Iranian Journal of Medical Physics

ijmp.mums.ac.ir



Radiobiological Model-Based Comparison of Three-Dimensional Conformal and Intensity-Modulated Radiation Therapy Plans for Nasopharyngeal Carcinoma

Asghar Mesbahi^{1,2*}, Naser Rasouli¹, Behnam Nasiri Motlagh^{3,4}, Mohammad Mohammadzadeh³

¹Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

² Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

³Department of Radiation Oncology, Imam Hospital, Tabriz, Iran

⁴Radiation Department of Oncology, Tabriz International Hospital, Tabriz, Iran

ARTICLEINFO	ABSTRACT
Article type: Original Article	<i>Introduction</i> : Radiobiological modeling of radiotherapy plans are used for treatment plan comparisons. The current study aimed to compare the three-dimensional conformal radiation therapy (3DCRT) and intensity-
<i>Article history:</i> Received: Mar 11, 2017 Accepted: Jul 22, 2017	modulated radiation therapy (IMRT) plans for nasopharyngeal cancer using radiobiological modeling. <i>Materials and Methods:</i> This study was conducted on 10 patients with nasopharyngeal carcinoma, who were planned for 3DCRT and IMRT treatments by using the TiGRT treatment planning system. The planning target volume (PTV) doses of 70 and 72 Gy were administered for the 3DCRT and IMRT
Keywords: Nasopharyngeal Cancer Intensity Modulated – Radiotherapy Radiobiology	plans, respectively. The BIOLPLAN software and the Niemierko's equivalent uniform dose (EUD) model were utilized for the estimation of tumor control probability (TCP) and normal tissue complication probability (NTCP). The NTCPs of the spinal cord, brain stem, parotid glands, middle ears, temporomandibular joints (TMJ), mandible, and thyroid were calculated by using two radiobiological models. <i>Results:</i> According to the results, the mean TCPs for 3DCRT and IMRT plans were 89.92%±8.92 and 94.9%±3.86, respectively, showing no statistically significant difference (P=0.08). The NTCPs of the parotid glands, thyroid gland, spinal cord, TMJ, and mandible were considerably lower in the IMRT plans, compared to those in the 3DCRT plans. On the other hand, the calculated NTCPs for the middle ears and brain stem increased for the IMRT plans, which were not statistically significant. On average, the NTCPs of the critical organs were lower based on the EUD model than the Lyman-Kutcher-Burman model. <i>Conclusion:</i> From the radiobiological point of view, the IMRT plans were significantly advantageous over the 3DCRT plans with some small variations in each patient. On average, the two radiobiological models generated different NTCPs depending on the studied organs. Consequently, more studies are needed for the optimization of radiobiological models for the prediction of the treatment outcomes in radiation therapy.

Please cite this article as:

Mesbahi A, Rasouli N, Nasiri Motlagh B, Mohammadzadeh M. Radiobiological Model-Based Comparison of Three-Dimensional Conformal and Intensity-Modulated Radiation Therapy Plans for Nasopharyngeal Carcinoma. Iran J Med Phys 2017; 14: 190-196. 10.22038/ijmp.2017.22508.1213.

Introduction

Nowadays, the intensity-modulated radiation therapy (IMRT) techniques are utilized as a powerful method in treating all stages of non-metastatic nasopharyngeal carcinoma. This therapeutic modality provides higher sparing of parotid glands in early stage of the disease as compared to the threedimensional conformal radiation therapy (3DCRT). Furthermore, IMRT has some advantages, including tumor coverage, normal organ sparing, and dose escalation, in the locally advanced diseases.

There have been a lot of investigations on the dosimetric superiority of IMRT over 3DCRT in the treatment of nasopharyngeal cancer [1-3]. Moreover,

the recent studies have used radiobiological modeling to compare different treatment plans. According to these studies, IMRT provides better radiobiological outcomes in terms of tumor control probability (TCP) and normal tissue complication probability (NTCP) for nasopharyngeal carcinoma [2-5].

