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Original Article / Çalışma - Araştırma

Can carotid-sparing radiotherapy approaches replace with conventional techniques for the patients with T1 glottic laryngeal cancer?

T1 glottik larenks kanserli hastalarda karotis koruyucu radyoterapi yaklaşımları konvansiyonel tekniklerin yerini alabilir mi?

Fatma Sert, M.D.,[1] Ömür Karakoyun-Çelik, M.D.,[2] Mustafa Adnan Esassolak, M.D.[3]

[1]*Department of Radiation Oncology, Van Regional Training and Research Hospital, Van, Turkey;*
[2]*Department of Radiation Oncology, Medical Faculty of Celal Bayar University, Manisa, Turkey*
[3]*Department of Radiation Oncology, Medical Faculty of Ege University, İzmir, Turkey;*

Objectives: This study aims to compare the carotid artery doses applied with various radiotherapy techniques for the treatment of T_1N_0 glottic laryngeal cancer.

Patients and Methods: Five patients were simulated with using computed tomography (CT). Clinical (CTV) and planning target volumes (PTV) were created for T_1N_0 glottic laryngeal cancer. Planning risk volumes (PRV) were constructed for carotid arteries and spinal cord. Three irradiation planning, two dimension radiation therapy (2DRT), three dimension conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT) were done for each patient. Over 95% of planned target volumes were loaded with predetermined dose (a total of 62.25 Gy of 2.25 Gy daily dose).

Results: The comparison of the treatment planning of five T_1 glottic laryngeal cancer, three involving the right vocal cord and two involving the left vocal cord, the technique of IMRT planning was provided the best carotid-sparing doses. Mean carotid V35, V50, and V63 values including 2DRT, 3DCRT, and IMRT were 70%, 47%, 35%; 55%, 15%, 5% and 28%, 6%, 0%, respectively. The statistical comparison of V35, V50 and V63 revealed significant values for 2DRT and IMRT. Dose of spinal cord did not exceed 45 Gy for any of radiation treatment planning. Between the three techniques, there was no significant difference in terms of conformity index and dose distribution was homogenous with all techniques.

Conclusion: It is obvious that IMRT planning technique can decrease the carotid artery radiation doses in early stage glottic laryngeal cancer.

Key Words: Advanced radiotherapy techniques; carotis-sparing irradiation techniques; early stage glottic larynx carcinoma; T_1N_0 glottic larynx carcinoma.

Amaç: T_1N_0 glottik larenks kanseri tedavisinde çeşitli radyoterapi teknikleri arasında karotis arterlerinin maruz kaldıkları dozlar karşılaştırıldı.

Hastalar ve Yöntemler: Bilgisayarlı tomografi (BT) kullanılarak beş hasta simüle edildi. T_1N_0 glottik larenks kanseri için klinik (KHV) ve planlanan hedef volümler (PHV) oluşturuldu. Karotis arterleri ve spinal kord için planlanan risk volümleri (PRV) çizildi. Her hasta için iki boyutlu radyoterapi (2DRT), üç boyutlu konformal radyoterapi (3DCRT) ve basit yoğunluk ayarlı radyoterapi (IMRT) şeklinde üç planlama yapıldı. Planlanan hedef volümlerin %95'den fazlası tanımlanan dozu (2.25 Gy günlük fraksiyon dozundan 62.25 Gy toplam doz) aldı.

Bulgular: Üçü sağ ikisi sol vokal kord yerleşimli beş T_1 glottik kanserli olgunun tedavi planları karşılaştırıldığında, karotislerin koruması en iyi basit karotis koruyucu IMRT tekniği ile sağlandı. 2DRT, 3DCRT ve IMRT tekniklerine ait karotis ortalama V35, V50 ve V63 değerleri sırasıyla; %70, %47, %35; %55, %15, %5 ve %28, %6, %0 bulundu. V35, V50 ve V63 arasında yapılan istatistiksel karşılaştırmada, 2DRT ve IMRT için anlamlı değerler saptandı. Spinal kord dozu hiçbir planda 45 Gy'i aşmadı. Her üç planlama tekniğinde uygunluk indeksi arasında anlamlı fark saptanmadı ve homojen doz dağılımı elde edildi.

Sonuç: Erken evre glottik larenks kanserli hastalarda karotis arterlerinin maruz kaldığı radyasyon dozunu IMRT'nin azaltabildiğine şüphe yoktur.

