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Assessment of Physical Lung Dose-Volume Parameters in Patients Receiving Split Course Radiation Therapy for Advanced-Stage Non Small Cell Lung Cancer: Dosimetric Effect of Active Breathing Control and Clinical Implications: Analytical Research, Case-Control

İleri Küçük Hücreli Olmayan Akciğer Kanserinde Split Kurs Radyasyon Tedavisi Alan Hastalarda Fiziksel Akciğer Doz-Hacim Parametrelerinin Değerlendirilmesi: Analitik Araştırma, Vaka-Kontrol

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ABSTRACT Objective: Active breathing control (ABC) system serves as a viable technique for the management of respiratory motion by providing reproducible breath-holding. Herein, we assess physical lung dose-volume parameters of V20 (total lung volume receiving ≥20 Gy) and mean total lung dose (MLD) in a series of patients receiving split course radiation therapy (SCRT) for advanced-stage non-small cell lung cancer (NSCLC) with the incorporation of the ABC system. **Material and Methods:** A series of 22 patients receiving ABC-guided SCRT for advanced-stage NSCLC were evaluated for physical lung dose-volume parameters of V20 and MLD. Two different radiation therapy plans have been generated for every patient with and without the incorporation of the ABC system to investigate the dosimetric impact. **Results:** Mean V20 and MLD were 32.3% and 2,104 cGy, respectively at free-breathing. Mean V20 and MLD were 24.7% and 1,697 cGy, respectively with the incorporation of the ABC system. The decrease in V20 and MLD was 23.53% and 19.34%, respectively. **Conclusion:** Our study shows improved normal lung tissue sparing by incorporation of ABC system in SCRT of advanced-stage NSCLC. The reduction in V20 and MLD may have clinical implications. Improved normal lung tissue sparing by use of the ABC system may result in an improved toxicity profile of radiation delivery and thereby enable dose escalation in selected patients. Admittedly, clinical follow-up of patients should be performed to elucidate clinical reflections of dosimetric gains achieved by the ABC system.

Keywords: Advanced-stage non-small cell lung cancer; split course radiation therapy; active breathing control

ÖZET Amaç: Aktif solunum kontrolü (ABC) sistemi, tekrarlanabilir nefes tutmayı sağlayarak solunum hareketinin yönetimi için uygun bir teknik olarak görev yapar. Burada, ileri evre küçük hücreli dışı akciğer kanseri (KHDAK) için split kurs radyasyon tedavisi [split course radiation therapy (SCRT)] alan bir dizi hastada V20'nin (≥20 Gy alan total akciğer hacmi) ve ortalama total akciğer dozunun [mean total lung dose (MLD)] fiziksel akciğer dozu-hacim parametreleri, ABC sistemi dâhil edilerek değerlendirilmiştir. **Gereç ve Yöntemler:** İlerlemiş KHDAK için ABC kılavuzlu SCRT uygulanan 22 hastada, fiziksel akciğer doz-hacim parametreleri olan V20 ve MLD değerleri karşılaştırılmıştır. Dozimetrik etkiyi araştırmak için her hasta için, ABC sistemi dâhil olan ve olmayan 2 farklı radyasyon tedavisi planı oluşturulmuştur. **Bulgular:** Serbest solunumda ortalama V20 ve MLD sırasıyla %32,3 ve 2,104 cGy idi. ABC sisteminin dâhil edilmesiyle ortalama V20 ve MLD, sırasıyla %24,7 ve 1,697 cGy olmuştur. V20 ve MLD'deki düşüş sırasıyla %23,53 ve %19,34 olarak bulunmuştur. **Sonuç:** Çalışmamız, ileri evre KHDAK'nin SCRT tedavisine ABC sisteminin dâhil edilmesiyle normal akciğer dokusunun daha iyi korunduğunu göstermektedir. V20 ve MLD'deki azalmanın klinik sonuçlara etkisi olabilir. ABC sisteminin kullanılması, normal akciğer doku korumasında artış, radyoterapiye bağlı toksisite profilinde iyileşme ve seçilmiş hastalarda doz eskalasyonu ile sonuçlanabilir. ABC sisteminin sağladığı dozimetrik kazanımların kliniğe yansımalarını aydınlatmak için hastaların klinik takibi mutlaka yapılmalıdır.