The most common complications associated with the radiation therapy of nasopharyngeal carcinoma are xerostomia and dysphagia owing to the irradiation of parotid tissues, pharyngeal constrictors, esophagus, and larynx. The application of radiobiological models for evaluating and ranking the rival treatment plans is going to play a new role in radiation therapy planning.

^{*}Corresponding Author: Department of Medical Physics, School of Medicine, Attar Street, Tabriz, Iran, Tel: +98 0411-3364660, Email: amesbahi2010@gmail.com

In this regard, several radiobiological models have been studied in the previous investigations, some of which have been commercially utilized in the new treatment planning systems [4-7]. The intrinsic features of these models and their parameters make the radiobiological predictions different for the same treatment plan [2;5;7-10]. In a study conducted by Oinam et al., it was reported that NTCPs calculated by Lyman-Kutcher-Burman (LKB) and Niemierko's models were different for the brain stem, parotid, and larynx [9]. In the mentioned study, the Poisson model calculated slightly higher TCP for the head and neck tumors as compared to the Niemierko's model.

In addition, Moiseenko et al. compared four radiobiological models for the estimation of NTCP in radiation therapy [8]. They reported significant variability in the calculated NTCP values due to the intrinsic properties of models and input parameters. With this background in mind, the present study was conducted to compare the 3DCRT and IMRT plans of nasopharyngeal carcinoma using estimated radiobiological metrics of TCP/NTCP.

Both 3DCRT and IMRT plans were confirmed by physicists and physicians. The comparison was based on the estimated radiobiological parameters, namely TCP and NTCP, for our plans. The NTCPs results were estimated by two different radiobiological models of LKB and Niemierko's equivalent uniform dose (EUD) model; however, TCP was only calculated by the Poisson model.

Materials and Methods

This retrospective study was conducted on 10 patients with nasopharyngeal carcinoma, who were planned for 3DCRT and IMRT treatments by using the TiGRT treatment planning system without any interference in actual treatment procedure. The patients who were treated with 3DCRT plans were replanned retrospectively for IMRT treatment using the inverse planning approach on the same platform by means of TiGRT treatment planning system (Linatech, USA).

The patients with stage II to III tumors (according to the American Joint Commission on Cancer/International Union against Cancer 1997 staging system) were selected. The patients consisted of four males and six females with the age range of 25-45 years. All 3DCRT and IMRT plans were generated using 6 MV photon beams and modulated with 41 pairs multi-leaf collimator on a clinical linear accelerator (ONCOR-Impression, Siemens Medical Systems, Germany).

All dose calculations were performed with the full scatter convolution algorithm. The accuracy of TiGRT treatment planning system was evaluated previously for the small fields used in IMRT [11;12]. A team comprised of one radiation oncologist and one medical physicist generated the IMRT plans to avoid the variation of IMRT plan quality caused by the operator's experience and skill.

For 3DCRT, the treatment entailed three courses, including two parallel-opposed lateral fields containing planning target volume (PTV) and involving high-risk and low-risk lymph nodes. The first course entailed 22 sessions with a dose of 44 Gy while the ears and temporal lobes were shielded. In the second course, which consisted of eight sessions, the field was narrowed to exclude the spinal cord with the dose of 16 Gy. Finally, in the third course that was performed in 5 sessions, only PTV of 10 Gy was applied. Therefore, a total of 70 Gy was administered to PTV. All three courses were combined into a plan, and the resultant plan was analyzed for the organs receiving the dose and dose-volume histogram parameters.

For IMRT, the plans were designed for a single treatment course consisting of 36 sessions. We used seven coplanar fields with the angles of 0°, 52°, 103°, 154°, 205°, 256°, and 308°. A dose of 72 Gy was used for nasopharyngeal primary and gross nodal disease as well as the required margins (PTV1). Additionally, the doses of 60 and 50 Gy were applied for the highrisk (PTV2) and low-risk lymph nodes (PTV3), respectively.

