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Original Article

Radiotherapy Could Increase the Efficacy of Immunotherapy in Non-small Cell Lung Cancer

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ABSTRACT

Background In non-small cell lung cancer (NSCLC), immunotherapy is a treatment option in patients without targetable mutations in second and later lines. Nevertheless, there is no validated test that can predict immunotherapy response.

Material and Methods Our study aimed to investigate the effect of radiotherapy (RT) on survival in patients with NSCLC receiving immunotherapy after first-line chemotherapy. Twenty-five patients diagnosed with NSCLC and received immunotherapy after at least one previous chemotherapy line were included in our study.

Results The median age of the patients was 61.7 (26.6-81.2) years. 19 (76%) patients were male. 11 (44%) of the patients had received immunotherapy in the second-line and 14 (66%) in ≥3 lines. Patients had received a median of 5 cycles (1-27) of immunotherapy. RT to immunotherapy interval was 6.4 months (1.0-11.8). Partial response was observed in 12 patients, stable disease in 8 patients, progression in 1 patient, and hyperprogression in 4 patients. Median progression-free survival (PFS) was 4.4 months (95% CI; 3.2-5.6), and median overall survival (OS) was 16.4 months (95% CI; 5.6-27.3). 14 (56%) of the patients had received RT. RT was administered to 12 patients before immunotherapy, and two patients received RT to bones during immunotherapy. The patients who received RT had statistically longer PFS (4.9 vs 3.9 months, p=0.012) and OS (18.7 vs 7.3 months, p=0.023) comparing those without RT.

Conclusions Our findings showed that RT significantly improved the survival in patients who received immunotherapy, pointing that RT may have an influential role in immunotherapy response.

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Introduction

Despite all the improvements in diagnosis and treatment options today, lung cancer is the most common cause of cancer-related death in men and women worldwide.[1] On the other hand, especially in non-small cell lung cancer (NSCLC), which constitutes approximately 85-90% of all lung cancers, a significant increase in survival rates has been achieved with targeted therapies and immunotherapy in the treatment of metastatic disease.[2,3]

The programmed death (PD)-1 receptor expressed by activated T cells interacts with the PD-ligand 1 (PD-L1) and -ligand 2 (PD-L2) expressed by tumor cells and infiltrating immune cells. As a result of this interaction, the T cell activation is inhibited, and the escape of the tumor from the immune system is supported. Immune checkpoint inhibition agents, such as anti-PD-1 antibodies, nivolumab, and pembrolizumab, an anti-PD-1 antibody, atezolizumab, disrupt PD-1 mediated signaling and restore anti-tumor immunity.[4-6] In several clinical trials, anti-PD-1 and anti-PD-L1 antibodies have shown durable responses in 20% of patients, which have not been reported in any trial studying chemotherapeutic agents in advanced NSCLC.[7-10]

Therefore, immunotherapy is an important treatment option in metastatic NSCLC patients who do not carry driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene tyrosine-protein kinase 1 (ROS1), and progress after primary chemotherapy. National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend pembrolizumab to patients with PD-L1 tumor proportion score (TPS) >1% and atezolizumab and nivolumab regardless of PD-L1.[3,11] However, there is no validated test to determine which patient group will benefit more from immunotherapy in the second or later treatment lines for metastatic NSCLC.[3,11]

Radiotherapy (RT) may be administered to lung cancer patients for curative intent in the locally advanced-stage or palliative treatment in the metastatic stage.[3] Radiotherapy is studied to have three main effects in tumor treatment. Firstly it reduces the tumor burden with a direct toxic effect. The second effect is that RT provides stimulation of antitumoral response far from the irradiated area. This effect was first described as the abscopal effect by Mole et al. in 1953.[12] Finally, RT may lead to an increase in PD-L1 expression in the tumor microenvironment, resulting in inhibitory PD-1 receptors to bind to T cells and inhibiting T cell anti-tumor response.[13] On the other hand, data showing the effects of RT regarding the increase in immunotherapy response in patients with NSCLC is quite limited. Our study aimed to investigate the effect of RT on immunotherapy efficacy in NSCLC patients receiving immunotherapy in the second-line or later treatment.

