Dosimetric comparison of helical tomotherapy, intensity-modulated radiation therapy, volumetric-modulated arc therapy, and 3-dimensional conformal therapy for the treatment of T1N0 glottic cancer

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ABSTRACT

Various radiotherapy planning methods for T1N0 laryngeal cancer have been proposed to decrease normal tissue toxicity. We compare helical tomotherapy (HT), linac-based intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and 3-D conformal radiotherapy (3D-CRT) techniques for T1N0 laryngeal cancer. Overall, 10 patients with T1N0 laryngeal cancer were selected and evaluated. Furthermore, 10 radiotherapy treatment plans have been created for all 10 patients, including HT, IMRT, VMAT, and 3D-CRT. IMRT, VMAT, and HT plans vs 3D-CRT plans consistently provided superior planning target volume (PTV) coverage. Similar target coverage was observed between the 3 IMRT modalities. Compared with 3D-CRT, IMRT, HT, and VMAT significantly reduced the mean dose to the carotid arteries. VMAT resulted in the lowest mean dose to the submandibular and thyroid glands. Compared with 3D-CRT, IMRT, HT, and VMAT significantly increased the maximum dose to the spinal cord It was observed that the 3 IMRT modalities studied showed superior target coverage with less variation between each plan in comparison with 3D-CRT. The 3D-CRT plans performed better at the D_{max} of the spinal cord. Clinical investigation is warranted to determine if these treatment approaches would translate into a reduction in radiation therapy–induced toxicities.

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Introduction

Larynx cancer is one of the most common head and neck cancer malignancy, and approximately half of these malignancies present as an early stage (T1N0-T2N0). Successful treatment options include surgery and radiation therapy (RT), but no single modality has been proven to be superior to the other.[1] The end goal of treatment is larynx preservation, high voice quality, and minimal morbidity. Therefore, RT has been considered as a mainstay treatment approach for early-stage patients.[2,3] Conventionally, RT has been delivered using 2 small, parallel opposed radiation fields, often using hypofractionated schedules. This technique is proven to be very effective but unfortunately does not allow dose sparing of the organs at risk (OAR) in the neck including carotid arteries, skin, thyroid gland, and often submandibular glands. Carotid artery damage after radiotherapy leads to increased thickness of carotid intima-media, subsequently resulting in increased incidence of atherosclerosis and higher chance of cerebrovascular accidents.[4] Newer RT techniques such as tomotherapy and linac-based intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT) with RapidArc (RA) have been developed that allow superior dose conformality to treatment target volumes and provide steep dose gradients to nearby uninvolved structures.[5,6] Many institutions have recently incorporated IMRT with different devices into the treatment of early-stage glottic cancer for selected patients.[7] To date, there are limited data directly comparing all different radiotherapy modalities and treatment strategies for early-stage larynx cancer. This is the first study comparing

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dose-volume histograms (DVHs) of target volumes and normal tissue structures in tomotherapy-based IMRT *vs* RA-based VMAT plans using both fixed target volumes and adaptive planning for patients with early-stage larynx cancer.

Methods and Materials

A total of 10 patients with T1N0M0 squamous cell carcinoma of the vocal cord suitable for treatment using a hypofractionated radiotherapy schedule were selected for this study. All suspicious lesions were biopsied, and pathology slides were reviewed by an expert in head and neck pathology at Inonu University. Patients were staged with any combination of direct laryngoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) scans. Patients were immobilized in the supine position with a 5-point thermoplastic mask. Treatment planning CT scans were obtained from the top of the skull to the lower part of the neck with a 3-mm slice thickness. Intravenous contrasting agent (Iopamidol, 1 mg/kg of body weight) was used in all patients. All patients were treated using a helical tomotherapy (HT)—based IMRT technique. HT planning was performed using tomotherapy Hi-ART planning systems software version 4.2.1. Patients were treated to the larynx region without elective nodal irradiation. CT simulation data sets for the treatment of RT history were obtained for all 10 patients.