For all PTVs, 5 mm margin was added to CTVs, except in the areas adjacent to critical structures. The tolerance doses of normal tissues were based on the recommendations of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) (Table 1) [13]. The comparison between 3DCRT and IMRT plans is illustrated in Figure 1.

Table 1. Clinical dose-volume constraints used in the study

	- (2) 1 1 (2)
Volume	Dose (Gy) and volume (% or cm ^{^3})
PTV	V95>95% and V105%<5%
Spinal cord	46 Gy , max dose<50 Gy
Brain stem	54 Gy , max dose<60 Gy
Mandible and TMJ joints	70 Gy, max dose<75 Gy
Parotid	Single gland: mean dose<26 Gy
Middle ear	Mean dose<50 Gy
Thyroid	As low as possible

PTV: planning target volume, TMJ: temporomandibular joints





Figure 1. Comparison of dose distributions and dose-volume histograms of three-dimensional conformal radiation therapy and intensitymodulated radiation therapy plans for patient number 9

Table 2. Set of parameters used for the calculation of normal tissue complication probability by Lyman-Kutcher-Burman model

Organ	n	m	TD50(Gy)	α/β(Gy)	End point
Spinal cord	0.05	0.175	66.50	2	Myelitis/necrosis
Brain Stem	0.16	0.14	65	3	Necrosis/infarction
Parotid	1	0.18	28.40	3	Xerostomia
Middle ear	0.01	0.15	40	10	Acute serous otitis
Middle ear	0.01	0.095	65	3	Chronic serous otitis
TMJ	0.07	0.10	72	3.50	Limited joint function
Thyroid	0.22	0.26	80	3	Clinical thyroiditis
Mandible	0.07	0.10	72	3.5	Limited joint function

TMJ: temporomandibular joints

 Table 3. Parameters used to calculate Niemierko's equivalent uniform dose-based normal tissue complication probability for nasopharyngeal cancer

Organ	а	Y50	TD50(Gy)	α/β(Gy)	End point
Spinal cord	7.40	4	66.50	3	Necrosis
Brain Stem	7	3	65	3	Necrosis
Parotid	1	2.2	28.40	8	Xerostomia
Middle ear	31	3	40	10	Acute serous otitis
Middle ear	31	4	65	3	Chronic serous otitis
TMJ	14	4	72	3	Limited joint function
Mandible	14	4	72	3	Limited joint function

TMJ: temporomandibular joints

Calculation of Tumor Control and Normal Tissue Complication Probabilities Through BIOPLAN Software

The biological evaluation of the plans was performed using the BIOPLAN software (version 1.3.3) [14]. Differential dose-volume histograms (DVHs) were computed for the PTV and critical organs. The TCP was calculated for each plan using the Poisson model with the assumptions of α =0.4 Gy⁻¹, 6=0.09 Gy⁻¹, α/β =10 Gy, and homogenous clonogenic cell density=10⁷ cells/cm³. A default set of model parameters for nasopharynx was taken from

the BIOPLAN software. Additionally, the NTCP was estimated based on the LKB model. The NTCP calculation in LKB model is defined as:

$$NTCP(D,v) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left(-\frac{1}{2}x^{2}\right) dx$$
(1)

$$t = \frac{D - T D_{50}(v)}{m. T D_{50}(v)}$$
(2)

$$TD_{50}(v) = \frac{TD_{50}(1)}{v^n}$$
(3)

Where $TD_{50}(v)$ is the tolerance dose for a 50% complication probability caused by uniform

irradiation to a partial volume *v*. Parameter *n* is the volume exponent, and *m* is inversely related to the steepness of the dose-response curve. The corresponding sets of parameters for TD_{50} , *n*, *m*, and endpoints are displayed in Table 2.