Material and Methods

Study Population and Data Collection

Twenty-five patients diagnosed with NSCLC in Bursa Uludag University Faculty of Medicine Medical Oncology Department between 2018-2020 and received immunotherapy after at least one previous chemotherapy line were included in our study. Patients under age 18, with known small cell lung carcinoma and missing clinical data in the electronic database, who possess targetable mutations such as ALK, EGFR, ROS1, BRAF, RET, c-MET, neurotrophin receptor tyrosine kinase (NTRK) had a history of pneumonitis, had received immunotherapy or systemic immunosuppressive therapy, and had an active autoimmune disease were excluded from the study.

PD-L1 levels were determined using the DAKO 22C3 antibody clone from paraffin blocks at the time of diagnosis. Patients bore the costs of immunotherapy due to the reimbursement system in the health policy in our country. Atezolizumab 1200 mg every 21 days, nivolumab 240 mg every 14 days, and pembrolizumab 200 mg every 21 days were administered by intravenous infusion on day 1 of each cycle. The patients' demographic characteristics and histopathological features, treatments, treatment-related side effects, and the effects of the treatment on survival were analyzed retrospectively using hospitals' electronic medical records.

Radiotherapy was recorded in two parts, during and before immunotherapy. If the patient received RT for the treatment of NSCLC at any

time point before the first immunotherapy course, the elapsed time between the date of the RT and the immunotherapy was recorded. Adverse events and laboratory abnormalities were assessed using the Common Terminology Criteria for Adverse Events version 4.0.

Our study complied with the ethical standards of the institutional research committee and the Helsinki declaration of 1964. The Clinical Research Ethics Committee of the Bursa Uludag University Faculty of Medicine approved the study (Approval number: 2020-19/21).

Outcomes

Response assessment was conducted according to Response Evaluation Criteria in Solid Tumors (version 1.1). The duration of response was defined as the time from first documented evidence of response until progression. Progression-free survival (PFS) was calculated from the beginning of treatment with immunotherapy until disease progression or death from any cause. Overall survival (OS) was determined from the beginning of the immunotherapy until death from any cause. Hyper-progression was defined as PFS <2 months, >50% increase in tumor burden, and >2-fold increase in progression pace.[14] Immunotherapy was maintained beyond progression in case of evidence of clinical benefit.

Statistical Analysis

Median (minimum-maximum) values expressed continuous variables, and categorical variables were expressed by frequency and corresponding percentage values. Life expectancy was analyzed by the Kaplan–Meier method, and the log-rank test was used to investigate the effect of radiation therapy, smoking, age, agent, and site of metastasis on survival. The data were statistically processed using the IBM SPSS version 22 software, and a 5% type-I error level was used for statistical significance.

Results

The median age of the patients was 61.7 (26.6-81.2) years. 19 (76%) patients were male. The demographic and clinicopathological characteristics of the patients are displayed in Table 1. Eastern Cooperative Oncology Group (ECOG) score was 1 for 18 (72%) patients. 56% of the patients had a smoking history. The pathological assessment of most patients (64%) was consistent with adenocarcinoma. Fifteen (60%) patients had a PD-L1 level of $\geq$ 50%. Nearly half of the patients (48%) had de novo metastatic disease. Lungs were the most common metastasis sites.

The immunotherapy agents, treatment steps, treatment responses, and duration of the treatment are presented in Table 2. There were 11 patients receiving pembrolizumab, 8 receiving atezolizumab, and 6 receiving nivolumab. Eleven (44%) of 25 patients had received immunotherapy in the second line and 14 (66%) in the third or later lines. The median duration of follow-up was 14.7 (4.9-19.6) months. The median duration of treatment was 6.9 (2.1-14.2) months. Patients had received a median of 5 cycles (1-27) of immunotherapy. Partial response was observed in 48% and stable disease in 32% of patients. There was progression in 1 and hyperprogression in 4 patients. The median duration of response was 6.3 (4.1-10.3) months. Chemotherapy was planned for patients who progressed after immunotherapy. The median OS was 16.4 months (95% confidence interval [CI]; 5.6-27.3) (Figure 1A), and the median PFS was 4.4 months (95% CI; 3.3-5.7) (Figure 1B).