Anahtar Sözcükler: Gelişmiş radyoterapi teknikleri; karotis koruyucu ışınlama teknikleri; erken evre glottik larenks karsinomu; T_1N_0 glottik larenks karsinomu.

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Correspondence / İletişim adresi: Fatma Sert, M.D. Van Bölge Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi Kliniği, 65100 Van, Turkey.
Tel: +90 505 - 794 75 36 Fax *(Faks):* +90 432 - 212 19 54 e-mail *(e-posta):* gracilis81@yahoo.com

Early-stage glottic squamous cell carcinoma (SCC) is an extremely curable disease (>95%) when treated with simple parallel-opposed small-field radiotherapy. Although acute and late treatment toxicity experienced is low, minimal interest has been devoted to vascular effects that can present more than 10 years after therapy.[1] Numerous publications now suggest that neck radiotherapy (RT) for head and neck cancers increases the incidence of stroke and the other cerebrovascular events.[1-5] In the light of these publications, some researchers recommend that radiation oncologists abandon conventional RT techniques known as two dimension radiation therapy (2DRT), for early stage glottic laryngeal cancer treatment. They recommend a new technique using oblique beam angles to decrease carotid artery doses.[6] This research presents the dosimetric results of carotid arteries doses obtained from different RT techniques and discusses the literature regarding this issue.

PATIENTS AND METHODS

Computed tomography (CT) simulation data of five patients treated with RT for T_1N_0 SCC of true vocal cords were used in this study. All included patients received conventional 2DRT treatment. This dosimetric study and retrospective review including waivers of consent were approved by clinician. The CT images were obtained from 16-slice CT scanner (Toshiba Asteion, Japan) used in our clinic. Image slice thicknesses were 3 mm and the patients were scanned from vertex to clavicles. Computed tomography images were processed using a precise PLAN® 2.11 (Elekta, Crawley, UK).

Volume definitions

Thyroid cartilage, cricoid cartilage, arytenoid cartilages, true vocal cords, spinal cord, carotid arteries, clinical target volume (CTV), and planning target volume (PTV) were delineated for each CT slice particularly. The organ delineation techniques of the University of Florida[7] and MD Anderson Cancer Institute[8] were used as a guideline because there is no standard guideline for delineating carotid arteries, CTV and PTV in early stage vocal cord carcinoma.[7] A conventional 2DRT (5x5 cm field) was drawn by using described guidelines. The isocenter was established to true vocal cord level and the borders of the lateral fields were the center of the thyroid notch, below the level of cricoid cartilage, 1 cm posterior to the thyroid cartilage alae, flashing skin by 1 cm. A total dose of 62.25 Gy was delivered at the isocenter. The width of 95% isodose distribution was determined at the superior, inferior and posterior border of CTV. The most superior contour of the CTV was delineated at the most cranial border of arytenoid cartilages. The CTV was determined to reach out 1-1.5 cm below of the level of the true vocal cords. Posteriorly, the CTV covered the arytenoid cartilages and posterior commissure completely. The CTV was limited at the thyroid cartilage with the anterior commissure included in the CTV. A small mucosal line of subglottis was attempted to include CTV. The anatomical structures included in CTV were arytenoid cartilages, false cord vocals, posterior and anterior commissures, true cord vocals and 1-1.5 cm part of subglottis. PTV was created with giving 3 mm margin around the CTV on lateral and anterior directions. Figure 1 shows the PTV and CTV of the presented patient (patient 4).

The spinal cord and carotid arteries were defined as the critical structures. Organ at risk (OAR) volumes of spinal cord and carotid arteries were delineated to exceed PTV by 1 cm on superior and inferior directions. Planning risk volumes (PRV) for spinal cord and carotid arteries were determined to cover their OAR volumes with 3 mm at all sides. Non-target body volume was defined as the neck volume which was not containing PTV volume for intensity modulated radiation therapy (IMRT) planning.

