Original Article

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Effects of Low-Dose Radiation on the Survival of Lung Cancer Patients

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ABSTRACT

Objective: Some previous studies have shown that low-dose radiotherapy (RT) can increase tumor invasion and metastasis. Multiple RT fields are usually used to prevent the damage to the organs at risk. We performed a clinical study with a concern that low-dose RT might increase invasion or metastasis. Ionizing radiation (IR) can enhance the potential tumor micro-environment by modifying the host micro-metastatic cancer cells.

Methods: We conducted a retrospective study on 50 patients aged between 45 and 87 years, who were applied RT and/or chemotherapy, had the Eastern Cooperative Oncology Group performance status (ECOG) between 1 and 3 and stage II-III lung cancer, and were without any metastasis. RT was applied at daily fractions of 180–200 cGy (5 days/week) and a 54-66 Gy total dose. V5, V10, V20, V40, V50, and V60 values of the lung in a disease-free life, and general life effects statistically analysed with Mann-Whitney U and L Par testS.

Results: A lower RT dose range, which produced V5, V10, and V20 volume values of the lung, was analyzed. It was observed that the V5, V10, and V20 RT volumes of the lung provided a minimal positive effect on relapse-free and general survival according to the R-correlation values.

Conclusion: Larger studies are necessary according to these results to evaluate the impact of low-dose radiation and to increase the survival rates.

Keywords: V5, V10, V20, micro-environment, antiangiogenic

Introduction

Ionizing Radiation (IR) can increase the metastatic potential of host micro-cancer cells by altering the tumor microenvironment (1, 2). Leukocytes, macrophages, fibroblasts, myofibroblasts and nerve cells form the tumor microenvironment (3-6). In order to prevent damage to normal tissues and organs that are at risk and around the tumor, multiple RT fields with daily low-dose fraction are usually used. In this way; while effective, potential and high curative dose is applied to the tumor, low-dose RT volume that the tissues around the tumor receives increases (1, 2).

It was shown that daily doses of 0.5-0.8 Gy did not generate any DNA double-strand fractures, and did not perform arrest or apoptosis in the cell cycle. Low-dose RT increases endothelial cell migration and inhibits the endothelial cell-killing effect with VEGF neutralizing effect of the chemotherapeutic drug Bevacizumab. Moreover, low-dose RT may increase tumor growth and metastases by increasing angiogenesis (7, 8). According to the results of these studies, different studies can be conducted in order to increase the rates of survival by evaluating RT results from a different perspective.

Methods

A clinical retrospective cohort study was performed on 50 stage II-IIIB lung cancer patients in whom radiotherapy and /or chemotherapy was performed in Bezmialem Vakif University Medical Faculty Department of Radiation Oncology between January 2011 and January 2015, whose ECOG performance scores were between 1 and 3, ages were between 45 and 87, and who did not have any metastasis. This study was conducted in accordance with the Declaration of Helsinki.

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Table 1. Patient characteristics

Patient characteristics	Number of patients	%
Age		
45-60	18	36
61-70	23	46
71-87	9	18
Performance (ECOG)		
1-2	31	62
3	19	38
Pathology		
NSCLC	43	86
SCLC	7	14
Treatment		
RT-CT	39	78
RT	11	22
IMRT	15	30
3D Conformal	35	70
Total	50	100

ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; RT: radiotherapy; CT: chemotherapy

Table 2. RT Treatment characteristics

RT characteristics	Median	Minimum	Maximum
RT fraction dose (cGy)	200	180	200
GTV (mL)	125	8	806
PTV (mL)	516	163	2133
V5 lung (mL)	1702	35	3518
V10 lung (mL)	1266	16	2801
V20 lung (mL)	986	4	1892
V30 lung (mL)	766	1	1472
Number of patients receiving RT	3	2	7

RT: radiotherapy; GTV: Gros tumor volume; PTV: planned target volume; V5: volume of the lung that received 5 Gy radiotherapy; V10: volume of the lung that received 10 Gy radiotherapy; V20: volume of the lung that received 20 Gy radiotherapy; V30: volume of the lung that received 30 Gy radiotherapy

Table 3. Chemotherapy characteristics

CT characteristics	Number of patients
Cisp Gems	11
Tax Cisp/Carbo	14
Cisp Etop	7
Others	7
Total	39

