Radyoterapi Uygulanan Akciğer Kanseri Tanılı Vakalarda Radyasyon Pnömonisi Gelişimini Etkileyen Faktörler

Factors Affecting the Development of Radiation Pneumonitis after Radiotherapy in Patients with Lung Cancer

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Abstract: In this single-institution prospective study, we aimed to evaluate factors affecting the development of radiation pneumonitis (RP) in patients with lung cancer following 3D conformal radiotherapy (3D-CRT) with normal dose-volume histograms (DVH) limits. This study included 41 patients with lung cancer who received definitive 3D-CRT between February 2012 and July 2013. Thirty (73.2%) of these patients underwent concurrent chemotherapy, while eight (19.5%) underwent adjuvant radiotherapy (RT). The median RT dose was 60 (range: 30-64) Gy. The relationships between RP evolution and various treatment-related factors, including DVH parameters, levels of pretreatment diffusing capacity of carbon monoxide (D_{LCO}), serum procalcitonin, CRP, and TGF-β1 were analyzed. Within the follow-up period (median: 8 months, range: 6-24 months), RP occurred in 15 (36.6%) patients (grade I in 11 patients and grade II in 4 patients) and only 2 patients received steroid therapy (methylprednisolone 1 mg/kg/day). Univariate analysis revealed that lymph node involvement status, D_{LCO}, and pretreatment serum procalcitonin levels were significantly associated with RP incidence (p=0.018, 0.045, and 0.001, respectively). However, multivariate analysis of the same factors indicated that only pretreatment serum procalcitonin level was significantly associated with RP incidence (p=0.027). In conclusion, our current data indicate that pretreatment serum procalcitonin level can be used to predict RP in patients with lung cancer who are treated with 3D-CRT with normal DVH limits.
Key Words: 3 dimensional conformal radiotherapy (3D-CRT), lung cancer, procalcitonin, radiation pneumonitis

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Özet: Bu tek merkezli prospektif çalışmada 3 boyutlu konformal radyoterapi (3BKRT) ile tedavi edilen ve normal doz-volüm histogramına (DVH) sahip akciğer kanseri tanılı hastalarda radyasyon pnömonisi (RP) gelişimini etkileyen faktörleri değerlendirmeyi amaçlandı. Çalışmaya Şubat 2012-Temmuz 2013 tarihleri arasında küratif 3BKRT uygulanan 41 akciğer kanseri tanılı hasta dahil edildi. Otuz (%73,2) hastaya eş zamanlı kemoterapi verildi. Sekiz (%19,5) hastaya adjuvant radyoterapi (RT) uygulandı. Medyan RT dozu 60 (30-64) Gy idi. Tedavi sonrası RP gelişimi ile DVH parametreleri, tedavi öncesi karbon monoksit difüzyon kapasitesi (DLCO), serum prokalsitonin, CRP ve TGF-β1 seviyeleri gibi hastaya özgü faktörler arasındaki ilişki analiz edildi. Medyan 8 (6-24) aylık takip süresi içerisinde 15 (%36,6) hastada RP gelişti (11 hastada grade I, 4 hastada grade II) ve sadece 2 hastaya steroid (1 mg/kg/gün metilprednizolon) tedavisi uygulandı. Tek değişkenli analizde lenf nodu tutulumu, DLCO ve tedavi öncesi serum prokalsitonin düzeyinin RP gelişimi üzerine etkisi gösterildi (sırasıyla, p=0.018, 0,045, 0.001). Çok değişkenli analizde sadece tedavi öncesi serum prokalsitonin düzeyi ile istatistiksel anlamlı ilişki mevcut idi (p=0.027). Sonuç olarak tedavi öncesi serum prokalsitonin düzeyi 3BKRT ile tedavi edilen ve normal DVH değerlerine sahip akciğer kanseri tanılı hastalarda RP gelişimini tahmin etmede faydalı olabilir.
Anahtar Kelimeler: 3 boyutlu konformal radyoterapi (3BKRT),akciğer kanseri,prokalsitonin,radyasyon pnömonisi

