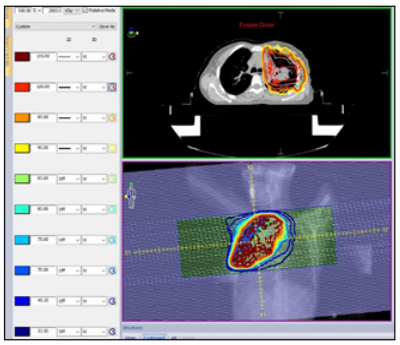

Figure 2. Mid-treatment Dose Distribution.

Table 1. Demographic profile (n=25 patients with non-small cell lung cancer)

Characterstics	N (Percent)
Age (years) [median (range)]	66 (51-75)
Gender	
Male	23 (92)
Female	2 (8)
Histology	
Squamous cell carcinoma	18 (72)
Adenocarcinoma	7 (28)
Composite Stage	
II	6 (24)
III	19 (76)
Nodal involvement	
Yes	17 (68)
No	8 (32)
Laterality of the Tumor	
Right	13 (52)
Left	12 (48)

Table 2. Tumor Volume at Baseline and Mmid-treatment Plan

Delineated structure	Pre-treatment mean ± SD (min-max)	Mid-treatment mean ± SD (min-max)	Mean Reduction (min-max)-percentage {Absolute Reduction cm^3}	p-value	95% Confidence interval
GTV primary (cm^3)	183.30 ± 86.05 (55.72-384.0)	107.84 ± 60.07 (33-225.86)	42.22 (2.42-81.40) {75.45}	0.001	58.568-92.451
GTV nodal (cm^3)	14.01 ± 11.39 (0.00-31.34)	6.57 ± 5.05 (0.00-13.23)	50.74 (33.33-70.22) {10.94}	0.001	4.617-10.266
PTV (cm^3)	390.22 ± 140.68 (160.23-700.34)	264.15 ± 113.75 (97.45-510.67)	33.33 (17.33-45.34) {126.06}	0.001	106.200-145.93

Table 3. DVH Parameters for Plan 1 and Plan 2

Dose parameters	Pre-treatment mean ± S.D. (range)	Mid-treatment mean ± S.D. (range)	Mean reduction (%)	p-value
Ipsilateral lung				
V20 (cm^3)	204.23 ± 52.22 (90-290.67)	102.50 ± 28.40 (40-151.43)	49.58	0.001
V5 (cm^3)	466.86 ± 51.9 (380.0-534.56)	348.52 ± 56.06 (220.0-430.43)	25.56	0.001
Mean (cGy)	12.15 ± 1.23 (9.87-14.91)	8.35 ± 1.53 (5.98-11.43)	31.52	0.001
Heart				
V5 (cm^3)	59.37 ± 19.40 (28.87-91.29)	32.56 ± 11.88 (16.43-53.32)	45.54	0.001
Mean (cGy)	4.54 ± 1.02 (2.56-6.46)	2.36 ± 0.588 (1.65-4.12)	47.23	0.001
Oesophagus				
Mean (cGy)	13.91 ± 4.99 (5.91-24.09)	10.45 ± 3.83 (4.24-17.34)	24.46	0.001

Heart

ART also led to notable heart dose reductions. The heart V5 dropped from a mean of 59.37 ± 19.40 cm^3 (range: 28.87–91.29 cm^3) to 32.56 ± 11.88 cm^3 (range: 16.43–53.32 cm^3), corresponding to a 45.54% reduction (p = 0.001). The mean heart dose was reduced by 47.23%, from 4.54 ± 1.02 Gy to 2.36 ± 0.588 Gy (p = 0.001), demonstrating substantial cardiac sparing.

Esophagus

The mean dose to the esophagus was also significantly reduced with ART. Pre-treatment mean dose was 13.91 ± 4.99 Gy (range: 5.91–24.09 Gy), which decreased to 10.45 ± 3.83 Gy (range: 4.24–17.34 Gy) at mid-treatment. This represented a mean reduction of 24.46% (p = 0.001).

Discussion

One of the main therapeutic options for people with unresectable lung cancer is radiotherapy. Administering an adequate radiation dosage to the tumour while minimising the exposure to OARs is one of the main problems of radiation therapy (RT) for lung cancer. This problem might be made worse by tumour shrinking that occurs throughout the course of therapy [11-13].

The median age in our study was 66 years with majority being male patients. This is in contrast with another study where majority of patients were females [14]. In our study more than 70% population was stage 3 which is similar to other researches in the past [14, 15]. We had more patients with squamous cell carcinoma than adenocarcinoma, likely because more than half of the study population (n = 17) were aged 65 years or older. It has been seen that squamous cell carcinoma is more common than adenocarcinoma in elderly lung cancer patients [16].