The clinical features of the patients related to RT are given in Table 3. 56% of patients had received RT. Radiotherapy was administered to 12 patients before immunotherapy, and two patients received concurrent immunotherapy and RT to the bone metastasis. Radiotherapy to immunotherapy interval was 6.4 months (1.0-11.8). Thoracic radiotherapy was applied to 5 patients with a total dose of 50-60 Gy in 30 fractions. Palliative bone RT was given to 6 patients with 20-30 Gy in 5-10 fractions. One patient had progressive cervical lymph node metastasis, and RT was administered 30 Gy in 10 fractions palliatively. Whole-brain irradiation was administered with 30 Gy in 10 fractions in a patient who had brain metastases. In another patient with bone and brain metastases, a total of 30 Gy palliative RT in 10 fractions was applied to both metastatic sites.

Patients receiving RT had a statistically longer OS and PFS comparing those not receiving RT (for OS; 18.7 months [95% CI: 17.3-20.2] vs 7.3 months [95% CI: 5.2-9.3], p=0.023 and for PFS; 4.9 months [95% CI: 4.4-5.8] vs 3.9 months [95% CI: 3.3-4.2], p=0.012), respectively (*Figures 2A, 2B*). The

log-rank test revealed that there was no statistical difference in PFS in terms of gender (p=0.203), age (65< vs ≥65, p=0.156), ECOG performance (p=0.466), smoking (p=0.188), immunotherapetic agent (p=0.617), stage at diagnosis (non-metastatic vs de novo metastatic, p=0.813), treatment lines (2 vs ≥3, p=0.389), presence of liver metastasis (p=0.495), histopathological group (p=0.497) and PD-L1 status (50%< vs ≥50%, p=0.091). Except for smoking, these findings were similarly statistically insignificant for the OS analysis (p=0.837 for gender, p=0.730 for ECOG performance, p=0.858 for immunotherapetic agent, p=0.665 for stage at diagnosis, p=0.638 for treatment lines, p=0.281 for presence of liver metastasis, and p=0.330 for PD-L1 status). For PFS; PDL-1 level (50%< vs ≥50%, p=0.091) and for OS; histopathological subgroup (p=0.075) and age (p=0.052) showed a trend towards significance. The p-value for comparison between smokers and non-smokers in the log-rank test in terms of OS was 0.044, but confidence intervals were overlapping (18.7 months [%95 CI: 5.9-31.5] versus 10.0 months [%95 CI: 0.1-21.0], p=0.044), therefore the difference was not statistically significant.

Table 1. Demographic and clinicopathological features of the patients.

		n (%)
Gender	Male	19 (76)
	Female	6 (24)
Age	Median (range) (year)	61.7 (26.6-81.2)
ECOG performance status score	0	3 (12)
	1	18 (72)
	2	4 (16)
Smoking	Non-smoker	11 (44)
	Smoker	14 (56)
Histopathology	Adenocarcinoma	16 (64)
	Squamous cell carcinoma	9 (36)
PD-L1	< %50	8 (32)
	≥ %50	15 (60)
	Missed data	2 (8)
Stage at diagnosis	Non-metastatic	13 (52)
	Metastatic	12 (48)
Site of metastasis	Cranial	2 (8)
	Liver	8 (32)
	Lungs	20 (80)
	Bone	12 (48)
	Adrenal gland	3 (12)

ECOG: Eastern Cooperative Oncology Group performance status.