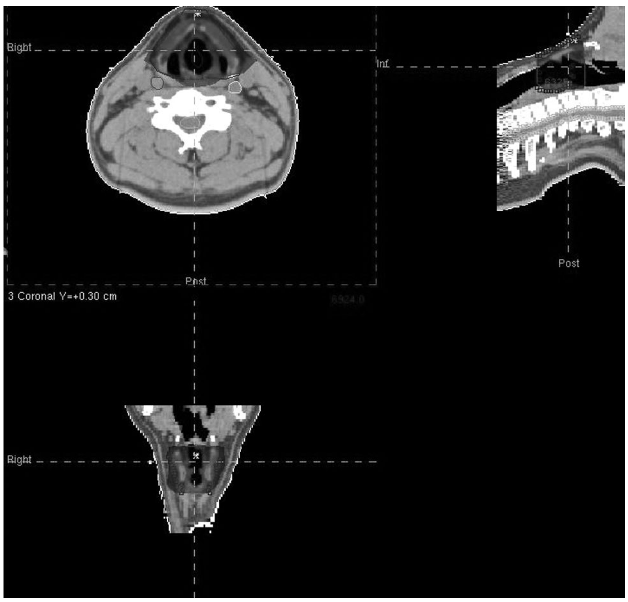

Figure 1. Planning target volumes, clinical target volume of presented patient.

Treatment planning and prescription dose

A total of 15 plans were done. One target volume for each patient was described from obtained CT data. Three treatment plans were created for each target volume; 2DRT, three dimension conformal radiation therapy (3DCRT), and IMRT. Photon beams with 6 MV energy were used for each plan. A total dose of 62.25 Gy was given with 2.25 Gy dose fractions per day. Each plan was normalized in order to give 100% of prescription dose to 95% of PTV.

Conventional 2DRT planning

Two dimension radiation therapy was used with its conventional technique. The borders of the field were designed as listed above. Wedges were used for each lateral field. Weightings were done equally in lateral fields.

3DCRT planning

Binary fields (right anterior oblique, left anterior oblique) were used to cover PTV completely and to protect PRV of carotid arteries optimally. Oblique fields were arranged to exclude OAR volumes of spinal cord and ipsilateral carotid artery. A block edge margin was given 1 cm around the PTV uniformly except the posterior area where the carotid artery was located. OARs were blocked on beam eye view. Lateral fields were wedged and all fields weighted optimally in order to provide sufficient coverage on PTV. Tissue equivalent material called bolus was used by the treatment planning system for the 3DCRT technique. The bolus was 0.5 cm thickness, 2 cm width (in order to cover whole true vocal cords), and 5 cm height. The center of the bolus was placed on the thyroid cartilage. Providing the optimal dose coverage in the anterior part of the PTV was the reason why the bolus was used. A bolus was not used in 2DRT and IMRT planning techniques because we could obtain optimal dose coverage with IMRT without bolus and the standard technique of 2DRT does not conventionally require bolus.

IMRT planning

A simple IMRT planning technique was chosen due to some important confusing and missing details in complex planning techniques. The feasibility of IMRT technique was another reason that we chose a simple technique. Three gantry angles were used for IMRT planning; anterior (G: 0), right oblique (G: 300), and left oblique (G: 70). Three different segments, called CTV, CTV-cord, and CTV-carotid arteries, were determined for each gantry angle. As a result, the irradiations were done with nine fields in total. So as to achieve appropriate dose distribution in treatment plans, each plan and dose distributions were done repetitively.

Table 1. Doses of carotid arteries

Planning risk volumes	Right carotid artery					Left carotid artery			
	Techniques	V35cc	V50cc	V63cc	D90cGy	V35cc	V50cc	V63cc	D90cGy
Patient 1	2DRT	1.795	1.320	0.556	1710	0	2.149	1.812	5805
	3DCRT	0.782	0.379	0.215	3042	0.980	0.474	0.260	3058
	IMRT	1.788	0.118	0.002	3217	0.970	0.097	0.000	2763
Patient 2	2DRT	2.043	1.280	0.433	1240	1.970	1.295	0.358	1302
	3DCRT	0.537	0.171	0.003	2656	1.005	0.162	0.000	2784
	IMRT	0.575	0.072	0.000	2660	1.082	0.239	0.000	1817
Patient 3	2DRT	1.570	2.524	3.070	793.5	2.791	2.405	1.384	792
	3DCRT	1.062	0.507	0.310	1500	1.570	0.639	0.320	1545
	IMRT	1.250	0.220	0.015	1704	1.690	0.750	0.000	1311
Patient 4	2DRT	3.402	2.580	0.960	631.8	2.565	1.575	0.210	508
	3DCRT	2.216	0.668	0.600	1600	2.638	0.850	0.100	1664
	IMRT	1.100	0.008	0.000	1843	0.650	0.006	0.000	1928
Patient 5	2DRT	2.920	3.614	4.070	2816	2.614	3.625	4.077	2607
	3DCRT	3.200	1.419	0.335	2704	2.815	0.723	0.002	2993
	IMRT	2.080	0.109	0.000	2543	1.400	0.094	0.000	2528

2DRT: Two dimension radiation therapy; 3DCRT: Three dimension conformal radiation therapy; IMRT: Intensity modulated radiation therapy.