Calculation by Equivalent Uniform Dose Model

The cumulative DVHs of both plans were exported from the TiGRT treatment planning system using the EUD model. We used a free program to calculate the Niemierko's EUD and EUD-based NTCP/TCP values [15]. According to the EUD model, for a dose of 2 Gy in each fraction, the EUD, equivalent dose, TCP, and NTCP were calculated by the following equations:

$$EUD = \left(\sum_{i=1}^{\infty} (V_i EQD_i^{a})\right)^{\frac{1}{a}} \& EQD = D \times \left(\frac{\frac{a}{\beta} + \frac{D}{n_f}}{\frac{a}{\beta} + 2}\right)$$
(4)

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}}$$
(5)

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}}$$
(6)

In all the above equations, *a* is a unitless model parameter for each normal structure or tumor of interest, and v_i is an unitless value representing the *i'th* partial volume receiving dose D_i (in Gy). Furthermore, *n*f and df=D/*n*f are the number of fractions and the dose per fraction size of the treatment course, respectively. The α/β is the tissue-specific Linear Quadratic parameter of the organ being exposed. In addition, TCD₅₀ is the tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated, and γ_{50} is a unitless model parameter that is specific to the tumor of interest and describes the slope of the dose-response

curve. Finally, TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval when the whole organ of interest is homogeneously irradiated.

The radiobiological parameters used for the EUD model calculations are summarized in Table 3. The difference between the models was evaluated statistically using the paired Student's t-test. P-value less than 0.05 was considered statistically significant.

Results

The mean doses of the studied normal organs have been tabulated for the 3DCRT and IMRT plans of nasopharyngeal cancer in Figure 2. According to the results, despite using 2 Gy higher dose for PTV in the IMRT plans, most of the organs, except the brain stem and middle ear, received lower dose in IMRT plans, compared to those in the 3DCRT. The largest discrepancy was observed in the parotid glands, since the mean dose for this organ reduced by four times in IMRT, compared to that in 3DCRT. Furthermore, the TMJ and mandible received approximately two times lower dose in IMRT, compared to those in 3DCRT. However, for all 3DCRT and IMRT plans, the received doses by all studied organs were lower than their tolerance doses.

The calculated TCPs of nasopharyngeal cancer for 3DCRT and IMRT plans are presented in Figure 3. The TCP was estimated using the BIOPLAN software and Poisson model. The mean percentage of TCPs for 3DCRT and IMRT were $89.92\pm8.92\%$ and $94.9\pm3.86\%$, respectively, showing no statistically significant difference between the two plans in this regard (P=0.08). Given the better coverage of PTV and higher doses in IMRT plans, the TCP was slightly higher for the IMRT plans, compared to that for the 3DCRT plans.



Figure 2. Calculated mean doses for nasopharynx tumor and studied normal organs in three-dimensional conformal radiation therapy and intensity-modulated radiation therapy plans, TMJ: temporomandibular joints, PTV: planning target volume



Figure 3. Comparison of tumor control probability for three-dimensional conformal radiation therapy (70 Gy) and intensity-modulated radiation therapy (72 Gy) plans using Poisson model for nasopharyngeal cancer

Table 4. Comparison of normal tissue complication probability for three-dimensional conformal radiation therapy and intensity

 modulated radiation therapy plans calculated by Lyman-Kutcher-Burman and equivalent uniform dose model

Organ (complication)	3DCRT (LKB)	IMRT (LKB)	3DCRT (EUD)	IMRT (EUD)
Middle ear (chronic serous otitis)	25.0±26.0	29.80±25.6	10.50±16.2	13.50±12.5
Middle ear (acute serous otitis)	98.10±3.2	99.70±1.0	93.10±8.5	97.30±4.30
Mandible (radio-necrosis)	22.60±10.9	0.01±0.03	23.00±10.5	0.02±0.04
Spinal Cord (myelitis)	5.90±7.6	0.38±0.57	0.16±0.44	0.001±0.003
TMJ (limited joint function)	14.70±16.8	0.10±0.03	15.40±15.8	0.02 ± 0.06
Parotid (xerostomia)	100.0±2.21	0.20±0.02	99.80±2.1	0.13±0.02
Thyroid (clinical thyroiditis)	4.58±2.77	0.17±0.06	NA	NA