Table 2. Immunotherapy agents and treatment responses.

	n (%)
Immunotherapy agents	
Pembrolizumab	11 (44)
Atezolizumab	8 (32)
Nivolumab	6 (24)
Lines of immunotherapy	
2nd line	11 (44)
≥3rd line	14 (56)
Median	3 (2-5)
Immunotherapy cycles median (range)	5 (1-27)
Immunotherapy treatment response	
Partial response	12 (48)
Stable disease	8 (32)
Progressive disease	1 (4)
Hyperprogressive disease	4 (16)
Duration of follow up median (range) (month)	14.7 (4.9-19.6)
Duration of treatment median (range) (month)	6.9 (2.1-14.2)
Duration of response median (range) (month)	6.3 (4.1-10.3)
Progression on immunotherapy	19 (76)
Death	14 (56)

Table 3. The clinical features of the patients related to radiotherapy.

		n (%)
Radiotherapy history	Present	14 (56)
	Absent	11 (44)
Radiotherapy timing	Before starting immunotherapy	12 (85.8)
	Receiving immunotherapy	2 (14.2)
Radiotherapy sites	Bone	6 (43)
	Thorax	5 (35.7)
	Cranial and bone	1 (7.1)
	Cranial	1 (7.1)
	Neck lymph nodes	1 (7.1)
Radiotherapy to immunotherapy interval median (range) (month)		6.4 (1.0-11.8)

Table 4. Adverse effects observed with the use of immunotherapy.

Adverse effects	Grade 1-2 n (%)	Grade 3-4 n (%)
Fatigue	7	-
Hepatic enzyme elevation	4	-
Anaemia	3	-
Hypothyroidism	2	-
Hypercalcemia	-	2
Pneumonitis	1	-
Cough	1	-

Treatment-related adverse events are shown in Table 4. Except for 2 cases with grade 3-4 hypercalcemia, there were no grade 3-4 side effects in any of the cases. Grade 1-2 fatigue in 7 patients, grade 1-2 transaminase elevation in 4 patients, grade 1-2 anemia in 3 patients, grade 1-2 hypothyroidism in 2 patients, grade 1-2 cough in 1 patient, and grade 1 pneumonitis in 1 patient were reported. No deaths or withdrawal of treatment due to adverse events were reported.

Discussion

Our study revealed that patients who received RT had longer PFS and OS in patients with NSCLC lacking predictive test for immunotherapy response in the second and subsequent lines.

Irradiation of the tumor results in the release of tumor-associated antigens and molecules called damage-associated molecular patterns that can produce an immunogenic response. This phenomenon is defined as in-situ vaccination.[15] Calreticulin translocation on tumor cells' surface due to radiotherapy is described as cancer cells' immunological death.[16] Co-stimulants such as deoxyribonucleic acid, adenosine triphosphate, high-mobility group box-1, and interferon β released due to this death cause the activation of dendritic cells, which increases antigen presentation to cytotoxic T cells.[16] Radiotherapy leads to vascular normalization with increased nitric oxide secretion from macrophages. Chemokines such as CXCL10 and CXCL16 cause an increase in cytotoxic T-cell in the tumor microenvironment.[16] Schaue et al.[17] revealed that RT increases tumor-specific T cells in patients during and after treatment. Several have shown that PD-L1 expression is increased in tumors and myeloid cells of mice treated with RT.[17-19] PD-L1 is upregulated as an escape mechanism from the radiotherapy-induced anti-tumor immune response.[20] However, in low immunogenic mouse tumors and most cancer patients, RT alone is insufficient to provide an effective immune response.[21] Demaria et al.[22] first demonstrated the synergistic effect between RT and an anti-T-lymphocyte-associated protein-4 inhibitor in a mouse with metastatic breast cancer. Preclinical studies have shown that anti-tumor is combined with radiation therapy.[17-19] In Gong et al.[23], it was found that RT could increase PD-1/PD-L1 as an immunosuppressive effect, and the use of immunotherapy agents could reduce the immunosuppressive effect and increase the abscopal effect. In the secondary analysis of the KEYNOTE 001, phase 1 trial of pembrolizumab in advanced stage NSCLC patients, it was found that patients who had previously received RT had longer PFS and OS than those who did not.[24] In the randomized phase 2 study in patients with advanced NSCLC, higher response rates, and longer PFS were obtained in patients who received pembrolizumab after stereotactic body RT (SBRT) comparing pembrolizumab alone.[25] Fiorica et al.[26] studied immunotherapy plus RT versus immunotherapy alone in patients with metastatic NSCLC. They found a statistically significant difference in OS

