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Adaptive Radiotherapy in Head and Neck Cancer

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Abstract:*The aim of this study is to document the changes in anatomy and dose distribution observed in patients diagnosed with head and neck cancer who are undergoing radiotherapy or chemoradiotherapy. 25 patients, who had been diagnosed with head and neck cancer, were included in our study. Cone Beam Computer Tomography (CBCT) was taken every other day and fused with images provided by CT. If tumor volume decreased, Magnetic Resonance Image (MRI) images were taken. By integrating MRI and CT images, critical organs and Planning Target Volume (PTV) were recontoured. Using the new contours, new Adaptive Radiation Therapy (ART) plan were made. The initial treatment plan and the ART plan were compared using T-Testing. If there was a significant difference, patients continued with treatment with the new ART plan. When the adaptive plan was made, there was a significant decrease in critical organ doses. The mean dose for the ipsilateral parotid gland shrank from 3279±608 cGy to 2656±399 cGy (p=0,001) this was a significant decrease. At the same time the mean dose for the contralateral parotid gland decreased from 3008,4 ±377,4 cGy to 2606,2 ± 325,5 cGy (p=0,002). The maximum dose for the spinal cord was decreased from 4542,2±58,5 cGy to 4433,2±55,3 cGy (p=0,001) this was a significant decrease. Adaptive radiotherapy is superior than non-adaptive radiotherapy. To increase the minimum dose in the target volume and reduce the maximum cumulative dose.*

Keywords:*Head and Neck Cancer, Adaptive Radiotherapy, Intensity Modulated Radiation Therapy, Cone Beam Computer Tomography.*

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I. INTRODUCTION

Head and neck cancers constitute approximately 10 to 15 % of all cancers. Worldwide morbidity (number of patients who become sick) and mortality (death) rates of head-neck cancers are lower in comparison to other common cancer types. Head-neck cancer is generally common in advance ages; however, it might be also seen in children. It is rate of incidence is higher in men than women and increase after the age of 50 years. Mortality rates of head-neck cancers are relatively lower than their morbidity rates [1]. Certain types are more common in certain geographical regions (e.g. nasopharynx cancer is more common in the far East countries). Smoking and alcohol consumption are the most important factors. Genetic susceptibility, malnutrition and vitamin deficiency are among the risk factors. Poor oral hygiene, use of unfavorable dentures, chronic infections, gastroesophageal reflux and especially viral infections (EBV, HPV) are the additional risk factor [2, 3].

Epidemiological and histological characteristics among head-neck cancers preclude surgical intervention due to their anatomical localization; however, nasopharynx cancer has a special importance because of their susceptibility to radiotherapy and chemotherapy [4]. Nasopharynx cancer shows direct spread in the early period in cranial bones and parapharyngeal space, and rich lymphatic connections cause close lymphatic involvement in the early period. In parallel with the high rate of lymphatic spread, the rate of systemic spread is also high in accordance to other head-neck cancers with squamous cells. These tumors cause structural degenerations and functional disorders in varying degrees depending on their localization and size [5].

Nasopharyngeal radiotherapy generally involves extensive areas and it is applied in high doses. Therefore, it is possible to observe a substantial sequel (tissue distortion) and side effects.

One of the important side effects is dryness of the mouth (xerostomia) as a result of vestigial parotid gland within high radiation (RT) area. The effect of dryness of the mouth on the quality of life by means of a long-term and sometimes permanent reduction raises the importance of parotid glands in RT [5].

In recent years, increasing environmental pollution, nutrition deficiencies, preservatives, genetically modified foods, contamination of water supplies and nature from industrial wastes, and atmospheric pollution negatively affect human health and life, and cause significant health problems and increase cancer rate [6].

II. PERFORMANCE BASED ANALYSIS

Twenty-five patients with head and neck cancer who received radiotherapy or chemoradiotherapy at the Radiation Oncology Clinic were included in the study. The thirteen patients had nasopharynx, three had hypopharynx, three had orapharynx, three had tongue root and three had larynx tumors.

The informed volunteer consent form was read to the patients who met the criteria stated before the treatment and side effects were explained and if the patients accepted, the form was signed. The patients who accepted the treatment were included in the study.

