Dosimetric Evaluation of Adaptive Therapy in Non-Small Cell Lung Cancer Patients Undergoing Palliative Thoracic Radiotherapy

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ABSTRACT

This study aimed to describe changes in gross tumour volume (GTV) that occurred during the course of radiotherapy (RT) in patients who underwent palliative thoracic radiotherapy (PTR), and to describe the role of adaptive treatment for protection of normal tissue. Twenty patients with non-small cell lung cancer (NSCLC) referred for PTR were treated using a total of 10 fractions and a dose of 300 cGy/day in accordance with the initial GTV, clinical target volume (CTV), and planning target volume (PTV). Computed tomography simulation (CTS) images were retaken for each patient at the end of the fifth fraction, and the second plan was created. The fractional volume reduction (FVR) of the GTV and the PTV were then calculated. The changes in normal tissue dose-volume histogram (DVH) parameters between the two plans were compared. Mean GTV and PTV values were 223.9 cc and 1113.3 cc for the first plan and 196.2 cc and 1029.7 cc for the second plan , respectively. After five fractionated treatments, the FVR was 15.9% of the GTV ($p < 0.001$) and 8% of the PTV ($p< 0.001$). The daily regression for GTV was 3.1 percent. A statistically non-significant decrease occurred for the normal tissue doses. The geometric changes in GTV and PTV positively influenced the DVH parameters, but were not statistically significant. The clinical implications of this approach to CTS plan assessment should be examined using prospective studies with adequate number of patients.

Keywords: Non-small cell lung cancer, Adaptive radiotherapy, Palliative radiotherapy

ÖZET

Palyatif Torasik Radyoterapi Uygulanan Küçük Hücreli Dişi Akciğer Kanseri Hastalarinda Adaptif Tedavinin Dozimetrik Değerlendirmesi

Bu çalışmada palyatif torasik radyoterapi uygulanan hastalarda radyoterapi süresince gözlenen görüntülenebilir tümör hacim (GTV) değişikliklerini ve normal doku korumadaki rolünü göstermek amaçlanmıştır. Palyatif torasik radyoterapi planlanan küçük hücreli dışı akciğer kanseri (KHDAK) tanılı 20 hasta, başlangıçtaki GTV, klinik hedef hacim (CTV) ve planlanan tedavi hacmine (PTV) göre yapılan planlama ile 300 cGy/gün ile toplam 10 fraksiyonda tedavi edilmiştir. Beşinci fraksiyon sonunda hastaların bilgisayarlı tomografi simülatör (BTS) görüntüleri tekrarlanmış ve yeniden GTV, CTV, PTV ve normal dokular tanımlanarak ikinci planlamalar yapılmıştır. Beşinci fraksiyondaki GTV ve PTV' de fraksiyone hacim azalması (FHA) hesaplanmış ve her iki planlama arasında normal doku doz-hacim histogramı (DVH) parametrelerindeki değişimler incelenmiştir. İlk planda ortalama GTV ve PTV değerleri sırasıyla 223.9cc ve 1113.3cc, 2. planda ise sırasıyla 196.2cc ve 1029.7cc olarak bulunmuştur. Beş fraksiyon tedavi sonrasında GTV' de FHA %15.9 ($p< 0.001$), PTV' de ise %8 ($p< 0.001$) olarak hesaplanmış, GTV için günlük regresyon oranı %3.1 olarak bulunmuştur. Normal dokuların dozları incelendiğinde ortalama kalp, özefagus, akciğer ve maksimum medulla spinalis dozlarında istatistiksel anlamlılığa ulaşmayan azalma tespit edilmiştir. Bu çalışmada radyoterapi süresince tekrarlanan BTS görüntülerinde GTV ve PTV' de gözlenen geometrik değişiklikler DVH parametrelerini olumlu yönde etkilemiş olmasına rağmen istatistiksel anlamlı düzeye ulaşamamıştır. BTS planlamaları üzerinden yapılan bu değerlendirmemizin klinik yansımalarının prospektif ve daha fazla hasta sayılı çalışmalarla yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, Adaptif radyoterapi, Palyatif radyoterapi

INTRODUCTION

Lung cancer accounts for 13% of all cancer patients and 18% of cancer deaths worldwide. Lung cancer was previously classified into two groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). To aid in choosing effective systemic therapy, NSCLC is also currently divided into the subtypes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1]