The HT multileaf collimator leaf width used is 6.25 mm in IEC-X direction at isocenter. Images and structure sets were then imported into treatment planning systems to create RA, linac-based IMRT, and 3-DCRT plans. Treatment plans were created by 3 separate medical physicists at 3 separate cancer therapy centers. Overall, 4 treatment plans were created for each treatment modality to be studied (HT, 3-D conformal radiotherapy [3D-CRT], IMRT, and VMAT). VMAT, linac-based IMRT, and 3-D CRT plannings were performed using an Eclipse version 13.0 (Varian Medical Systems Inc., Palo Alto, CA). For the IMRT and VMAT plans, Varian HD MLC

system with 2.5-mm leaf width was used. The target volumes were delineated following our institutional guidelines for contouring. The clinical target volume (CTV) extended superiorly from the cranial border of the thyroid cartilage, inferiorly till the caudal end of the cricoid cartilage, anteriorly included the anterior edge of the thyroid cartilage, posteriorly included the arytenoid cartilage, and laterally the entire thyroid cartilage was included within the CTV. A 5-mm margin was applied to CTV in all axes as per institutional policy to create the planning target volume (PTV). OARs contoured included the spinal cord, bilateral carotid arteries, submandibular glands, and thyroid gland. Bilateral carotid arteries were contoured from superior edge of the skull base up to inferior edge of the sternoclavicular joint. We contoured a ring that extends the PTV by 8 mm in all directions to have a more homogeneous plan. All plans used the same OAR, CTV, and PTV delineations.

The dose prescription was 6300 cGy in 225 cGy fractions over a course of 38 days, and plans were normalized as at least 95% of the PTV was required to be covered by the at least 95% isodose of 63 Gy. No point dose outside PTVs was >105% of the prescribed dose and no point dose within PTVs was >110% of the prescribed dose. DVHs of PTVs and OARs were generated for 3-D CRT, IMRT, Tomoterapy, and RA plans to compare doses with tumor volumes and normal structures.

The 3D-CRT plans used the traditional opposing 2-field lateral coplanar or noncoplanar beams. Beams were individually optimally weighted to provide adequate PTV coverage. Bolus was not required for these plans. IMRT plans used 3 optimally positioned beams per patient with "step and shoot" treatment delivery. RapidArc treatment plans used 2 partial arcs for treatment. HT uses field width, pitch, and modulation factor variations to optimize plans. A field width of 1 cm, modulation factor of 2.3, and pitch of 0.287 were used to produce the HT plans. All plans were generated with 6-MVphotons using a multileaf collimator. An example of typical patient plans and DVHs with the 4 treatment modalities is shown in the Fig.
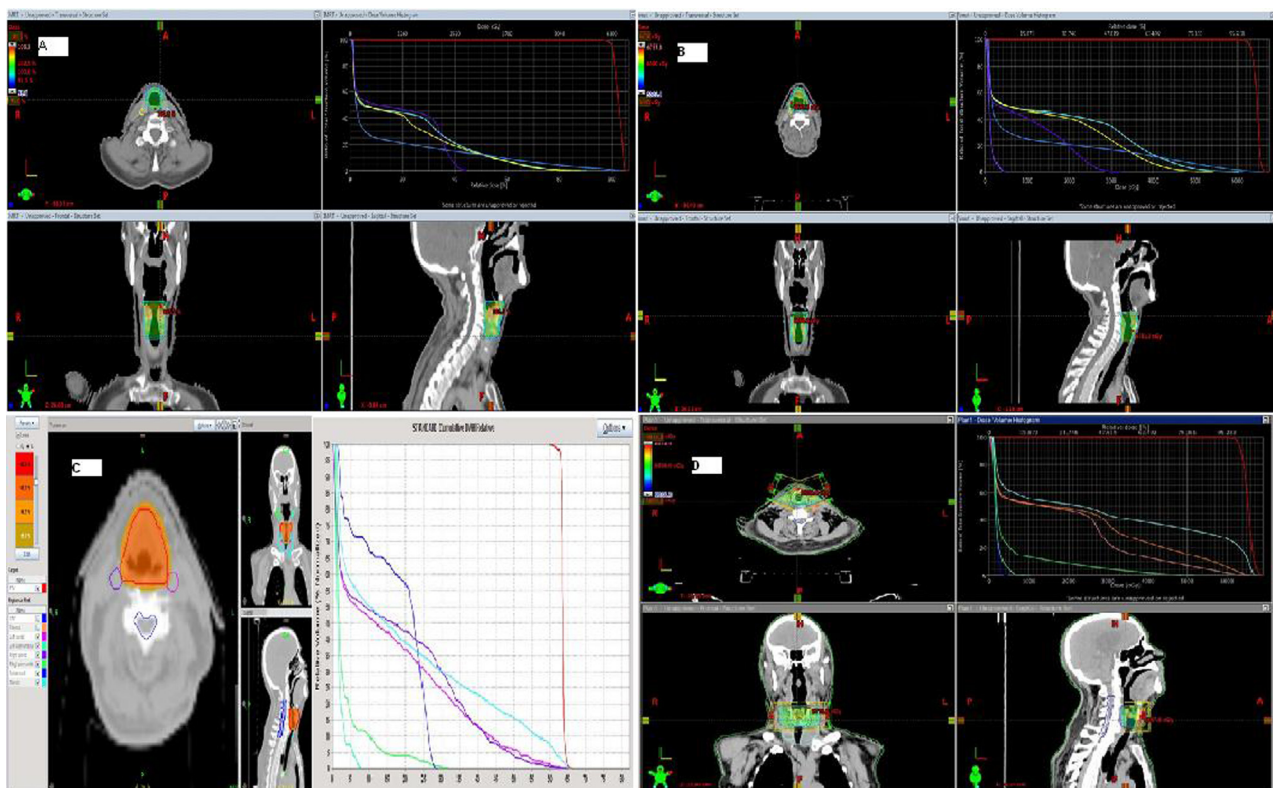