Anahtar Kelimeler: İleri evre küçük hücreli olmayan akciğer kanseri; split kurs radyasyon tedavisi; aktif solunum kontrolü

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By far, pulmonary malignancies are among the prominent reasons for cancer-associated mortality universally.[1,2] It composes a global health burden resulting in morbidity and mortality. However, advances in management have affected treatment outcomes with a reduction in mortality in recent years.[3] Non-small cell lung cancer (NSCLC) comprises the greater portion of pulmonary malignancies, and follows a better outcome compared with small cell lung cancer (SCLC).[4] There have been several advances in surgery, radiation therapy (RT) and systemic therapies over the years which have been reflected in patient outcomes.[3,4] Unprecedented advances along with innovative technological developments have contributed to precise radiotherapeutic management.[5-18]

NSCLC is most frequently detected in advanced-stages which limits the utilization of curative therapeutic approaches to a certain extent. Systemic treatment is a primary mode of management for advanced-stage NSCLC, however, surgery and RT may be used for selected patients. Apart from palliative intent, RT may also be incorporated into aggressive treatment protocols for selected patients with oligometastatic disease. Addressing primary cancer along with oligometastases may result in improved therapeutic outcomes. Nevertheless, RT has a significant contribution to the treatment of patients suffering from advanced-stage NSCLC. The undesirable toxicity of irradiation comprises an important limitation against the administration of higher doses of RT to achieve improved therapeutic outcomes. In the context of NSCLC, a major obstacle to the delivery of higher RT doses is radiation pneumonitis. Predictors of pulmonary injury by irradiation may be closely associated with physical lung dose-volume parameters. Among several predictors of pulmonary RT toxicity, V20 (lung volume receiving ≥20 Gy) along with mean lung dose (MLD) are very relevant to consider the risk of radiation pneumonitis. Several strategies have been developed to optimize the therapeutic ratio in radiotherapeutic management of pulmonary malignancies. The active breathing control (ABC) system serves as a viable technique for management of respiratory motion by providing reproducible breath-holding.[18-22] Herein, we assess physical lung dose-volume parameters of V20 and MLD the with incorporation of the ABC system.

MATERIAL AND METHODS

Twenty two patients treated by ABC-guided SCRT were prospectively evaluated for physical lung dose-volume parameters of V20 and MLD. All patients gave written informed consent before radiotherapeutic management with institutional tumor board approval at our tertiary cancer center, and the study has been performed in compliance with the Declaration of Helsinki principles and its later amendments. Physical lung dose-volume parameters of V20 and MLD were extracted from the dose-volume histograms and comparatively analyzed. All patients had histopathologically proven NSCLC at an advanced-stage which was documented by imaging. Patient, tumor and treatment characteristics are summarized in Table 1.

Out of the total 22 patients, 15 (68.18%) patients had Stage III disease and 7 (31.82%) patients had Stage IV disease. The majority of patients received platinum-based chemotherapy. Management of patients with SCRT has been decided after a thorough multidisciplinary assessment by experts from radiation oncology, and other thoracic oncology disciplines including thoracic surgery, medical oncology, and pulmonology. Treatment approaches were evaluated on an individual basis with consideration of patient, tumor, and treatment characteristics. All patients received a total radiation dose of 39 Gy delivered in 13 fractions using a fraction dose of 3 Gy. ABC procedure was performed in compliance with our published protocol.[18] Briefly, all patients were trained and instructed about the ABC system (ABC, Elekta, UK) to get familiar with the system and to determine individualized breath-holding levels. Typically, the breath-holding threshold has been adjusted to 75% of maximal inspiration volume which has been referred to as moderate deep inspiration breath-holding (mDIBH). Patients were taught to provide reproducible breath patterns to be used in computed tomography (CT) simulation and treatment. Preparatory breath-holding was practiced to ensure a satisfactory and reproducible level of mDIBH. Following instructions and educatory sessions, scanning has been performed at free-breathing and mDIBH at CT simulator (GE Lightspeed RT, GE Healthcare, Chal-

TABLE 1: Patient, tumor and treatment characteristics.

Characteristic	Number	%
Number of patients included in the study	22	
Median age (range)	64 (43-81) years	
Median Karnofsky Performance Status (range)	80 (60-100)	
Radiation dose	39 Gy delivered in 13 fractions (3 Gy per each fraction)	100
Gender		
Men	14	63.64
Women	8	36.36
Disease stage		
Stage III	15	68.18
Stage IV	7	31.82
Systemic therapy		
Platinum-based chemotherapy	17	77.27
Other regimes	5	22.73
Treatment device		
Linear accelerator (LINAC)	22	100
Beam energy	6 MV	100

font St. Giles, UK) with arms above head, immobilized by use of a Wing-Board (CIVCO, Kalona, IA, USA). A nose clip has been utilized for ensuring that patients breathed by their mouths only. Visualization of the breathing pattern has been enabled by the use of a mirror. After CT simulation images were acquired, image sets were transferred into a contouring workstation with a network connection. Delineation procedures have been performed for target and critical structures using the breath-holding and free-breathing scans. For this study, we extracted lung dose-volume parameters of V20 and MLD out of the individual dose volume histograms and performed a comparative evaluation.