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1. Introduction

Lung cancer is the most common cancer worldwide; it is responsible for 18% of cancer-related deaths (1-4). Radiotherapy (RT) is important in the treatment of lung cancer. Several studies have shown efficacy of RT in the local control of inoperable non-small cell lung cancer (NSCLC) and limited-stage small cell lung cancer (SCLC) (5-7). Studies have also shown that RT can prevent local recurrence in cases with positive surgical margin and mediastinal lymph node involvement, but plays no role in survival (8,9). In thoracic RT, the lung is the dose-limiting organ, as it has limited regeneration capacity, while radiation pneumonitis (RP) and fibrosis are the most important dose-limiting pathologies. Radiotherapy-related tissue damage can be affected by age, RT dose, RT volume, RT fractionation, concurrent chemotherapy (ChT), performance status, other coexisting chronic diseases, oxygenation, and regeneration capacity of the tissue.

Procalcitonin, the precursor of calcitonin, is a 116 amino acid protein that is mainly synthesized by the thyroid gland; however, the extrathyroidal synthesis of procalcitonin has been reported. Importantly, serum procalcitonin can be used as a biomarker for the early diagnosis of bacterial infections as well as a prognostic marker for sepsis. It has been shown that procalcitonin levels increase in the presence of tumors with a neuroendocrine component or in liver metastases of lung cancer (10,11).

The transforming growth factor beta-1 (TGF-β1) gene controls proliferation and cellular differentiation, and it has also been shown to play a role in the development of irradiation-induced tissue fibrosis. In fact, several studies have shown that TGF-β1 is a major regulator of radiation-induced lung injury (12-16).

In the current study, we aimed to determine whether we could predict the development of RP in patients treated with three-dimensional conformal radiotherapy (3D-CRT) in normal dose-volume histogram (DVH) limits. To this end, we prospectively evaluated factors affecting the development of RP after 3D-CRT in patients with lung cancer.

2. Methods

Study design and patient selection

This study was approved by the Ethics Committee of the Human Studies Review Board of Eskisehir Osmangazi University Medical Faculty, and all participants provided informed consent. The inclusion criteria were as follows: age 18-75 years, Karnofsky Performance Score (KPS) ≥70, cytological or histological diagnosis of lung cancer (SCLC or NSCLC) that was radiographically measurable on X-ray or thoracic tomography (CT), adequate hematologic reserve, and adequate renal function. All patients were assessed with pulmonary function tests for forced expiratory volume in 1 s (FEV 1.0 L) and diffusing capacity of carbon monoxide (D_{LCO}). Further, it was confirmed that none of the participants had any pneumonic infiltration, and patients with metastatic disease were excluded from this study.

Radiotherapy

All participants were stabilized with a T-bar in the supine position with their arms above their head, and then CT (Toshiba Aquilion 64 slice®) was performed with 5mm interslice intervals between the cricoid cartilage and L2 vertebra. The CT images were transferred to the treatment planning system (TPS), and the critical organs and target volumes were delineated according to the ICRU 50 and The International Commission on Radiation Units and Measurements (ICRU) 62 on CMS XiO 4.2.®(10,11). Clinical Target Volume CTV margins were adjusted according to each patient's clinical profile and critical organ tolerance dose. Elective nodal irradiation was performed only in SCLC patients with lymph node involvement. We noted the ipsilateral (i), contralateral (c), and total (t) lung volumes of 5, 10, 20, 30, 40, 50, and 60 Gy (e.g. iV5, tV20, cV30), the mean lung dose (MLD), and the target volumes on DVH.

Chemotherapy

Concurrent ChT was prescribed in patients with good Karnofsky Performance Score(KPS) who did not have any liver or renal problems. Patients with SCLC were prescribed cisplatin 60 mg/m^2 every 3 weeks (starting at day 1) and etoposide 100 mg/m^2 on days 1, 2, and 3; patients with NSCLC

were prescribed cisplatin 40 mg/m^2 every week.