3DCRT: three-dimensional conformal radiation therapy, LKB: Lyman-Kutcher-Burman, IMRT: intensity-modulated radiation therapy, EUD: Lyman-Kutcher-Burman, TMJ: temporomandibular joints

The calculated NTCPs for all studied organs are presented in Table 4. The highest difference in the calculated NTCP was found in the parotid glands. For the parotid glands, the NTCP for 3DCRT and IMRT plans were about 100% and 0.2%, respectively (P=0.00001). Nevertheless, the difference between the two radiobiological models was negligible for the parotid glands.

The TCP for the thyroid was calculated only by the LKB model. Due to the lack of parameters in the literature, we were unable to calculate it for the EUD model. The mean percentages of NTCPs were $4.5\pm2.77\%$ and $0.17\pm0.06\%$ for 3DCRT and IMRT plans, respectively (P=0.0001). The NTCP for chronic serous otitis is shown for both therapeutic modalities using the two radiobiological models (Table 4).

The mean percentages of NTCPs for the 3DCRT and IMRT plans were 24.8% and 29.78% in the LKB model, and 10.54% and 13.47% in the EUD model, respectively. As indicated, the results of the LKB model were two times higher than those of the EUD

model. Furthermore, the comparison of the two techniques demonstrated a slightly higher NTCP for the IMRT plans, compared to that of the 3DCRT plans. The difference in NTCP between the 3DCRT and IMRT plans was not statistically significant in both LKB and EUD models (P=0.68, P=0.58).

For acute serous otitis, the mean percentage of NTCPs were 98.12% and 99.67% for the LKB as well as 93.12% and 97.36% for the EUD models, respectively. The probability of acute complication was considerably higher (3-4 times) than the chronic complication, which was slightly higher for the IMRT plans than that for the 3DCRT plans. However, the difference in calculated NTCP between the 3DCRT and IMRT plans was not statistically significant for both LKB and EUD models (P=0.19).

As can be seen in Table 4, the calculated NTCPs obtained for the osteoradionecrosis of mandible were very close together using the two models. However, there was a significant difference in calculated NTCP between 3DCRT and IMRT plans. Additionally, the mean percentages of the NTCPs of

mandible necrosis for 3DCRT and IMRT were respectively 23.04% and 0.02% for the EUD model as well as 22.56% and 0.01% for the LKB model (P=0.001).

The NTCP of the spinal cord was estimated in terms of myelitis/necrosis. In both models, the NTCP was higher for the 3DCRT plans. However, the NTCP for IMRT was around zero using the EUD model. The difference between 3DCRT and IMRT was statistically significant (P=0.048) for the LKB model; however, it was not meaningful for the EUD model (P=0.28).

The NTCP of TMJ complication for limited joint function is shown in Table 4. The NTCP for IMRT plans was estimated to be less than 0.1% in both models. On the other hand, for 3DCRT, the mean NTCP was as high as 16.82, and the difference between 3DCRT and IMRT was statistically significant for both radiobiological models (P=0.022).

Discussion

In the current study, dosimetric and radiobiological comparisons were made between ten nasopharynx 3DCRT and IMRT plans. From dosimetric point of view, the IMRT plans were superior to the 3DCRT in terms of PTV coverage. In addition, in the IMRT plans, most of the organs at risks received lower dose, compared to those in the 3DCRT plans. The exceptions were the brain stem and temporal lobes, which had higher mean dose in the IMRT plans that caused higher estimated NTCP for acute and chronic otitis.