Statistical analyses

Dose volume data for PTV, carotid PRV, and spinal cord PRV were collected from precise planning system regarding 15 treatment plans. V35, V50, and V63 for carotid arteries, D90 for spinal cord and conformity index (CI) of treatment plan were evaluated from dose-volume histograms. JMP version 10.0.1 software program was used for all statistical analysis (SAS Institute, Cary, NC). A repeated-measures analysis of variance with a Bonferroni adjustment of the results provided statistical estimates of the differences between the following pairs of techniques: 2DRT versus 3DCRT, IMRT versus 2DRT, and IMRT versus 3DCRT. A repeated measures analysis of variance was appropriate because multiple techniques were considered for a given patient. The Bonferroni adjustment controls the experiment-wise error rate at*=0.05.

RESULTS

Dose volume data for PRV of carotid arteries are presented in Table 1 and illustrated in Figure 2. The median dose of carotid PRV was lowest with IMRT technique as expected. Median doses of carotid PRV for different planning systems were 48 Gy, 30 Gy, 10 Gy, for 2DRT, 3DCRT, IMRT, respectively. All comparisons, including 2DRT versus 3DCRT, 2DRT versus IMRT, and 3DCRT versus IMRT, were statistically significant (p≤0.05). Mean carotid V35, V50, and V63 values concerning 2DRT, 3DCRT, and IMRT were 70%, 47%, 35%; 55%, 15%, 5%; and 28%, 6%, 0%, respectively. The comparisons done between 2DRT and IMRT regarding V35, V50, and V63 values were statistically significant for each.

Key	Structurs	Plan	Min dose (cGy)	Max dose (cGy)	Mean dose (cGy)	Total vol (cc)
——	Carotid arteries	Current	302	5111	3016	5.0
—▲—			185	6794	4267	5.0
——			286	6635	3454	5.0

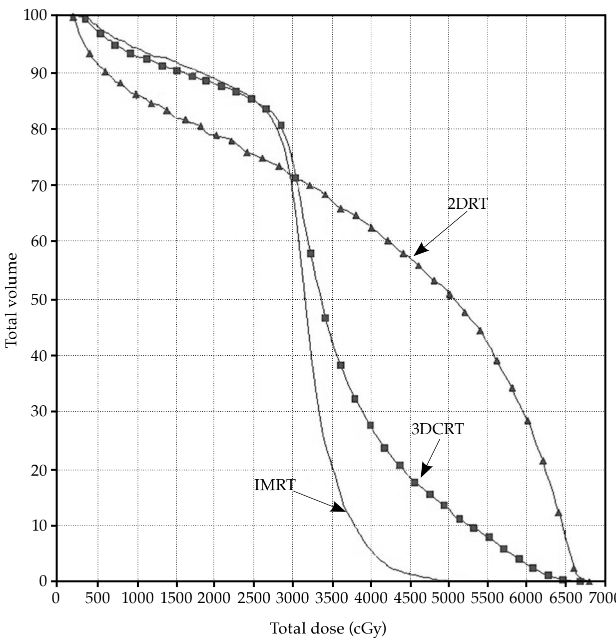

Figure 2. *Dose volume distribution of presented patient for carotid arteries. 2DRT: Two dimension radiation therapy; 3DCRT: Three dimension conformal radiation therapy; IMRT: Intensity modulated radiation therapy.*

Dose to PTV

For all treatment planning techniques, 100% of prescription dose (62.25 Gy) covered ≥95% of PTV. Conformity index data can be found in Table 2. Median maximum point dose for IMRT was 71 Gy, although it was 68 Gy both 2DRT and 3DCRT (for 2DRT versus 3DCRT and 3DCRT versus IMRT was p<0.05). Beam arrangements for the presented case (patient 4) with different plans are shown in Figure 3a, 3b, and 3c. Dose distributions are also shown in Figure 4a, 4b and 4c.

PRV spinal cord dose

Maximum dose of PRV spinal cord was ≤45 Gy for all different treatment plans.