Fig. Dose distributions and dose-volume histograms of 4 planning techniques: (A) IMRT, (B) VMAT, (C) HT, and (D) 3D-CRT. (Color version of figure is available online.)

Various methods were employed to minimize bias in the present study. Overall, 10 consecutive patients who required replanning were included in this study to minimize sampling bias. All contours were performed by a single radiation oncologist (C.S.) and approved by at least 2 additional radiation oncologist. A standard treatment planning optimization strategy was used for all plans. Conformity indexes, homogeneity indexes, and DVHs were assessed to ensure comparable PTV coverage between plans to minimize any bias when comparing normal tissue dosimetry between plans.

Treatment plans for the 4 different treatment techniques were compared using DVHs parameters. Minimum, mean, and maximum dose (D_{min}, D_{mean}, and D_{max}); homogeneity index (HI); and conformation index (CI) were compared for the PTV between all 4 treatment modalities. HI was used to evaluate dose homogeneity within target volume. HI is calculated from the following formula:

$$HI = (D_2 - D_{98}/D_p) \times 100\%$$

where D_2, D_{98}, and D_p represent the doses to 2%, 98%, and prescribed dose to the PTV, respectively, and where[8] HI formula shows that lower HI values indicate a more homogeneous target dose (0 is the ideal value).

We used a CI value that was previously proposed by Van't Riet et al.[9] This CI simultaneously takes into account irradiation of the target volume and irradiation of the healthy tissues. CI is calculated from the following formula:

$$CI = (TVRI/TV)(TVRI/VRI)$$

where TVRI is the target volume covered by the reference isodose (95% of the prescribed dose), TV is the target volume, and VRI is the volume of the reference isodose. The CI ranges from 0 to 1, where 1 is the ideal value.

For OAR, the values of D_{mean}, V_{35}, and V_{50} for carotid arteries; D_{mean}, V_{30}, and V_{50} for thyroid gland; D_{mean} for submandibular glands; and D_{max} for spinal cord were evaluated and compared. For this analysis, V_x was defined as the percentage of a given tissue volume receiving at least x Gy. Additionally, for all treatment plans, the DVH of the normal tissue sparing (body-PTV) and monitor unitsettings required for each plan were calculated and compared. In comparing the data, if parametric conditions were provided, analysis of variance post hoc was used, otherwise, the Kruskal-Wallis test was used. In the paired group comparisons of quantifiable data, if parametric conditions were provided the Bonferroni modified test was applied, otherwise the Mann-Whitney *U* test was used. All statistical tests were 2 sided, with a threshold for statistical significance of $p < 0.05$. Statistical analysis was conducted using SPSS version 13.

Results

Dose coverage and dose distribution

Average mean doses for PTV were 63.60, 64.47, 64.24, and 65.57 Gy for HT, VMAT, IMRT, and 3-DCRT plans, respectively. In all cases, 95% of the prescription dose covered at least 95% of each PTV. No point dose outside PTVs was > 105% of the prescribed dose, and no point dose within PTVs was > 110% of the prescribed dose. The average maximum and minimum PTV doses were 66.27 and 59.60 Gy for HT, 67.28 and 57.54 Gy for VMAT, 66.17 and 56.89 Gy for IMRT, and 68.64 and 53.49 Gy for 3-D CRT plans, respectively. Statistically significant differences for HT *vs* VMAT, HT *vs* 3-D CRT, and IMRT *vs* 3D-CRT plans were observed for mean and maximum doses. Also, significant differences observed for HT *vs* 3D-CRT plans for minimum doses. Concerning the calculated heterogeneity and conformity indices, HT was the technique with the most conformed dose distribution. Statistically significant differences were observed between HT, VMAT, IMRT *vs* 3D-CRT, and IMRT and HT *vs* VMAT plans, respectively. The dose statistical dosimetric evaluation and comparison of the 4 planning techniques for PTV were listed in Table 1.