In all cases, contrast-enhanced head and neck MRI and PET-CT were requested in the treatment position with the treatment mask. The hemogram and routine biochemistry were requested before the beginning of treatment. Head and neck patients who have been given radiotherapy decision in the clinic are informed about the treatment and procedures to be prepared first and it is aimed to prepare them psychologically.

The patient was immobilized with a thermoplastic head and neck mask. For the patient to be comfortable during the treatment process, the most suitable pillow with various slopes and heights was used. The fixing system consists of a mask, cushion and fixing plate. Once properly positioned, sponge is wrapped around the patient's face before the mask is placed. The mask is kept in hot water at 70-75 C° for 1-2 minutes. Becomes able to take the desired shape. It is placed on the face of the patient to take the shape of the head. The patient stays that way until the mask cools down. After the mask is finished, the name of the patient and the number of the pillow used are written on it. Using the arm pull, the shoulders are pulled down. The tongue press was used in 3 patients with tongue root cancer. Planning CT and MRI images were taken under conditions that the patient would receive treatment. The imaging was performed at 3 mm cross-sectional intervals.

All normal tissue and target volumes were drawn by a single physician. The contouring of the target and critical organs was made using 3-mm spaced planning CT sections using Radiation Therapy Oncology Group (RTOG) atlas. MRI and PET-CT planning were performed by CT fusion. The organs at risk are the eye, lens, optic nerve, chiasm, pituitary, mandible, temporal lobe, brain stem, spinal cord, parotid glands, submandibler gland, oral cavity, temporomandibler joint, larynx, thyroid gland, cochlea, pharyngeal muscles and brachial plexus was evaluated.

All cases were planned with Eclipse, version 10.0 treatment planning system with 6 MV energy using Intensity Modulated Radiotherapy (IMRT) and volumetric ARC method. Simultaneous integrated boost (SIB) technique was preferred in 20 patients.

In the 13 of these patients, treatment was given in a total of 33 fractions of 70 Gy to tumor and involved lymph nodes, 60 Gy to medium risk region, and 54 Gy to low risk region. PTV 70 and PTV 54 volumes were defined in the other 7 patients.

The five cases were planned to receive 50 Gy on elective irradiated area and 70 Gy on tumor site and involved lymph nodes by sequential boost technique. The doses taken by the organs at risk and the target volume were evaluated in the dose volume histogram (DVH). As shown in Table 1, the standard dose limitations and optimization parameters applied by our clinic were used for tolerance doses.

Table 1: The standard dose limitations and optimization parameters

Organs	Tolerance doses
Brain stem	Dmax<54 Gy
M. Spinalis	Dmax<45 Gy
Brachial Plexus	Dmax<66 Gy
Parotid	Mean <26 Gy
Submandibler	Mean <35 Gy
Thyroid	Mean <45 Gy
Larynx	Mean <50 Gy, Dmax<66 Gy
Pharyngeal Muscles	Mean <50 Gy
Optic nerve	Dmax ≤ 54 Gy
Kiazma	Dmax≤ 54 Gy
Mandible	Dmax ≤ 70 Gy, Mean ≤ 35-45 Gy
Kohlea	Dmax ≤ 60 Gy, Mean ≤ 50 Gy
Oral cavity	Dmax ≤ 45 Gy, Mean ≤ 35-40 Gy
Temporal lobe	Dmax ≤ 60 Gy
Lens	Dmax ≤ 5 Gy
Temporomandiblejoint	Dmax<70 Gy

The patient's treatment plan was approved by the doctor and was treated with a Varian Trilogy linear accelerator. OBI (Varian Medical Systems, Palo Alto, CA) used in the Varian Trilogy linear accelerator was used for CBCT imaging. The CBCT image of the patient was matched with the planning CT.

The patients were treated with IGRT by online correction with kV taken every day and CBCT taken every other day. The weight of the patients was measured and recorded at the beginning of thetreatment and throughout the treatment period. Oral nutrition solution support was provided to the patients. The supportive treatment was applied for other acute side effects during the treatment.

A CBCT image was taken at the 5th week of the treatment and fusion was performed on the Planning CT imaging device. A decrease in GTV tumor volume was observed due to the patient's weight loss and radiotherapy as well as abundance in the mask of the patient.