DISCUSSION

Carotid artery doses were found to be lower with IMRT than other conventional techniques in our data. Rosenthal et al.[8] found similar results in terms of carotid artery doses in their dosimetric study by using the same IMRT technique at the MD Anderson Cancer Institute. The threshold dose for carotid artery damage with RT has not been established, the obvious difference between planning techniques is important and must be discussed in academic forum. New data obtained suggests that there is a dose-response threshold for radiation effects on the carotid arteries. Martin et al.[9] found that intimal-medial thickness was statistically significant at doses of ≥35-50 Gy. So we selected the fractional volume of both carotids receiving 35 Gy (V35) and 50 Gy (V50) as reference dose-volume parameters. Our results showed the lowest values were obtained with IMRT planning. Additionally mean carotid doses were decreased about 90% rates with IMRT when compared with conventional opposed lateral fields (39 Gy with opposed lateral planning versus 4 Gy with IMRT planning). Intensity modulated radiation therapy significantly reduced unnecessary radiation dose to the carotid arteries compared with conventional opposed lateral fields while maintaining clinical

Table 2. Conformity index data

		Dose homogeneity			Conformity index		
	Techniques	D99(Gy)	D01(Gy)	DH(Gy)	V99(ptv)	Vptv	CI%
Patient 1	2DRT						
					61.627		0,974
	3DCRT	60.48	74.15	13,7	60.595	63.3	0.957
	IMRT	55.26	76.63	21.4	60.640		0.958
Patient 2	2DRT						
					48.200		0,969
	3DCRT	59.15	69.52	10.4	44.740	49.7	0.900
	IMRT	60.47	79.60	19.1	47.870		0.963
Patient 3	2DRT						
					62.684		0,957
	3DCRT	57.58	73.08	15.5	59.490	65.5	0.908
	IMRT	55.25	75.88	20.6	59.950		0.915
Patient 4	2DRT						
					88.918		0,967
	3DCRT	61.69	71.69	10.0	88.900	92.0	0.966
	IMRT	59.01	73.41	14.4	88.800		0.965
Patient 5	2DRT						
					54.778		0,961
	3DCRT	62.47	72.20	9.7	55.030	57.0	0.965
	IMRT	54.05	78.34	24.3	54.420		0.955

2DRT: Two dimension radiation therapy; 3DCRT: Three dimension conformal radiation therapy; IMRT: Intensity modulated radiation therapy.

target volume coverage.[8] Still, there is not enough data to favor or disfavor the use of carotid sparing irradiation with only these materials. The question is not whether or not IMRT could decrease the risk of carotid artery damage in early stage glottic laryngeal cancer patients. The main question is whether or not this potential benefit could balance the uncertain risks associated with IMRT usage. In this respect, the main risk of IMRT usage is uncertainty of defining the target volume, complications derived from high dose hot spots, target motion and the treatment complexities for beginners.

When carotid doses become a high priority, radiation oncologists tend to make CTV as small as possible. The main topic regarding the abovementioned issue is fully including or not including the contralateral cord or posterior border of the ipsilateral vocal cord. The carotid artery doses will have been increased very quickly with each millimeter when we include those volumes. For this purpose, Levendag et al.[10] investigated the single vocal cord irradiation with a competitive treatment strategy in early glottic cancer in 2011. They compared the IMRT planning done with 1-2 mm margin to single vocal cord with other treatment strategies in terms of adverse effects, disease control and survival parameters. They concluded that evidence based medicine randomized trials for the outcome of single vocal cord irradiation by IMRT techniques are absent but are definitely needed in order to make a more balanced comparison for these competitive techniques.[10] As can be seen all these academic discussions, the irradiation volume chosen for IMRT planning in order to decrease unnecessary doses to carotid arteries is not yet clear, when taking into mind the excellent local control and survival period of the disease. In addition to all these debates, there are many researches regarding head and neck cancer recurrences after IMRT treatment because of not including the CTV areas covered by conventional techniques.[11-13] An anecdotal publication examined recurrences appearing with IMRT used in early stage glottic laryngeal cancer.[14]

When the plans for significantly decreasing the carotid artery doses were analyzed, it was seen that some parts of the larynx were exposed to unexpected high doses above prescription dose. A case from our data had approximately 72 Gy maximum doses to larynx with IMRT planning. Despite hot spots volumes were generally small, but it was presumed that this kind of dose heterogeneity effected larynx functions in some patients.[7]