Biochemical Analysis

Blood samples were collected from each patient prior to undergoing RT, and at 1 and 3 months following RT. Within 30 minutes of collection in EDTA tubes, the blood samples were centrifuged at 3,000 x g for 5 minutes and stored at -80°C until further analysis. TGF-β1 levels were determined via ELISA (Human TGF-β1 Platinum ELISA BMS249/4/BMS249/4TEN kit, eBioscience, Vienna, Austria),C-reactive protein CRP levels were determined with an immunoturbidometric method (Roche/Hitachi Modular system, Mannheim, Germany), and procalcitonin levels were measured with a sandwich immunoluminometric method (Kryptorautoanalyzer, BRAHMS AG, Germany).

Patient Follow-up

While undergoing RT, patients were seen in clinic twice a week, and CBC and biochemistry profile were performed at each of these visits; lung X-ray was performed every 2 weeks. Patients were seen at the first and third month following RT, and thorax CT was performed during these visits. The severity of RP was evaluated by the National Cancer Institute Common Toxicity Criteria 3.0 (NCICTC). Patients with RP were treated with inpatient service.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 to determine whether there were any relationships between RP and different patient- and treatment-related factors, such as DVH parameters and pretreatment levels of serum procalcitonin and TGF-β1. Univariate analyses were performed using Student's t test or the chi-square test, and multivariate analyses were performed using a logistic regression test. Values of $p<0.05$ were considered significant for the log-rank test and for the univariate-multivariate analyses.

3. Results

Of the participants, 38 (92.7%) were male, the median age was 60 (range: 39-79) years, and the main histopathology was non-small cell carcinoma (82.9%). The tumor localization was upper lobe in 23 (56.1%) patients, lower lobe in 16 (39%), and middle lobe in 2 (4.9%). Twenty-eight (68.3%) patients were positive for mediastinal lymph node involvement, and 8 (19.5%) had no hilar or mediastinal lymph node involvement. Thirty-eight (92.7%) patients received ChT before RT, 30 (73.2%) were subjected to concurrent ChT and RT, while 8 (19.5%) underwent adjuvant RT. The median RT dose was 60 (range: 30-64) Gy. Of the participants, 32 (78%) underwent 6-MV photon alone, 5 (12.2%) were subjected to 18-MV photon alone, and 4 (9.8%) underwent a 6/18-MV photon combination. The median mean lung dose MLD was 11.4 (range 4.8-17.8) Gy, the median tV5 was 29% (range: 14-50), the median tV20 was 20% (range: 10-40), and the median maximum lung dose was 64.8 (32.3-74.5) Gy (Table 1). Levels of pre- and post-treatment serum CRP, procalcitonin, and TGF-β1 are shown in Table 2.

Table 1.
Patient Characteristics (n = 41)

Age (Years)	**39-79 (median 60)**
Gender	
Female	3 (7.3%)
Male	38 (92.7%)
KPS	70-90 (median 80)
Smoking History	
Yes	40 (median 47.5, range: 20-90 package year)
No	1
Baseline FEV1.0	0.60-3.42 (median 2.18)
Histopathology	
NSCLC	34 (82.9%)
SCLC	7 (17.1%)
Tumor lobe	
Upper	23 (56.1%)
Middle or Lower	18 (43.9%)
Lymph Node Involvement	
Yes	33 (80.5%)
No	8 (19.5%)
tV20 (Gy)	10-40 (median 20)
Mean Lung Dose (MLD) (Gy)	4.80-17.8 (median 11.4)
Total Radiotherapy Dose (Gy)	30-64 (median 60)
Total Radiotherapy Duration (Day)	32-58 (median 41)

Table 2.
Pre and posttreatment serum CRP, Procalcitonin, and TGF-β1 levels

	Pretreatment	Posttreatment	p
Serum CRP (mg/dl)			
Range	0.3-221.3	0.4-197.0	NS
Mean	14.6	16.3	
Serum Procalcitonin (ng/ml)			
Range			
Mean	0.02-0.37	0.02-0.33	NS
	0.07	0.06	
Serum TGF-β1 (pg/ml)			
Range	10265.9-106240.5	-	-
Mean	61295.7		