In recent years, various efforts have been made to improve the therapeutic ratio. In Thailand, rising incidence and persistently low survival highlighted the need for more effective, accessible therapies [17]. Real-world variability hampers the application of personalized lung cancer treatment. A study by Mandal et al. demonstrated that PET-CT–based radiotherapy planning offers advantages over CT-based planning [18]. However, as PET-CT is not universally available, adaptive radiotherapy (ART) serves as a viable alternative. The main objective of ART for lung cancer is to reduce the amount of normal tissue exposed to radiation. This goal necessitates careful thought and research as marginal recurrences in a moving target are likely. Enhancing target coverage and dosage escalation are two further goals of ART. The exact time when re-planning should be done has not been clearly defined in the literature. We replanned patients after 40Gy/20

fraction RT with median gross tumor reduction of 40% and gross node size reduced by nearly half. Thirty five percent shrinkage after 20 fraction was observed by Ding et al [19]. In their research, Fox et al. (2009) demonstrated median GTV decreased by 44 % at a treatment of 50 Gy and nearly by 30% after 30 Gy [7]. Furthermore, 13 patients treated by Guckenberger et al. (2011) observed continuous tumour reduction of 1.2% each day [6] which was in excellent agreement with the findings of Kupelian's study [20]. Replanning was performed following the delivery of 40 Gy, in alignment with published data indicating that tumor volume reduction of approximately 35–45% typically occurs between 40 and 50 Gy [6, 7, 16]. Initiating replanning prior to this dose may underestimate tumour regression; while postponing it further may reduce the opportunity for improved sparing of adjacent OARs.

Adverse events increase as dosage increases but decrease as radiation volume decreases. Diminished radiation field made it possible to use contemporary methods to accomplish significant dose escalation without increasing the incidence of these problems over tolerable levels [6]. Because normal tissues surpass their limitations, a comparable dosage to target volume in phase 2 would have been limited in the current investigation. Therefore, it was believed that tumour reduction as assessed by second planning CT during RT would help to save vulnerable organs and enhance the chances of dosage escalation. The same was also proposed by Gillham [21]. We observed that the mean lung doses reduced by 31.5% while the mean V20 and V5 reduction of 49.6% and 25.56% was seen, and all were statistically significant. This was similar to the study was Kataria et al [15]. However, in their investigation, Spoelstra et al.25 found no discernible changes in lung doses when replanned after 30 Gy [22]. Though re-planning was done twice using 3D-CRT, it only managed to achieve a dose drop of less than 10% [6]. This emphasises on the fact that both the timing and technique of re-planning is crucial for the desired results. Also motion management plays a significant role. We used 4DCT to generate the ITV, thus reducing the chances of missing the target in the process of sparing the normal tissue. Mean heart dose reduction in our study was more than 45% and that to the esophagus was 24%. However, we believe that the reduction in heart and esophagus dose is not solely attributable to adaptive radiotherapy; other factors, such as tumor location, also play a significant role in determining the outcome. Also, it has been seen that cardiac toxicity is influenced not only by the location of the lung tumor but also by the specific cardiac substructures irradiated. Radiation dose to the superior vena cava, right atrium, aortic root, left main coronary artery, and proximal segments of the left anterior descending and right coronary arteries has been associated with increased risk of cardiac events and mortality [23].

Repeated planning, simulation, and offline quality assurance in ART are time-consuming processes. To avoid allocating additional resources to plan modifications without clear justification, visual assessment of tumor shrinkage on cone-beam CT can help conserve manpower. However, not all tumors exhibit similar shrinkage following a given radiation dose, due to molecular differences and tumor heterogeneity, there is lot yet to discover.

Limitations

The small sample size and single-institution design limit the generalizability of our findings. Additionally, the offline adaptive imaging made the re-planning process more labor-intensive; integrating online ART could streamline adaptive planning and improve clinical efficiency. Although dose escalation was not fully implemented, our findings suggest that ART offers a promising pathway for individualized treatment intensification while maintaining safety. Future multi-institutional studies with larger cohorts and the incorporation of advanced imaging modalities are warranted to validate these results and refine ART protocols.

In conclusion, our study reinforces the critical role of ART in the management of unresectable lung cancer. Tumor shrinkage during treatment offers a unique opportunity to minimize radiation exposure to surrounding OAR without compromising target coverage. By incorporating re-planning after 40 Gy, we achieved significant reductions in lung, heart, and esophageal doses, supporting the potential for safe dose escalation. However, our findings also highlight that timing, technique, and motion management such as the use of 4DCT for ITV generation are essential to optimize the benefits of ART. While promising, the variability in dose reduction outcomes across studies underscores the need for standardized protocols and further research to identify the most effective strategies for implementing ART in routine clinical practice.

Conflict of Interest

None.

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