It was documented that the larynx could move 20-25 mm in craniocaudal directions and 3-8 mm in anterior-posterior directions during swallowing.[15-17] Interfractional swallowing period could be as small as 0.43% of total irradiation period during all conventional RT treatment.[18] Target motion problem is an important issue for IMRT which has long treatment period and has critical mechanisms between leaf segments and target as well. All aspects of RT planning and

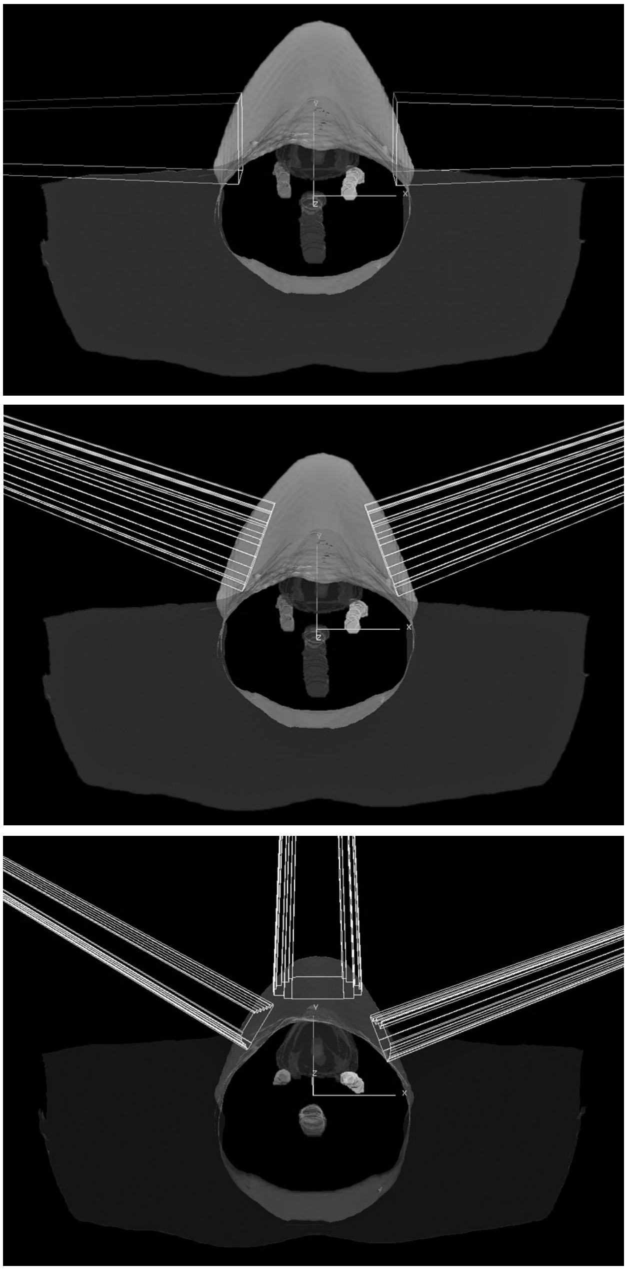

Figure 3. *Beam arrangements for presented patient.*

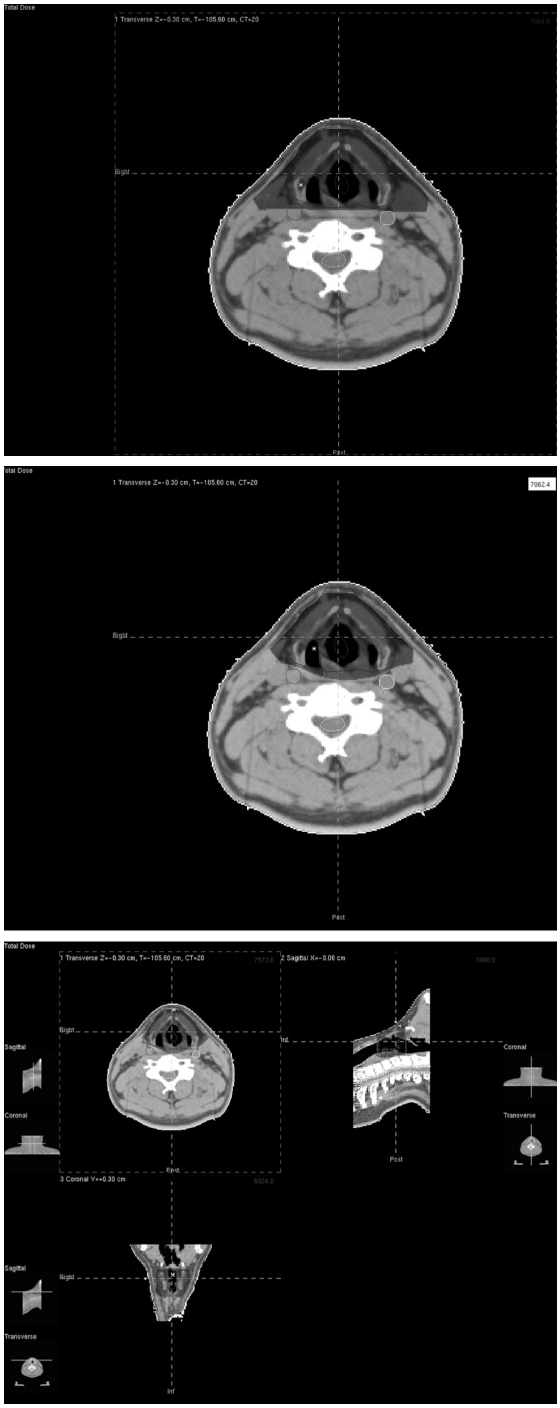

Figure 4. *Dose distributions for presented patient.*

delivering in IMRT technique are more complex than the conventional techniques which use opposed lateral beams. Increased complexity causes increased tumor recurrences and/or possibility of complication occurrence which arise from increased treatment error risks.

In order to evaluate balance between potential risks and benefits of carotid-sparing IMRT, we must estimate the risks of cerebrovascular events derived from RT. Cheng et al.[19] reported that the annualized progression rate from <50% to ≥50% stenosis in irradiated arteries was 15.4%, compared 4.8% in non-irradiated vessels and determined time from RT (>6 years) as an important risk factor. In that case, when >5 years disease-specific life expectancy will be our problem, morbidity reasons (stroke and secondary malignancies) will take the place of recurrences. This explanation can be interpreted as the lowest carotid artery doses with IMRT planning will have a contribution for decreasing morbidity in this long life expectancy patient group. The best studies regarding the relationship between the RT and cerebrovascular events include wide range of tumor status and advanced stage diseases. Most of these studies show that RT to the neck increases cerebrovascular events with small magnitude but are statistically significant.[2-4] The retrospective cohort study from Netherlands Cancer Institute reported their results including 367 patients treated with RT for head and neck cancer.