This can be explained by the fact that in the IMRT plans, higher priorities were given to the optimization of the parotid glands, TMJ, and mandible doses, whereas the temporal lobe and brain stem received lower priories in this regard. As a result, there was a rapid dose fall-off around the parotid glands, TMJ, as well as mandible, and higher doses were observed for the brain stem and temporal lobes. On the other hand, in the 3DCRT plans, the parotids, TMJ, and mandible could not be avoided in lateral fields, and consequently receive a considerable dose.

The comparison between 3DCRT and IMRT plans showed higher mean TCP for IMRT plans as compared to that for the 3DCRT plans (P=0.08). We could not find the proposed parameters for TCP calculations using the EUD model. However, it should be noted that the difference between the mean PTV doses in two techniques was statistically significant (P=0.007). In other words, the magnitude of dosimetric difference between the 3DCRT and IMRT plans would not result in the same difference in radiobiologic metrics.

In two patients (i.e., patients 4 and 10), the TCP was considerably lower for 3DCRT plans, compared

to the other participants. This was due to the fact that the 3DCRT plans had large PTV, which made the 95% isodose coverage difficult. Moreover, in patient 2, the TCP was the same for both techniques since the CTV was small, and both 3DCRT and IMRT plans covered it properly. In patient number 3, the 3DCRT plan showed better results in terms of TCP than the IMRT plan, as in this case, the CTV was not symmetric and was extended inside the normal tissues; therefore, it was covered more efficiently by 3DCRT, compared to IMRT. However, this caused higher NTCP results in 3DCRT plans.

The estimation of NTCP for clinical thyroiditis by the LKB model showed a significant difference between the 3DCRT and IMRT plans. The NTCP was about 23 times higher in the 3DCRT plans, compared to that in the IMRT plans. However, the mean doses of 3DCRT plans were on average 1.65 times higher than those of the IMRT plans. This could be regarded as one of the advantages of IMRT plans over 3DCRT, which reduces the probability of hypothyroidism and other complications after nasopharynx radiation therapy [16].

The mean dose delivered to the temporal lobes was slightly higher in the IMRT plans; accordingly, the mean NTCP was higher for IMRT as compared to that for 3DCRT. However, the statistical analysis showed no significant difference between the resulted NTCP of the two techniques for acute and chronic otitis. In line with our results, Kam et al. showed that in IMRT plans, the brain stem received higher doses than that in the 3DCRT.

However, for the temporal lobes, the DVH curves were comparable for the IMRT and 3DCRT plans [17]. Furthermore, for the mandible, spinal cord, and TMJ, the IMRT plans delivered lower doses, compared to the 3DCRT plans. Considering the results of these two radiobiological models, our results were in close agreement with those reported by Moiseenko et al., who concluded that the observed variability in the NTCP results stems from radiobiological models and applied parameters [8].

To sum up, our calculated NTCPs were consistent with the published data comparing IMRT and 3DCRT. Owing to uncertainties in model parameters, it has been widely recommended not to consider the absolute values of the calculated NTCP with biological models in the clinical evaluation of the treatment plans. However, these values provide an invaluable tool for the comparison of rival treatment plans.

Conclusion

In the present study, the radiobiological comparisons were made between the 3DCRT and IMRT plans of nasopharyngeal cancer patients. In terms of the estimated radiobiological outcomes, the IMRT plans were advantageous over 3DCRT plans with some small variations in each patient. The radiobiological evaluation of the treatment plans provides more data for the comparison of these plans. However, it was shown that the studied radiobiological models generated different NTCPs depending on the studied organs. Therefore, in accordance with the previous studies, more clinical and animal studies are recommended to optimize and validate the accuracy of radiobiological models in the prediction of the treatment outcomes.

Acknowledgements

This project was financially supported by Immunology research center of Tabriz University of Medical Sciences. The authors would like to thank Radiation Oncology department of Tabriz International Hospital for their valuable contribution in this research.