NSCLC accounts for more than 85% of all lung cancer cases. Approximately 75-85% of patients have advanced disease. The mean survival time of these patients is 6 to 9 months. Palliative thoracic radiotherapy (PTR) is applied to most of these patients for the palliation of intrathoracic symptoms (e.g., cough, haemoptysis, dyspnoea, and chest pain). Palliation is provided at least 50% of the survival time, but the palliation level of each symptom differs. Haemoptysis and chest pain response to PTR are greater, compared with the other symptoms.[2-5]

The goal for patients who are referred for PTR should be optimal control, acceptable treatment toxicity, limitation of treatment time, and avoidance of hospitalization. It is unclear, however, which fractionation scheme offers the best response and the lowest toxicity. The result of previous studies indicated that short fractionation scheme PTR (e.g., 10 Gy/1f, 16–17 Gy/2f, and 20 Gy/5f) results in good symptomatic improvement in patients with thoracic symptoms and who, in general, have a poor performance status. The short fractionation schemes for patients who receive palliative systemic treatment for recently initiated thoracic symptoms are inserted between chemotherapy cures to ensure that patients can continue treatment without interruption. Longer fractionation schemes, such as 36Gy/12f, are recommended for patients who are in a generally good performance status because there is a survival benefit in spite of the disadvantages associated with the increased toxicity risks and extended treatment times. There is currently no specific long fractionation scheme that provides maximum survival and symptom palliation with minimal toxicity.[6,7]

Adaptive radiotherapy is defined as the renewal of the treatment plan during radiotherapy (RT). It incorporates the changes in tumour volume, shape, and position revealed by weekly computed tomography simulation (CTS) images.[8] The results of several studies that evaluated adaptive treatment for locally advanced-stage NSCLC have been published. Tumour volume decreases during definitive RT in patients diagnosed with locally advanced-stage NSCLC. Kupelin, et al. reported a daily tumour volume reduction of 1.2% (0.6%-2.3%) in 10 patients.[9] During treatment, safe dose distribution can be achieved via customization of field size and treatment dose for each patient in accordance with gross tumour volume (GTV) reduction.[10] Ramsey et al. found a mean GTV reduction of 31% (21%-41%) during adaptive treatment compared with non-adaptive treatment. The ipsilateral lung volume receiving over 20Gy decreases 21% (17%-23%) and there is 17% (11%-24%) less reduction in lung perfusion.[11] RT outcomes can be improved by systematic evaluation of treatment variations and re-optimization of the treatment plan during adaptive treatment.[10]

The objectives of this study were to examine the extent of change in GTV during PTR. Tumour volume and localization changes, external contour changes (e.g., weight loss) and presence of atelectasis, and the effects of volume changes on treatment quality and on the total treatment plan (i.e., initial and new plan) were included in the assessment.

PATIENTS AND METHODS

We evaluated retrospective computerized RT planning data (1 June 2010 - 30 April 2011) from 20 patients diagnosed with NSCLC, and treated using PTR (Akdeniz University Faculty of Medicine, Department of Radiation Oncology, Antalya, Turkey). The study was approved by the institutional ethics committee.

Patient Characteristics

The mean patient age was 61 (range, 50-82); the NSCLC stages were identified as IIIB and IV ac-

Table 1. Characteristics of the treatment plans.

	Plan I	Plan II
Number of patients	20	20
CT	Pretreatment	Pretreatment and after 5th fraction
Fraction (f)	10	5+5
GTV	GTV1(10 f)	GTV1 (5 f) GTV2 (5 f)
PTV	PTV1= CTV1+ 10-15 mm (10 f)	PTV1 (5 f) PTV2= CTV2+ 10-15 mm (5 f)
Treatment plan & DVH	Single treatment plan and DVH evaluation with pretreatment CT images	Combined treatment plan and DVH evaluation with pretreatment and after 5 fraction CT images

GTV: Gross tumour volume; CTV: Clinical target volume; PTV: Planning target volume; DVH: Dose-volume histogram; CT: Computed tomography.

cording to the tumour, node, and metastasis (TNM) staging system. Eastern Cooperative Oncology Group (ECOG) performance status before RT was between 1 and 3. Seven (35%) patients (stage IIIB disease) who were not suitable candidates for definitive treatment due to low performance status and comorbid disease were referred for PTR. The remaining 13 (65%) patients (stage IV disease) were also initially treated using PTR.