[3] In this report, a 12% cumulative stroke risk and 5.6 relative risk were seen in a 15-year period. Also 14 ischemic strokes were reported. "Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort program" study from M.D. Anderson Cancer Institute reported that the 10-year incidence of cerebrovascular events was 35% in patients treated with RT alone and 26% in patients treated with surgery alone. In addition to these data, they could not show any increase concerning cerebrovascular events in patients treated with surgery and adjuvant RT.[2] The study of SERR software and Medicare from Mt. Sinai Medical Center found a statically significant increase in stroke incidence by 2.5% point in the head and neck cancer patients who were treated with RT.[4] But there were no difference in stroke mortality; the 10-year stroke rate was 10% with RT, 7.5% without RT (p=0.01).

Disagreements exist about how IMRT could balance its potential benefits and risks when decreasing the carotid arteries doses. There are marginal recurrences after IMRT in oropharengeal cancer patients although there is no data regarding recurrences by using carotid-sparing IMRT techniques in early stage laryngeal cancer.[20] In addition to all these results, most of the recurrences occur from delineating errors.[11-13] When considering under discussed results, it is inevitable that one can come to face to face with disagreement about using these new carotid sparing techniques. Long-term results of Florida University were excellent although conventional opposed lateral technique was used for treating early stage glottic laryngeal cancer as in our case.[21] Therefore we consider that the risks of IMRT application outweigh its potential benefits in spite of decreasing the exposure dose of carotid arteries significantly.

There is no question that IMRT planning techniques can decrease the radiation doses of carotid arteries in early stage glottic laryngeal cancer. The main issue is whether or not IMRT planning techniques can balance the tumor recurrence risk derived from delineating faults and organ motion in addition to dose heterogeneity complication risks. This is the issue over which many researchers disagree and have academic debates. In our opinion, its risks outweigh the benefits with our current evidence. Therefore we suggest conventional 3DRT fields and techniques for T1 glottic laryngeal cancer treatment.

Declaration of conflicting interests

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