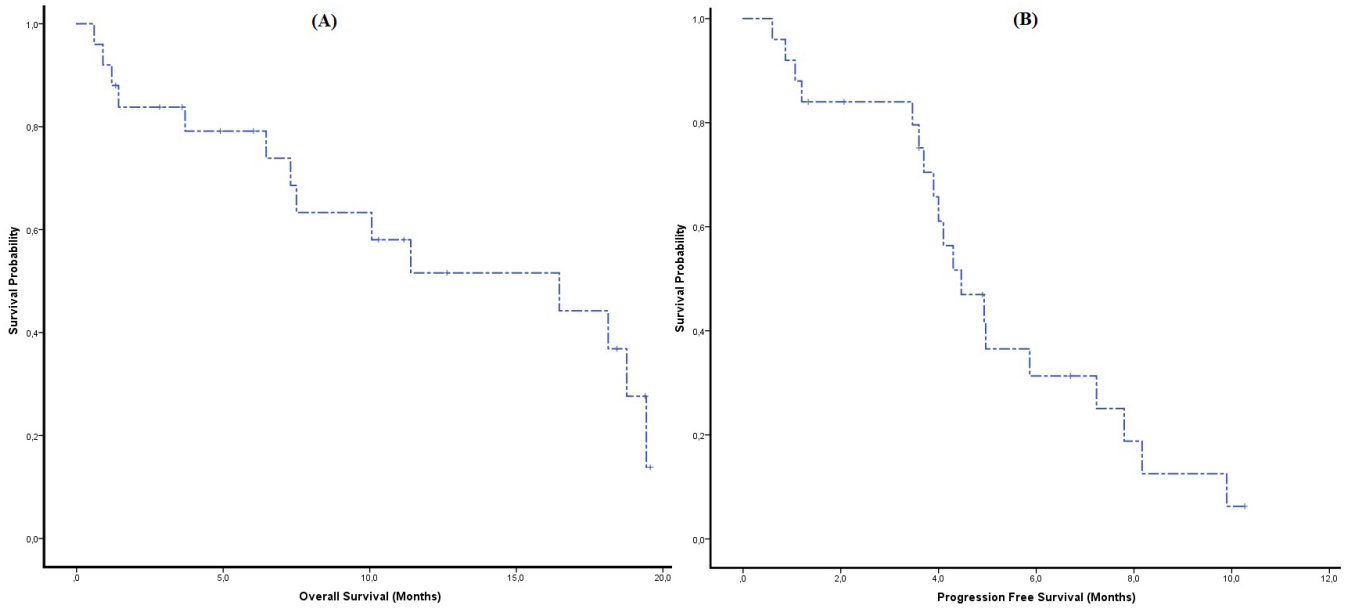

Figure 1. Overall survival (OS) (A) and progression-free survival (PFS) (B) of all patients.