The patient underwent MRI and CT imaging again, and these newly acquired images were fused and the patient's treatment mask re-performed. In the second CT, the shrinking GTV volume and critical organs were re-drawn by the doctor over CT. The patient's plan was redesigned and the patient continued treatment according to the new plan. A maximum of 3 days was allowed for the creation of a new plan. For the second plan, the doses were considered to be calculated as missing a maximum of 3 fractions. Planning CT and the target volume at the fifth week and the volumetric changes and dosimetric differences in normal tissues were compared.

If the adaptive plan was made, the treatment gain was evaluated. The twenty-two patients received chemotherapy simultaneously with radiotherapy. The descriptive statistical methods such as mean and standard deviation were used to evaluate the study data.

T-test was used to compare the dose values to be given if adaptive CT and adaptive plan were not performed in order to compare the volume and doses in the CBCT taken in the fifth week of treatment with planning CT.

III. PERFORMANCE EVALUATION OF STRUCTURES

Of the patients, 3 were female and 22 were male. The median age was 53 years. The concurrent radiotherapy and chemotherapy was performed on 22 patients, three patients received only radiotherapy. As shown in Table 2, the mean weight loss was determined as -7,5 kg when all patients were evaluated.

Table 2: Adaptive plan fraction and weight loss of the patients.

Patient no	Fraction no when adaptive plan is performed	Adaptive plan	Weight loss in patients
1	23	+	-10
2	24	+	-6
3	25	+	-7,6
4	25	+	-8,4
5	24	+	-9
6	22	+	-7
7	23	+	-6,5
8	23	+	-8
9	23	+	-6,3
10	25	+	-10
11	25	+	-8
12	25	+	-6
13	25	+	-9
14	24	+	-8
15	24	+	-8
16	22	+	-7
17	22	+	-7
18	25	+	-7
19	24	+	-10
20	23	+	-5
21	24	+	-6
22	23	+	-8
23	24	+	-6
24	23	+	-8
25	25	+	-7

Statistical Analysis Results of Mean Ipsilateral Parotid Dose:

Anderson-Darling test was performed in order to test whether the data were normally distributed or not (Anderson-Darling test is a probability distribution in statistics. It was first published by American statisticians, T. W. Anderson Jr. and D. A. Darling, in 1952 to test the distribution of the sample data as presented in Figure 1 and Table 3.

Hypothesis:

H_0: Data are normally distributed.

H_1: Data are not normally distributed.

Comment:

As H_0 is accepted, H1 is rejectedand P>α, data are normally distributed at the significance level of α=0.01. Thus, the t-test is performed for statistically matched data as data are normally distributed and n<30.

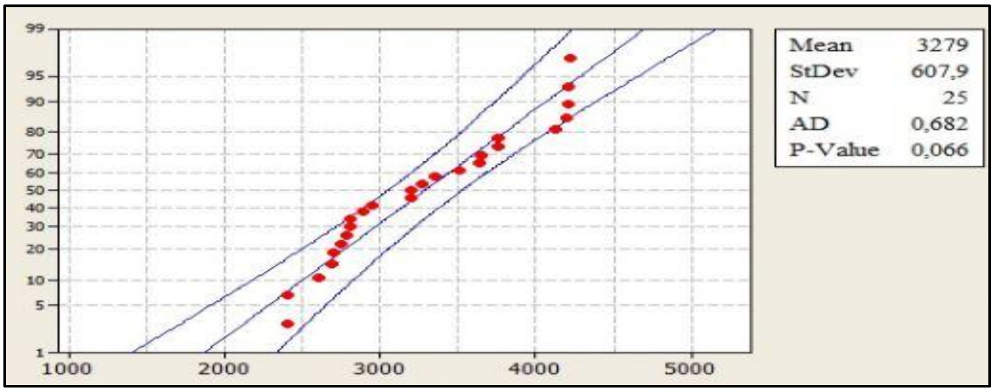

Fig. 1.Distribution and analysis results of mean ipsilateral parotid dose

Statistical Analysis Results of Mean Contralateral Parotid Dose:

Anderson-Darling test was performed in order to test whether the data were normally distributed or not as shown in Figure 2 and Table 3.

Hypothesis:

H_0: Data are normally distributed.

H_1: Data are not normally distributed.

Comment:

As H_0 is accepted, H_1 is rejected and P> α, data are normally distributed at the significance level of α=0.01. Thus, the t-test is performed for statistically matched data as data are normally distributed and n<30.