References

- 1. Ferreira BC, do Carmo LM, Mateus J, Capela M, Mavroidis P: Radiobiological evaluation of forward and inverse IMRT using different fractionations for head and neck tumours. Radiat Oncol 2010;5:57. doi: 10.1186/1748-717X-5-57.:57-5.
- 2. Narayanasamy G, Pyakuryal AP, Pandit S, Vincent J, Lee C, Mavroidis P, Papanikolaou N, Kudrimoti M, Sio TT: Radiobiological evaluation of intensity modulated radiation therapy treatments of patients with head and neck cancer: A dual-institutional study. J Med Phys 2015;40:165-169.
- Taheri-Kadkhoda Z, Pettersson N, Bjork-Eriksson T, Johansson KA: Superiority of intensity-modulated radiotherapy over three-dimensional conformal radiotherapy combined with brachytherapy in nasopharyngeal carcinoma: a planning study. Br J Radiol 2008;81:397-405.
- 4. Peters LJ, Withers HR: Applying radiobiological principles to combined modality treatment of head and neck cancer--the time factor. Int J Radiat Oncol Biol Phys 1997;39:831-836.
- Wu PM, Chua DT, Sham JS, Leung L, Kwong DL, Lo M, Yung A, Choy DT: Tumor control probability of nasopharyngeal carcinoma: a comparison of different mathematical models. Int J Radiat Oncol Biol Phys 1997;37:913-920.
- Roberts SA, Hendry JH: A realistic closed-form radiobiological model of clinical tumor-control data incorporating intertumor heterogeneity. Int J Radiat Oncol Biol Phys 1998;41:689-699.
- 7. Zhong H, Chetty I: A note on modeling of tumor regression for estimation of radiobiological parameters. Med Phys 2014;41:081702.
- Moiseenko V, Battista J, Van DJ: Normal tissue complication probabilities: dependence on choice of biological model and dose-volume histogram reduction scheme. Int J Radiat Oncol Biol Phys 2000;46:983-993.
- 9. Oinam AS, Singh L, Shukla A, Ghoshal S, Kapoor R, Sharma SC: Dose volume histogram analysis and comparison of different radiobiological models

using in-house developed software. J Med Phys 2011;36:220-229.

- Surega A, Punitha J, Sajitha S, Ramesh B, Pichandi A, Sasikala P: A statistical quantification of radiobiological metrics in Intensity Modulated Radiation Therapy evaluation. Gulf J Oncolog 2015;1:15-23.
- 11. Mesbahi A, Dadgar H: Dose calculations accuracy of TiGRT treatment planning system for small IMRT beamlets in heterogeneous lung phantom. 2015;13:345-354.
- 12. Mesbahi A, Zergoug I: Dose calculations for lung inhomogeneity in high-energy photon beams and small beamlets: A comparison between XiO and TiGRT treatment planning systems and MCNPX Monte Carlo code. 2015;12:167-177.
- 13. Marks LB, Ten Haken RK, Martel MK: Guest editor's introduction to QUANTEC: a users guide. Int J Radiat Oncol Biol Phys 2010;76:S1-S2.
- 14. Sanchez-Nieto B, Nahum AE: BIOPLAN: software for the biological evaluation of. Radiotherapy treatment plans. Med Dosim 2000;25:71-76.
- 15. Gay HA, Niemierko A: A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. Phys Med 2007;23:115-125.
- Bakhshandeh M, Hashemi B, Mahdavi SR, Nikoofar A, Vasheghani M, Kazemnejad A: Normal tissue complication probability modeling of radiationinduced hypothyroidism after head-and-neck radiation therapy. Int J Radiat Oncol Biol Phys 2013;85:514-521.
- 17. Kam MK, Chau RM, Suen J, Choi PH, Teo PM: Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. Int J Radiat Oncol Biol Phys 2003;56:145-157.