Cisp: cisplatin; Gems: gemcitabine; Carbo: carboplatin; Etop: etoposide

Radiotherapy

After FDG 18 PET CT (Positron Emission Tomography Computed Tomography) images were obtained at the RT planning position and the images were obtained from CT simulation; RT was planned with the LINAC device, in MLC blocks and with the conformal or IMRT technique by overlapping the involved areas in PET CT. RT was applied with 180-200 cGy fraction daily. PTV areas were created by giving 0.5-1 cm margin to GTV region. The involved lymph nodes in the mediastinum were also included in the region. After the administration of 40-46 Gy, the dose was increased to 60-66 Gy by giving 0.3-0.5 cm margin to the GTV tumor site (Table 2). Volume 5, volume 10 and volume 20 (V5, V10, V20) were defined as the volume of lungs receiving the doses of 5, 10, and 20Gy, respectively. The minimum GTV volume was 8 mL, the maximum GTV volume was 806ml, and the minimum V5 was found as 35mL and the maximum V5 was found as 3518 mL (Table 2). The median conformity index was found as 97% and the median homogeneity index was 0.35. The targeted PTV received 90-95% of the 95% surface isodose. RT was performed with 6-18MeV X rays in Median 3 area.

Chemotherapy

Chemotherapy (CT) was performed in thirty-nine patients. While CT was given in 18 patients simultaneously with RT, it was given before RT in 11 patients and after RT in 10 patients. CT regimens containing cisplatin and gemcitabine were applied in 11 patients, and CT regimens containing Taxol cisplatin/Carboplatin were applied in 14 patients (Table 3).

Statistical analysis

RT planning data of the patients were collected and analyzed (Table 2). The effects of V5, V10, V20, V40, V50, V60 values of the lung on disease-free survival and overall survival were analyzed statistically with lLPar and Mann-Whitney U test.

Results

It was determined that the V5, V10 and V20 values forming the low-dose RT areas of the lung affected the recurrence-free survival and overall survival positively at a minimal level in reference to r correlation values. r was determined as 0,055 for recurrence-free survival V5, as 0,115 for overall survival V5, as 0.154 for recurrence-free survival V10, as 0.120 for overall survival V10, as 0,048 ecurrence-free survival V20, and as -0,021 for overall survival V20. A daily dose of 180 cGy was found to have a positive effect on the rate of recurrence-free survival (r=0.388). Median recurrence-free survival was found as 6 months and median overall survival was 10 months. Although it was not included in the hypothesis of the study, the complete response was found to be the most important factor affecting

the overall survival positively in the results of statistical analyses (p=0.024). In early recurrences, brain metastases were rather found significant (p=0.006).

Grade II (10%) radiation pneumonia was seen in five patients and grade III (2%) radiation pneumonia was seen in one patient in whom RT and CT were applied simultaneously. Grade I-II hematological toxicity was seen in 47 patients (94%) and grade III hematological toxicity in 7 patients (14%). Grade I-II esophagitis developed in 45 patients (90%).

Discussion

There are studies about the pro-metastatic effect of radiation in the literature (2). With the effect of RT, there are findings that there is a tendency for metastases, because of resistant cells occurring during or after RT and because RT rapidly changes the tumor microenvironment. It has also been shown that radiation increases pro-angiogenic molecules (4). In addition, it is known that high-dose radiation is involved in the adjuvant and radical RT protocols with significant anti-angiogenic and cytotoxic effects and that it prevents recurrences (9-11).

Because there are findings in the literature showing that 50-80 cGy daily doses increase metastases (1); V5, V10 and V20 lung doses, which are closest to the daily dose of 50-80cGy, have been targeted.

It was observed that V5, V10 and V20 values forming the low-dose RT areas of the lung did not cause a significant increase or decrease in the recurrence-free survival and overall survival rates in reference to the p value. Minimal positive values were obtained only at r correlation values. Median recurrence-free survival was 6 months and median overall survival was 10 months. Although it was not included in the hypothesis of the study, the complete response was found to be the most important factor affecting the overall survival positively in the results of statistical analyses (p=0.024). The toxicity rates are low.

Conclusion

In this study, it was shown that high levels of V5, V10 and V20, which are low RT dose areas of lung, have a minimal positive effect on recurrence-free and overall survival. This study has been conducted with the assumption that RT may have a negative contribution due to the metastases seen in patients with lung cancer during or after treatment. Because multiple areas have large advantages, there is the problem of more multiple areas and more low-dose RT areas with new technologies, and this makes us uneasy. This is an original study. It has been shown that low-dose RT areas do not shorten survival rates and may even provide a minimal contribution in a 4-year period. However, because the number of patients is low and heterogeneous, more homogeneous studies with more patients are needed.

Ethics Committee Approval: Academic committee approval was received for this study from the Academic committee of Bezmialem Vakif University, Faculty of Medicine, Deparment of Radiation Oncology at 20.12.2014 with no:35/2011.

Informed Consent: Written informed consent was obtained from patients or patients' parents during the treatment who participated in this study. It has not been approved for this study because it is a retrospective study and there are no circumstances that would violate patient rights.

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