RESULTS

A total of 22 (14 male, 8 female patients) patients with advanced-stage NSCLC were assessed. Median Karnofsky Performance Status was 60 (range: 80-100). The median age was 64 (range: 43-81 years) years. Out of the total 22 patients, 15 (68.18%) patients had Stage III disease and 7 (31.82%) patients had Stage IV disease. The majority of patients (77.27%) received platinum-based chemotherapy. The total radiation dose was 39 Gy delivered in 13 fractions using a fraction dose of 3 Gy for all patients. Radiation treatment planning was accomplished by expert radiation physicists with consideration of relevant reports and guidelines. Two different RT plans have been created for every subject with and without the incorporation of the ABC system to investigate the dosimetric impact. A critical priority was the coverage of the clinical target volume by the 95% isodose line, however it has not been possible to provide planning target volume coverage with the 95% isodose line for 5 (22.73%) patients to respect critical organ dose limitations. Nevertheless, the clinical target volume was encompassed within the 95% isodose line for all patients. Treatment delivery was performed by Elekta Synergy (Synergy, Elekta, UK) Linear Accelerator (LINAC) using 6 MV photons. Physical lung dose-volume parameters of V20 along with MLD have been retrieved and comparative assessment was carried out for each patient. Lung dose-volume parameters of V20 and MLD acquired from treatment plans with and without incorporation of the ABC system are demonstrated in Table 2.

Mean V20 and MLD were 32.3% and 2,104 cGy, respectively at free-breathing. Mean V20 and MLD were 24.7% and 1,697 cGy, respectively with the incorporation of the ABC system. The decrease in V20 and MLD was 23.53% and 19.34%, respectively.

TABLE 2: Lung dose-volume parameters of V20 and MLD acquired from treatment plans with and without incorporation of the ABC system.

	Dose-volume parameter (mean)	
	V20 (%)	MLD (cGy)
Radiation treatment planning at free-breathing (without ABC-mDIBH)	32.3%	2,104 cGy
Radiation treatment planning with ABC-mDIBH	24.7%	1,697cGy
Decrease in physical lung dose-volume parameter with incorporation of ABC system (%)	23.53%	19.34%

MLD: Mean lung dose; ABC: Active Breathing Control; mDIBH: moderate deep inspiration breath-holding.

DISCUSSION

Pulmonary malignancies are considered among the most common causes of cancer- associated mortality on a universal basis.[1,2] NSCLC constitutes the bigger proportion of pulmonary malignancies, and the disease is mostly detected at advanced stages. Optimal management of NSCLC is of utmost importance, and every effort is being made to improve radiotherapeutic outcomes. SCRT has been introduced as a radiotherapeutic modality with a condensed treatment schedule and typically shorter overall treatment time. Over the years, several studies have addressed the utility of SCRT both for symptomatic palliation and management of locally advanced NSCLC.[23-28] A variety of dose-fractionation schedules have been utilized for SCRT without a standard scheme.

Apart from dose and fractionation, management of respiratory motion is an intriguing area of active investigation for NSCLC. As per the International Commission on Radiation Units and Measurements reports, an internal margin is required to account for respiratory motion in RT practice. However, the range and magnitude of respiratory motion may be high. Within this context, optimal consideration of respiratory motion is a critical requirement for radiotherapeutic management of NSCLC. Several contemporary approaches have been utilized including motion encompassing techniques, respiratory-gated strategies, breathing synchronized techniques and breath-holding approaches for respiratory motion management. Among these techniques, breath-holding during treatment simulation and RT delivery deserve the utmost attention. Breath-holding techniques may be categorized as voluntary breath-holding, breath-holding at deep or moderate-deep inspiration, breath-holding without respiratory monitoring, self-breath-holding with respiratory monitoring, and breath-holding with the ABC system.

ABC system has been initially introduced by Wong et al. as a viable technique for respiratory motion management.[19] The system includes a digital spirometer and a balloon valve connected to it. In the ABC technique, the patient breathes through the mouthpiece in free- breathing. Then the system is activated and the balloon valve closes at the defined breath-holding phase. Patients are taught to a achieve determined threshold pulmonary capacity following a few preparative free breaths. The valve is expanded by an air compressor for a predetermined time so that the patients can hold their breath. The breath-holding time typically ranges between 15 to 30 seconds and the duration of breath-holding time depends on the individual performance of the patient. Following a short resting period, the patient should be able to achieve consequent and reproducible breath holds.