Radiotherapy

For planning the RT, CTS images of the patients were taken (adjacent axial slice spacing 2.5 mm; GE-Lightspeed64® computed tomography simulator, GE, Fairfield, USA) while their hands were placed on their heads. The entire thorax, from the apex to the diaphragm, was included in each image. Diagnostic computed tomography (CT) thoracic images were also taken of the 13 patients with stage IV disease to identify target volume. Additional positron emission tomography (PET-CT) was used for the other seven patients. The tumour volume, which included the primary tumour and the mediastinal lymph nodes, was contoured as GTV. To determine the clinical target volume (CTV), 7 mm was added to the GTV. The planning target volume (PTV) was obtained by adding 15 mm in the superior-inferior direction, and 10 mm for the right-left and anterior-posterior directions to the CTV. To determine the treatment volume, an extra margin of 10 mm was added to the PTV. The oesophagus, heart, lung, and medulla spinalis volumes were also determined. The isocentre was located to the centre of the PTV using RT planning software (Precise, ELEKTA®, Stockholm, Sweden). The RT was planned to ensure that the prescribed dose distribution was ± 5 percent. A total of 3000 cGy RT was planned (10 fractions, daily fractional dose of 300 cGy, mean PTV dose of 3098 cGy [3008 cGy-3197 cGy]). Three-dimensional conformal RT was scheduled for each patient. Patients were treated with a linear accelerator (ELEKTA®, Synergy Platform, West Sussex, UK) using 10 MV photon beams.

The study examined the tumour volume dependent changes in dose-volume parameters for the patients, for whom new plans were developed for the last five fractions of the treatment. CTS images were retaken of each patient after the fifth treatment fraction. The same doctor again identified GTV, CTV, PTV, and normal tissue volumes of the oesophagus, heart, medulla spinalis, and both lungs.

Two groups of plans were developed to compare tumour volume changes and dose-volume histogram (DVH) parameters (Table 1). For the first plan, the CTS images that were taken before treatment were used for every patient. GTV1, CTV1, PTV1, and normal tissues were identified. The treatment was planned as 30Gy/10f, with the isocentre in the centre of PTV1. DVH parameters were recorded for the first plan. For the second plan, GTV2, CTV2,

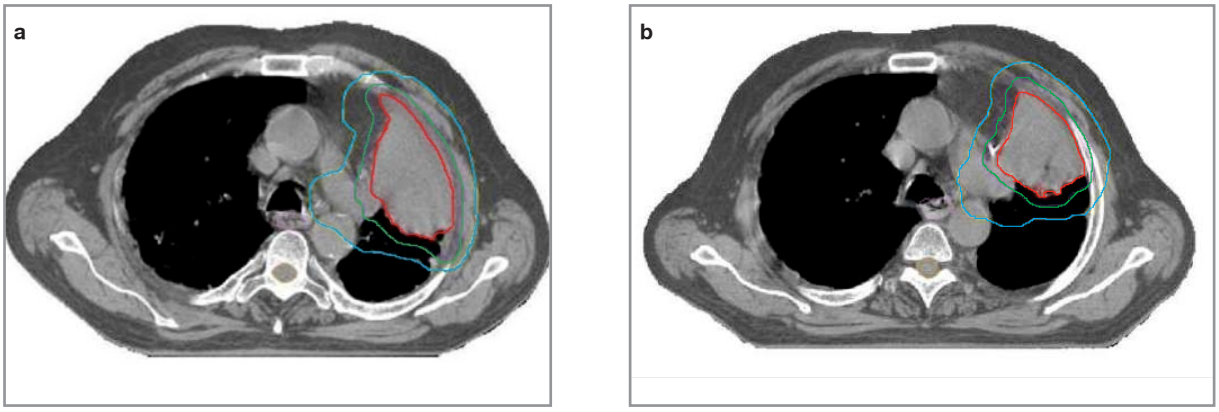

Figure 1. Gross tumour volume (red line), clinical target volume (green line), and planning target volume (blue line) defined in the axial section in computed tomography simulation images of the same patient before treatment (a) and after the fifth fraction (b).

PTV2, and normal tissues were identified in the CTS images of each patient, taken after the fifth fraction (Figure 1). A treatment plan using a total of 30Gy/10f was developed in two stages. It included the first five fractions using the CTS images (isocentre in the PTV1 centre) and the last five fractions using the CTS images taken after the fifth fraction (isocentre in the centre of PTV2).

Each patient's DVHs associated with the first and second RT plans were assessed separately. For normal lung tissue, the PTV was subtracted from the whole lung volume, and the mean lung dose was estimated using the remaining volume. The lengths of the medulla spinalis and oesophagus, their mean and maximum doses, and the mean dose for the heart, were calculated.