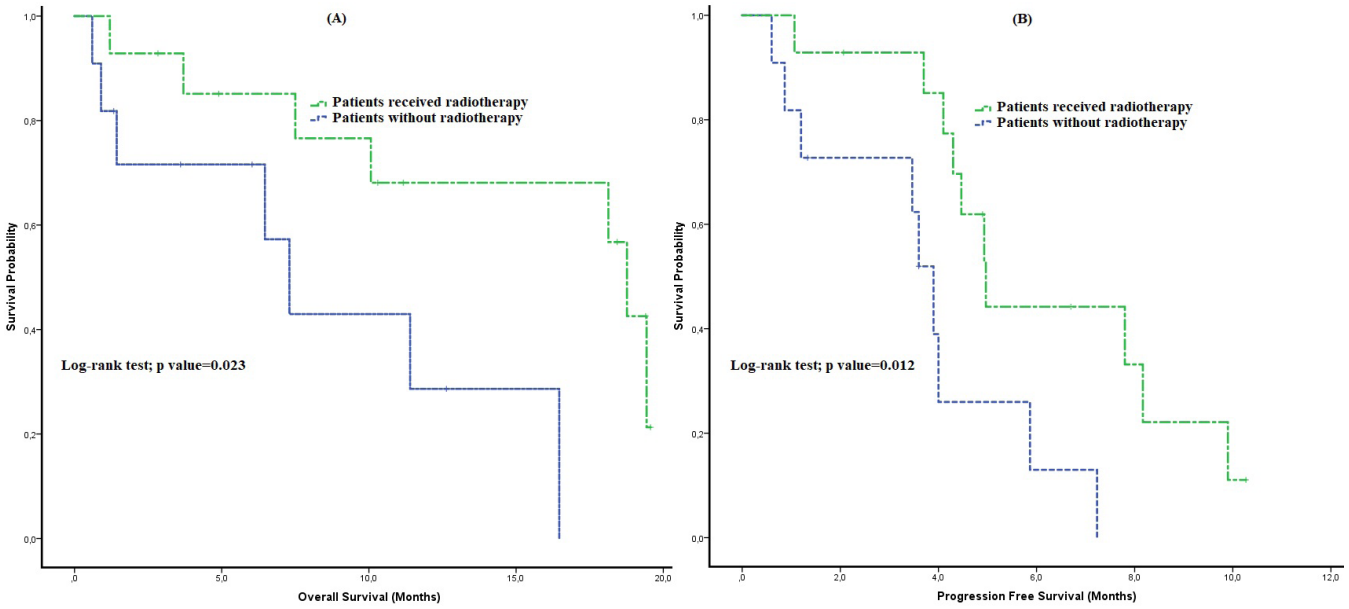

Figure 2. Overall survival (OS) (A) and progression-free survival (PFS) (B) according to radiotherapy.

and PFS in patients receiving hypofractionated RT plus nivolumab compared to those receiving nivolumab alone. Although these data support the effectiveness of RT on immunotherapy, there is no consensus on the RT dose and site (primary or metastatic site).[27] Therefore, there are no recommendations regarding RT in this setting in the current international guidelines.[3,11]

For immune cells to have a cytotoxic effect on tumor cells, tumor recognition via antigen presentation and T cell activation is required. Radiotherapy is considered to improve the anti-tumor immune response priming, and anti-tumor activity is obtained by removing checkpoint inhibition with immunotherapy.[28] We think that the better PFS and OS results obtained with immuno-RT compared to immunotherapy studies in the second and subsequent lines are due to the synergistic effect of RT on immunotherapy.[29-32]

There are concerns about increased side effects associated with the combination of RT and immunotherapy.[19,33] In patients who had previously received thoracic RT, pulmonary toxicity of any severity was observed in 63% (15 of 24 patients) in the KEYNOTE 001 trial.[24] In our study, the rate of grade 1 pulmonary toxicity was 20% (1 in 5 patients receiving thoracic RT). There is no consensus on how long immunotherapy treatment can be safely initiated after RT and which patient group is riskier for pulmonary toxicity in patients receiving thoracic radiotherapy. Patients who have previously received thoracic RT should be followed up more closely for pulmonary side effects.[24] Prospective randomized controlled studies are needed to address these uncertainties. Although stage 1-2 transaminase elevation was observed in two patients who received simultaneous immunotherapy and RT for bone metastasis and whose RT area was close to the lungs, pulmonary toxicity was not observed.

Limitations

Our study's main limitations are the retrospective nature, the limited number of patients, the use of different immunotherapy agents, and the inability to determine the PD-L1 level after RT. Also, we could not perform multivariate analysis due to the small number of patients.

Conclusions

It remains unclear which patient would benefit from immunotherapy in second-and later lines in NSCLC treatment. However, our findings have revealed that patients receiving RT had more prolonged survival significantly on immunotherapy in patients with NSCLC, claiming that RT may be used to increase immunotherapy efficacy. These findings should be supported by further studies involving a larger number of patients.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: BO, SS; Study Design: BO, ABS; Supervision: BC; Data Collection and/or Processing: BO, BD, KG, BC; Statistical Analysis and/or Data Interpretation: BO, OT, ABS; Literature Review: BO, AD, EC, TE; Manuscript Preparation: BO; and Critical Review: SS, AD, OT, EC, TE.

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