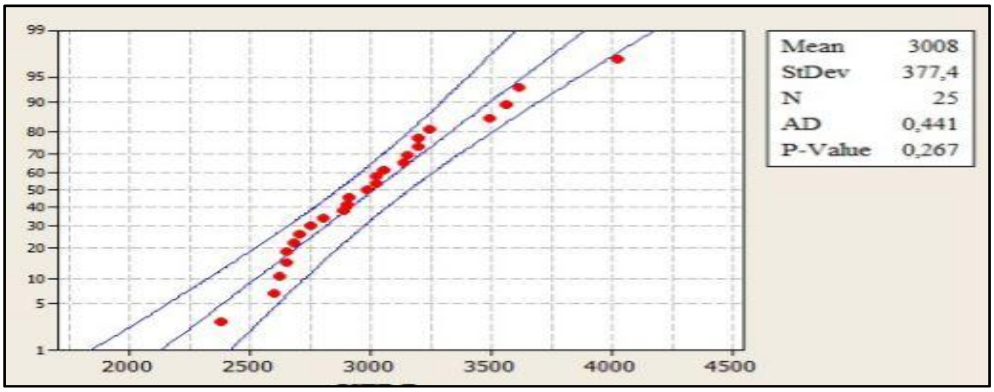

Fig. 2.Distribution and analysis results of mean contralateral parotid dose.

Statistical Analysis Results of Mean PTV 70 Dose:

Anderson-Darling test was performed in order to test whether the data were normally distributed or not as shown in Figure 3 and Table 3.

Hypothesis:

H_0: Data are normally distributed.

H_1: Data are not normally distributed.

Comment:
As H_0 is accepted, H_1 is rejected and $P>\alpha$, data are normally distributed at the significance level of $\alpha=0.01$. Thus, the t-test is performed for statistically matched data as data are normally distributed and n<30.

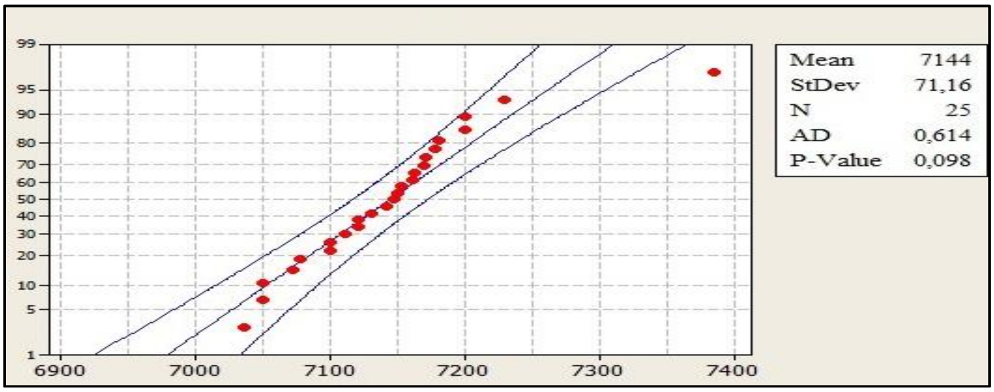

Fig. 3.Distribution and analysis results of mean PTV 70 dose

Statistical Analysis Results of Maximum Spinal Cord Dose:
Anderson-Darling test was performed in order to test whether the data were normally distributed or not as presented in Figure 4 and Table 3.

Hypothesis:
H_0: Data are normally distributed.
H_1: Data are not normally distributed.

Comment:
As H_0 is accepted, H_1 is rejected and $P>\alpha$, data are normally distributed at the significance level of $\alpha=0.01$. Thus, the t-test is performed for statistically matched data as data are normally distributed and n<30.