The fractional volume reduction (FVR) in GTV and PTV in the fifth fraction was calculated using: FVR= 100 x (V1-V2)/V1 (V1= volume before treatment, V2= volume in the fifth fraction). The GTV daily regression rate was calculated as a ratio of fractional volume reduction to treatment duration.

Statistical Analysis

The paired sample t test was used to determine the significance of the tumour volume changes in the repeated CTS images. The unpaired sample t test was used to compare differences in tumour volumes and DVH parameters between the adaptive and non-adaptive planning groups.

RESULTS

The 20 patients who were diagnosed with NSCLC and treated with PTR were assessed. The CTS images taken before treatment and after the fifth fraction were taken at a 9-day interval.

Volumetric Assessment

The results for the first plan indicated that the mean GTV values were 223.9 cc (22.5 - 747.4 cc) before, and 196.2 cc (13.8 - 742.9 cc, $p< 0.001$) after the five-fraction treatment. The mean PTV values were 1113.3 cc (306.8 - 2561.2 cc) before, and 1029.7 cc (274.9 - 2507.5 cc) after the fifth fraction. The fractional volume reduction was 15.9% (7.7 - 41.5; $p< 0.001$) for GTV and 8% (1.4 - 27.9; $p< 0.001$) for PTV (Table 2). The GTV daily regression rate was 3.1%, calculated as a ratio of fractional volume reduction to treatment duration.

The results for the first plan also indicated that the mean field size was 261 cm^2 (110 - 478.6 cm^2) before, and 245.2 cm^2 (106.8 - 483 cm^2) after, the fifth fraction. The mean reduction in field size was 5% (1.7 - 21.7; $p= 0.003$).

The mean oesophagus length measured in the treatment field was 12.9 cm (4.2 - 21.9 cm) for the first plan, and 12.9 cm (2.5 - 20.8 cm) for the second plan. The mean medulla spinalis length was 11.7 cm (1.0 - 22.9 cm) for the first plan, and 11.2 cm (0.5 - 22.2 cm) for the second plan. There were differences between the two plans in terms of the lengths of the oesophagus and medulla spinalis.

Table 2. Volumetric assessment of gross tumour volume (GTV), planning target volume (PTV), and field size.

	Plan I	Plan II	Reduction (%)	p value
GTV	223.9 cc	196.2 cc	15.9	< 0.001
	(22.5- 747.4 cc)	(13.8- 742.9 cc)		
PTV	1113.3 cc	1029.7 cc	8	< 0.001
	(306.8- 2561.2 cc)	(274.9- 2507.5 cc)		
Field Size	261 cm2	254.2 cm2	5	0.003
	(110- 478.6 cm^2)	(106.8- 483 cm^2)		

Dosimetric Assessment

The results for the doses for the normal tissues indicated that the mean heart, the mean oesophagus, the mean lung, and the maximum medulla spinalis, doses all decreased. The result for the dosimetric values for the heart, oesophagus, lung, and medulla spinalis are presented in Table 3.

The results for the dosimetric data for the normal tissues indicated that the decreases in maximum mean doses were 3.3% (–14.9% - 17%; p= 0.077) for the heart, 1.35% (–28.5% - 23.5%; p= 0.599) for the oesophagus, 2.9% (–18.5% - 52%; p= 0.336) for the lung, and 1.2% (–36.6%–23.4%; p= 0.630) for the medulla spinalis (dmax) doses. These findings were not statistically significant.

DISCUSSION

PTR is used for most stage III NSCLC patients who have poor prognostic factors for the palliation of intrathoracic symptoms (e.g., cough, haemoptysis, dyspnoea, and chest pain). PTR is also used to treat patients with stage IV NSCLC. There is currently no consensus regarding the fractionation scheme that should be used for the most effective, minimally toxic, treatment.

Using a randomized study design, Erridge et al. compared the 30Gy/10f and 10Gy/1f treatment schedules in 148 patients (12). The median survival times were 28.3 and 22.7 weeks (p= 0.197), respectively. The longer fractionation scheme did not provide a statistically significant survival ad-

Table 3. Dosimetric assessment of normal tissues

	Minimum (cGy)	Maximum (cGy)	Mean (cGy)	Reduction (%)	p value
Heart					
Plan I	15	2603	1156		
Plan II	15	2556	1113	3,3	0.07
Oesophagus					
Plan I	232	2681	1566		
Plan II	247	2574	1543	1.3	0.59
Lung					
Plan I	251	1922	770		
Plan II	251	1016	715	2.9	0.33
Medulla Spinalis					
Plan I	830	3390	2769		
Plan II	675	3338	2764	1.2	0.63

vantage and deterioration in dyspnoea was frequent. However, levels of anxiety declined in this group after treatment, there was overall greater general improvement, and there was a statistically significant palliative effect on chest pain. The treatment-based morbidity rates were similar between groups.