Table 3.
Pre and posttreatment serum CRP, Procalcitonin, and TGF-β1 levels

	Radiation Pneumonitis		p
	Yes (n=15)	No (n=26)	
Total lung V5			
Range	19-50	14-38	NS
Mean	32.3	27.4	
Total lung V10			
Range	17-42	12-34	NS
Mean	27.0	23.4	
Total lung V20			
Range	15-40	10-30	NS
Mean	22.5	19.6	
Total lung mean			
Range	5.2-17.8	4.8-16.9	NS
Mean	11.9	10.5	

The median follow-up interval was 8 (range: 6-24) months. Radiation pneumonitis (RP) occurred in 15 (36.6%) patients (grade I in 11 and grade II in 4 patients), and only 2 of these received steroid therapy (methylprednisolone 1 mg/kg/day). We performed univariate analyses to determine whether there was any relationship between patient- and treatment-related factors (i.e., age, gender, KPS, smoking history, baseline FEV 1.0, D_{LCO}, tumor localization (upper lobe vs. middle or lower lobe), lymph node involvement status, total RT dose, total RT duration, tV20, MLD, pretreatment serum CRP, procalcitonin and TGF-β1 levels) and the development of RP. We found that lymph node involvement status, $D_{LCO,}$ and pretreatment serum procalcitonin levels were significantly associated with the incidence of RP (p=0.018, 0.045, and 0.001, respectively). The relationship between pretreatment serum procalcitonin levels and RP grade is shown in Figure 1. Multivariate analyses of the same factors (using logistic regression analysis) revealed that only pretreatment serum procalcitonin levels were significantly associated with RP (p = 0.023); there were no correlations between DVH parameters and RP using this method (Table 3).

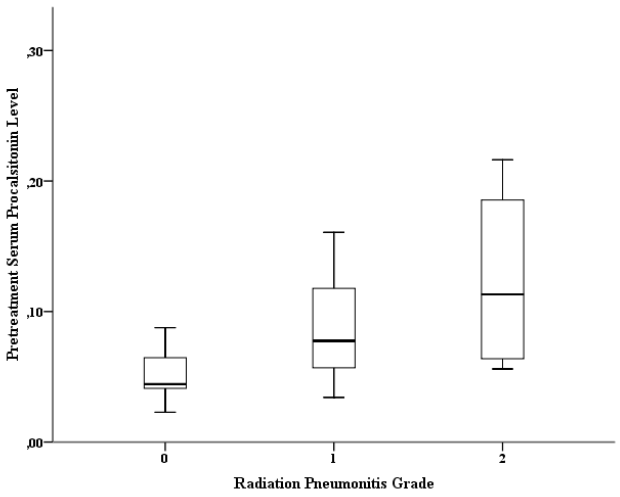

Figure 1. *Relationship between pretreatment serum procalcitonin level and RP grade.*

4. Discussion

RP, also known as exudative phaseoccurring, is the lung's response to irradiation; it typically occurs between 3 to 6 months after irradiation. RP is characterized by an infiltration of inflammatory cells (i.e., macrophages and lymphocytes) and edema in the airway and interstitial spaces. Animal studies have shown that damage from irradiation immediately causes changes in the expression of growth factors such as TGF-β, platelet-derived growth factor (PDGF), and interleukin-1 (IL-1). Activated growth factor receptors can cause the activation of collagen genes, thereby increasing the production of collagen (17). Several studies have shown that TGF-β is an important mediator of tissue damage in a variety of conditions characterized by excessive collagen production and accumulation (18-21). TGF-β is a cytokine that stimulates fibroblast and lymphocyte recruitment to injured tissue. This increase in fibroblast proliferation and the stimulation of collagen and fibronectin production causes an increase in the amount of extracellular matrix. Several experimental studies have shown that there is increased TGF-β in irradiated fibrotic lung tissue (18-22). In addition, it has been shown that post-treatment plasma TGF-β, when combined with the volume of lung irradiated, can reliably be used to predict the outcome of radiation therapy (23). However, results of our current study did not reveal any correlation between pre-treatment serum TGF-β1 levels and the development of RP.