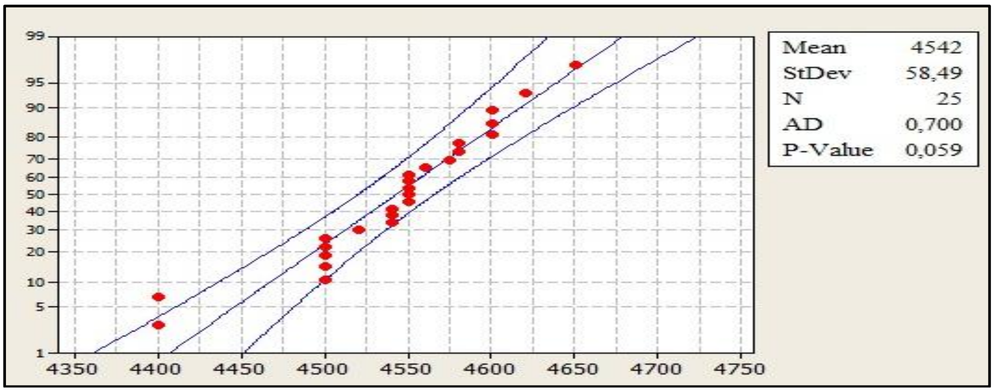

Fig. 4.Distribution and analysis results of maximum Spinal Cord dose.

Table 3: The variation between first CT plan and adaptive CT in terms of variations in PTV 70 and critical organ doses

	1st plan CT (cGy)	Adaptive CT (cGy)	P value
PTV 70 (Mean)	7143.7 ± 71.2	7147.4 ± 74.1	0.224
Ipsilateral parotid (Mean)	3279.0 ± 608.0	2656.0 ± 399.0	0.001
Contralateral parotid (Mean)	3008.4 ± 377.4	2606.2 ± 325.5	0.002
Spinal Cord (Max)	4542.2 ± 58.5	4433.2 ± 55.3	0.001

Mean PTV 70 dose showed variation from 7143.7 ± 71.2 cGy to 7147.4 ± 74.1 cGy. The difference in mean PTV 70 dose was not statistically significant in terms of involving target volume as *p* value was at the rejected site (*p*=0.224) as shown in Table 3. The variation in critical organ doses were statistically significant as ipsilateral mean parotid dose was decreased from 3279 ± 608 cGy to 2656 ± 399 cGy; contralateral parotid dose was decreased from 3008.4 ± 377.4 cGy to 2606.2 ± 325.5 cGy and maximum dose of spinal cord was decreased from 4542.2 ± 58.5 cGy to 4433.2 ± 55.3 cGy.

IV. CONCLUDING REMARKS

The anatomy of the patients receiving radiotherapy for head-neck tumors are significantly changed during the treatment. The migration of tumor, due to expansion or shrinkage of tumors and weight loss during the treatment, reveal the necessity of target detection. These variations result in receiving potentially inadequate doses of the target mass or over-exposure of normal tissues to the radiation.

The importance of volume, shape or position-dependent variations in target tissues or risky organs is emphasized during the treatment [7, 8]. Therefore, imaging methods and image-guided radiotherapy (IGRT) during the treatment have been developed. It enables the implementation of radiation at higher doses safely to the surrounding critical organs by means of lesser safety margin.

The position of stabilizing apparatus has been changed in time depending on the migration of tumor. Although it shows harmony with conventional radiotherapy techniques, the use of modern tools has caused the appearance of significant concern [9].

Nowadays, radiotherapy depends on a single CT scanning prior to the treatment. This treatment involves suggestion-based certain values regarding potential microscopic spreads and it might reveal certain uncertainties, such as possible organ movements and variation following the procedure. In theory, adaptive RT is performed by using the principle of exposure of the target tissue to the intended radiation doses and preservation of normal tissue from these high doses. In this analysis, a linear correlation was detected between time and quantity-variation ratio [7].

Variations in the patient's positions and anatomy might affect dosimetric parameters in the course of IMRT treatments for head and neck cancers and causes clinical implications at wide spectrum. Mutual interaction between simultaneous positional variations and anatomic variations occurring in time require careful examination [10]. Anatomical variations, such as weight loss and shrinkage of tumor) in addition to the positioning factor of the patients were associated with dosimetric points. When the degree of variations was examined, it was found that existing uncertainties in the region involving lower neck and jaw was detected in 7 mm upwards direction at an unpredictable degree with the confident interval of 95% [11].

Ahn et al. revealed the presence of small systematic but extended random variations in rotational and translational position. When these movements were considered by using theoretical IMRT plans, opposite and predictable variations were detected in dose amount [11].

Re-planning in the patients having significant weight loss or who were chosen due to shrinkage in tumor volume provided improvement as part of PTV and dose reduction in spinal cord, brain stem and right parotid gland. In the present study, the variation in the PTV 70 dose was not found to be statistically significant in terms of involving target volume as p value was at the rejection site in which mean PTV 70 dose was increased from 7143.7 ± 71.2 cGy to 7147.4 ± 74.1 cGy (p =0.224).