Kramer et al. randomly assigned 297 symptomatic patients (stage III and IV with poor performance or loss of weight) to 30 Gy/10f or 16Gy/2f treatment groups.[13] The one-year survival rate was greater in the 30Gy/10f group (19.6% vs. 10.9%, p= 0.03). The palliation effect was also significantly longer (p< 0.001). The subgroup analyses revealed that this advantage was experienced by the patients who had a generally good performance status. Symptom palliation and treatment-based toxicity rates were similar in both groups.

In our clinic, the 30Gy/10f treatment is applied to patients with good performance because it has survival benefits. This treatment is given in accordance with the guidelines of the palliative thoracic RT clinical application manual of the American Society for Radiation Oncology (ASTRO).[7] The 16Gy/2f treatment is applied to patients with poor performance to obtain similar symptom palliation outcomes.

Adaptive RT is one of the methods used for NSCLC patients being treated curatively. This method results in decreased toxicity to normal tissue and allows for an increased tumour dose. To the best of our knowledge, no studies have been published on the applicability of adaptive RT to patients who are treated for palliation.

In a study performed by Yan et al. to identify the between-fraction changes, the investigators predicted, based on repeated imaging during the course of treatment, that PTV margin size could be reduced.[14] They suggested that this method could be the most effective option for adaptive control. They also suggested that RT accuracy could be improved by using adaptive planning to correct systemic set-up errors. In our study, the RT plans of our patients were renewed based on CTS images taken during the fifth treatment fraction.

Table 4. Daily regression ratios for adaptive radiotherapy series from lung cancers[17], compared with the results of the current study.

	Number of patients	Daily regression (%)
Erridge et al.	25	0.9
Kupelian et al.	10	1.2
Siker et al.	25	2.4
Bosmans et al.	23	0.39
Underberg et al.	40	1.4
Britton et al.	8	1.3
Woodford et al.	17	0.79
Van Zwienen et al.	114	0.6
Fox et al.	22	1.2
Feng et al.	14	1.4
Current study	20	3.1

The results of a study of 114 NSCLC patients indicated that tumour volume decreased in only 40% of the patients and that the rate of daily regression was 0.6%.[15] A study on daily volume decrease was also performed by investigators from the Johns Hopkins Hospital.[16] CTS images were retaken twice (after 30 Gy and 50 Gy) during the course of RT for 22 NSCLC patients with stage I, II, or III cancer. The mean decrease in GTV was 24.7% after 30 Gy and 44.3% after 50 Gy. The decrease in daily tumour volume was 1.2%.

The results of a review of the role of adaptive RT for lung cancer treatment indicated that the daily regression rates in tumour volumes of NSCLCs ranges between 0.39% and 2.4% (Table 4).[17] The results of our study indicated that GTV values decreased by 15.9% (7.7 - 41.53) after the fifth treatment fraction (1500 cGy), and that the daily regression in tumour volume was 3.1%. These palliative treatment results were similar to the results of other curative adaptive RT studies.

Woodford et al. assessed three groups of 17 NSCLC patients with locally advanced-stage cancer who were separated according to the decrease in GTV.[18] They suggested that adaptive planning would increase the therapeutic ratio in the first group of patients, all of whom had experienced a significant decrease in GTV. They also suggested that adaptive planning could be considered if the GTV regression exceeded 30% after the 22nd fraction for the patients in the second group, and that adaptive planning would not be beneficial in the third group of patients, who had experienced a rate of regression below 30 percent. They suggested that using resources and labour to develop an adaptive plan would be without benefit if the GTV regression did not exceed the suggested threshold value of 30%.

In our study of the application of palliative thoracic RT, no statistically significant benefits were obtained using normal tissue doses. The results did reveal that there were statistically significant decreases in GTV (15%), PTV (8%), and field size (5%). These changes might have occurred because our patients had large, locally advanced-stage, centrally placed tumours. The low number of patients included in our study might also have contributed to these results. Our results were consistent with the results of Woodford et al., who found that adaptive RT is not beneficial unless a threshold rate of 30% is reached or exceeded.[18]

In conclusion, adaptive palliative thoracic RT can be applied to NSCLC patients. The clinical implications of the results of this assessment of CT plans should be examined using prospective studies with large sample sizes and utilizing new and advanced treatment technologies.

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