Gopal et al. used pulmonary function tests (PFT) before and after RT to study the relationship between radiation dose and loss of lung function. Results of that study indicate that treating a small volume of normal lung with a high dose of radiation leads to fewer deleterious effects than treating a high volume of normal lung with a low dose of irradiation (24). With regards to the irradiation response of varying lung regions, animal studies have shown that the base lung has increased sensitivity when compared with the apex, as a larger portion of the base lung is occupied by gas exchange units (25-27). Similarly, Yamada et al. reported that the risk of pneumonitis in patients varied with the location of the irradiated volume (28). Further, two different studies revealed that the risk of RP is better correlated with irradiation to the inferior aspect of the lung or an inferior tumor location rather than superior locations (29,30).

Choi et al. reported that the functional changes caused by lung irradiation vary according to pulmonary reserve before treatment. Interestingly, patients with less functional compromise before RT (e.g., FEV1.0 L> 50% of the predicted value) lost more pulmonary function and showed higher airway resistance following RT than did patients with less pretreatment reserve. Those with an FEV1.0 L < 50% of the predicted value before RT had improved or minimally reduced pulmonary function after RT (31). Results of our current study did not reveal any correlation between the development of RP and tumor location or FEV1.0 L; this is most likely due to differences in treatment, tumor size, and tumor localization between participants. However, our current results indicate that patients with high D_{LCO} were more likely to develop RP, and we believe that this correlation may be associated with similar mechanisms.

Brady et al. confirmed the relative safety of giving effective irradiation doses to modest treatment volumes, and RTOG confirmed that the volume irradiated is much more important than the dose given. In those studies, it was shown that increasing the total dose from 60 to 74.4 Gy did not increase the frequency of acute or late pulmonary toxicity (32-35). In our current study, the frequency of RP was higher in patients with lymph node involvement; this is most likely because these patients had a larger irradiated volume.

Several studies utilizing various treatment options have shown a correlation between the development of RP and different dosimetric parameters, including tV10, tV13, tV20, tV25, tV30, tV65, iV5, iV20, MLD, and NTCP (normal tissue complication probability) (29,30,36-47). Results of these studies have shown that MLD is more predictive of RP than the various Vx values (36,48,49).

In our current study, the median RT dose was 60 Gy (range: 30-64), the median tV20 was 20% (range: 10-40%), and the median MLD was 11.4 Gy (range: 4.8-17.8). All DVH

parameters were within normal limits. We believe that we did not detect any correlation between the development of RP and DVH parameters (as shown in the literature) due to the use of the above parameters. Although the DHV parameters used in the current study were within normal limits (tV20 ≤ 35%, tV5 ≤ %65%, tMLD ≤20 Gy), RP occurred in 15 (36.6%) patients, and 4 of these were grade II. In our current study, we believe that the most important result was that there was a correlation between the development of RP and preradiotherapy serum procalcitonin levels. In daily practice, procalcitonin is used as a marker of sepsis, particularly in cases where the lung is the primary site, because it is thought to provide earlier and more specific detection than CRP. Secondary to TGF□-1, TNFα. also induces the production of procalcitonin. Avrillon et al. reported that lung cancer may cause false positives for procalcitonin, particularly in cases with neuroendocrine cancers, or in the presence of multiple metastases (11). To our knowledge, our current study is the first to determine the effect of procalcitonin on determining the development of RP.

5. Conclusion

Our results indicate that the incidence of RP is significantly related to pretreatment serum procalcitonin levels. Thus, pretreatment serum procalcitonin levels may be able to predict RP in patients with lung cancer who were treated with 3D-CRT in normal DVH limits.

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