A major advantage of using the ABC system may be considered as the minimized or eliminated internal margins to account for respiratory motion which could lead to decreased exposure to normal lung tissues. Also, expansion of the lungs at mDIBH may reduce the dose to the normal lung and other adjacent critical organs including the heart, coronary arteries, pericardium, main bronchi and arteries, pleura and bones. From this standpoint, an important contribution in terms of improved normal tissue sparing may be achieved by the utilization of the ABC system. Several studies have indicated that dose-volume parameters including V20 and MLD are among the critical predictors of radiation pneumonitis in the radiotherapeutic management of NSCLC.[29-31]

Pan et al. performed a retrospective analysis of 166 patients receiving chemoradiotherapy for lung

cancer.[31] The incidence of Grade 3 or higher radiation-induced lung injury was 23.8% in the study. Univariate analysis revealed that total radiation dose, V20, MLD and neutrophil to lymphocyte ratio were significantly associated with grade 3 or higher radiation-induced lung injury. Multivariate analysis indicated that total dose ≥60 Gy, V20 ≥20%, MLD ≥12 Gy, and neutrophil to lymphocyte ratio ≥2.2 were independent predictive factors for radiation-induced lung injury.[29]

Ramella et al. evaluated lung dosimetric constraints correlated with radiation pneumonitis in NSCLC patients receiving 3-dimensional RT and concurrent chemotherapy.[32] A total of 97 patients receiving concomitant radiochemotherapy for locally advanced NSCLC were assessed. Patients were treated only if the percentage of V20, V30, and MLD did not exceed the constraints of 31%, 18%, and 20 Gy, respectively. Ipsilateral lung V20 and ipsilateral lung V30 were among the most statistically significant factors for the prediction of pneumonitis when the preset dose constraints to the total lungs were respected. The authors concluded that the addition of ipsilateral V20 and V30 to the classical total lung constraints could decrease pulmonary toxicity for patients receiving concurrent chemoradiation for locally advanced NSCLC reported ipsilateral V20 and V30 were important if total lung V20, V30, and MLD did not exceed the constraints of 31%, 18%, and 20 Gy, respectively.[30]

Fujiwara et al. assessed the incidence and grade of radiation pneumonitis after volumetric modulated arc therapy (VMAT) for the management of NSCLC.[33] A total of 50 patients were included in the study, and radiation pneumonitis developed in 38 (76%) patients, 11 of whom suffered from ≥grade 2 radiation pneumonitis. The authors reported that the percentage of lung volume receiving a dose over 5 Gy (V5), 10 Gy (V10), 20 Gy (V20) and 30 Gy (V30), and MLD in the bilateral and ipsilateral lung were significantly associated with the development of grade ≥2 radiation pneumonitis.[31]

Several studies have addressed the use of the ABC system for radiotherapeutic management of NSCLC.[18-22] Sager et al. assessed ABC-mDIBH in a series of 23 patients with NSCLC.[18] Individual tumor motion of patients with and without incorporation of ABC-mDIBH was documented and a comparative evaluation was performed. ABC-mDIBH resulted in improvement in physical lung parameters which are predictors of radiation pneumonitis, and it was concluded that ABC-mDIBH improved critical organ sparing in NSCLC RT.[18]

A recent study by Bainbridge et al. performed a comparison of isotoxic dose-escalated RT in lung cancer with the mDIBH, mid-ventilation and internal target volume techniques.[29] The study revealed that mDIBH technique resulted in reduced normal tissue complication probability for the heart and lung. The authors concluded that decreased normal tissue doses could be advantageous for treatment tolerance and outcome considering the concerns about pulmonary and cardiac toxicity, particularly in an era of consolidation immunotherapy.[29] Also, cardiopulmonary toxicity is a critical concern regarding radiotherapeutic management of NSCLC in the recent Lung ART Phase III randomized trial.[30]

It is pertinent to respect lung dose-volume constraints in radiotherapeutic management of NSCLC to avoid radiation pneumonitis as evidenced by the aforementioned studies and recent guidelines.[31-33] Violation of dose-volume constraints may result in severe radiation pneumonitis which may lead to morbidity, deterioration in the quality of life, and mortality in fragile patients with comorbidities such as chronic obstructive pulmonary disease.[34,35] Also, patients with radiation pneumonitis may suffer from additional burdens due to the requirement of therapies such as antibiotics and steroids. Within this context, breathing adapted RT by using the ABC system may be considered to improve the toxicity profile of radiation delivery in eligible patients.

CONCLUSION

In conclusion, our study shows improved normal lung tissue sparing by incorporating of the ABC system in SCRT of advanced NSCLC. The decreases in V20 and MLD were 23.53% and 19.34%, respectively which may have clinical implications. Improved normal lung tissue sparing with ABC technique may result in improved toxicity profile of radiation delivery and thereby enable dose escalation in selected patients. Admittedly, clinical follow-up of patients sho-

uld be performed to elucidate clinical reflections of dosimetric gains achieved by the ABC system.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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