In a CT scanning study involving 8 patients, Ballivy et al. examined weekly CT scan images of head and neck tumors. They found that contralateral parotid gland and spinal cord exposed to higher dose that the previously planned levels. In addition, the dose received by the spinal cord was higher than 45 Gy in 57% of the CT scans.

Ahn et al. investigated anatomical variations occurred by positioning variability in radiotherapy and cervical two vertebrae. They found that parotid gland of almost more than half of the patients exposed to radiation dose in the range of 5 to 7 Gy in the planning CT which was higher than expected. They also detected that the dose of parotid gland was increased almost 10% as a result of tumor shrinkage during the treatment despite of the absence of a significant variation in the dose exposed to the target [12]. Adaptive radiotherapy (ART) means correction for tumor and normal tissue variation of IMRT target masses and planning by means of daily online or offline modifications [12].

According to the results of initial dosimetric analysis, the ratio of dose preservation was maintained in contralateral mean parotid dose and ipsilateral parotid mean dose, 2.8% and 3.9%, respectively, in ART treatments. The findings of ART performed in the middle of the treatment showed consistency with the findings of Wu et al [13].

While a straight DVH curve is obtained for target tumor volume in IMRT, surrounding organs-at risk are preserved better than classical 3D conformal RT [14].

The consequences of anatomical variations with IMRT are more dramatic in comparison to conventional treatments as there are sharp dose gradients between the tips of target mass and critical OARs. Therefore, high ratio of conformal IMRT plans that are based on single-plan CT might cause unexpected complications single-plan [12].

The purpose of ART in patients with head and neck cancer is the preservation of same parotid gland as planned during the treatment. The shrinkage of the tumor changes the location of parotid gland and affects the electron intensity of the organs. According to the study results of 11 patients, it was detected that weekly planning provided a significant contribution to 1/3 of parotid glands and also decreases the risk of dryness of the mouth in 13% of the patients [15].

In a study performed on a patient having large head-neck tumor, the efficacy and accuracy of the CBCT images were investigated in dose planning procedure of IMRT treatment, and the tumor volume was found to be varied significantly during the treatment [16, 17].

In a study conducted by Schwartz et al., a total of 24 patients with local and advance oropharynx cancer were included and 22 of them were investigated. Basic table shifting and daily online IGRT were performed to correct systematic and random planary set-up errors.

In each treatment, contour matching was performed according to C2 vertebrae in company with CT and deformable matching was done in case of the presence of anatomical and contour-based differences, and IMRT was re-planned. Of the participants, 22 received re-planning implementation (ART1); 8 participants received twice re-planning implementation (ART2). ART1 plan reduced the dose of mean parotid dose to 0.6 Gy (2. 8%; p=0.003) and 1.3 Gy (3.9%; p=0.002) in contralateral and ipsilateral positions in comparison to IGRT, respectively. On the other hand, mean parotid dose was decreased to 0.8 Gy (3.8%; p=0.026) and 4.1 Gy (9%; p=0.001) in patients receiving ART2 in contralateral and ipsilateral positions, respectively. The ART doses of 40 Gy and 60 Gy significantly decreased the dose of integral body in the present study, the doses of mean ipsilateral and contralateral parotid were significantly reduced from 3279 cGy and 3008.4 cGy to 2656 cGy and 2606.2 cGy, respectively [18].

Wu et al. declined the margins of PTV to 0 mm from 3 mm in the middle of the treatment, and they found that mean parotid dose decreased in between 2 and 4 Gy as a result of re-planning. Thisstudy revealed reduction in mean parotid dose, and significant and quantifiable improvements in salivation when the treatment was continued with ART plan [13].

The results we found in our study are compatible with the literature. Adaptive radiotherapy was superior than non-adaptive radiotherapy. It increases the minimum dose in target volume and reduces cumulative maximum dose.

In post-treatment 3rd and 6th months, total or nearly total regression was determined in patients during image guided controls. At the 5th week of the treatment, as tumor shrinkage was observed in the tumor volume by means of the tumor response to radiotherapy or weight loss, it is recommended to perform re-planning between the fractions of 21 and 25 in the patient.

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