Minimum treatment time was provided with VMAT plans in IMRT treatment modalities. Average treatment times for our each 10 patients were 300, 121, 159, and 40 seconds for HT, VMAT, IMRT, and 3-DCRT plans, respectively.

Carotid arteries

Compared with 3D-CRT, all other treatment modalities showed superiority for dose sparing of the left and right carotid arteries. Significant differences were found in mean dose values when 3D-CRT plans were compared against IMRT and VMAT plans for right carotid arteries. No significant differences were found between HT *vs* VMAT, HT *vs* IMRT, HT *vs* 3D-CRT, and VMAT *vs* IMRT plans for right carotid arteries. Significant differences were found in mean dose values when 3D-CRT plans were compared with 3 other modalities. No significant differences were found between HT *vs* VMAT, HT *vs* IMRT, and VMAT *vs* IMRT plans for left carotid arteries. Similar results were found for carotid arteries in volume-based criteria (V_{35} and V_{50}). The statistical dosimetric evaluation of doses and comparison of the 4 planning techniques for OARs were listed in Table 2.

Submandibular glands

The average mean doses to the right submandibular glands were 8.20, 5.08, 6.08, and 11.65 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. Statistically significant differences were found in mean doses when 3D-CRT compared with VMAT and IMRT plans. Also, significant differences were found in mean dose values when VMAT plans were compared with HT plans for right submandibular glands. The average mean dose values to the left submandibular glands were 5.88, 3.00, 4.11, and 7.28 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. Similar statistically significant results were found for left submandibular glands.

Table 1
Dose statistics comparison for planning target volumes

Parameter PTV	HT	VMAT	IMRT	3D-CRT	HT *vs* VMAT	HT *vs* IMRT	HT *vs* 3D-CRT	VMAT *vs* IMRT	VMAT *vs* 3D-CRT	IMRT *vs* 3D-CRT
D_{max} (Gy)	66.27 ± 0.45	67.28 ± 0.34	66.17 ± 0.86	68.64 ± 1.06	0.034	*n*	0.0001	*n*	*n*	0.001
D_{mean} (Gy)	63.60 ± 0.17	64.47 ± 0.19	64.24 ± 0.25	65.57 ± 0.31	0.011	*n*	0.0001	*n*	*n*	0.011
D_{min} (Gy)	59.60 ± 1.22	57.54 ± 0.65	56.89 ± 2.39	53.49 ± 4.17	n	*n*	0.006	*n*	*n*	N
$V_{59.85}$ (%)^{xx}	99.8 ± 0.11	96.2 ± 0.21	96 ± 0.28	99.6 ± 0.17	0.005	0.005	0.073	*n*	0.005^x	0.005^x
V_{105} (%)	0.001 ± 0.001	0.02 ± 0.02	0.001 ± 0.001	0.37 ± 0.11	0.034	*n*	0.0001	*n*	*n*	0.0001
HI	1.05 ± 0.001	1.06 ± 0.001	1.05 ± 0.001	1.08 ± 0.01	0.005	*n*	0.007	0.005^x	0.025	0.009
CI	0.86 ± 0.03	0.81 ± 0.04	0.71 ± 0.06	0.68 ± 0.11	0.028	0.005	0.007	0.005	0.013	*n*

X = second one is better than first one, *n* = statistically not significant; xx = percentage of the PTV volume receiving at least 95% of the prescription dose for various treatment modalities.

Table 2
Dose statistics comparison for organs at risk

Parameter	HT	VMAT	IMRT	3D-CRT	HT *vs* VMAT	HT *vs* IMRT	HT *vs* 3D-CRT	VMAT *vs* IMRT	VMAT *vs* 3D-CRT	IMRT *vs* 3D-CRT
Right carotid										
D_{mean}	14.38 ± 1.68	12.17 ± 1.58	13.24 ± 1.48	26.08 ± 4.05	n	n	n	n	0.0001	0.002
V_{35} (%)	0.16 ± 0.04	0.09 ± 0.07	0.13 ± 0.04	0.40 ± 0.10	n	n	0.034	n	0.0001	0.006
V_{50} (%)	0.03 ± 0.02	0.00 ± 0.01	0.02 ± 0.01	0.31 ± 0.11	n	n	n	n	0.0001	0.019
Left carotid										
D_{mean}	14.57 ± 1.75	12.94 ± 3.48	13.47 ± 1.61	26.09 ± 4.72	n	n	0.006	n	0.002	0.003
V_{35} (%)	0.18 ± 0.05	0.12 ± 0.10	0.13 ± 0.04	0.37 ± 0.10	n	n	n	n	0.003	0.002
V_{50} (%)	0.05 ± 0.03	0.03 ± 0.05	0.03 ± 0.03	0.31 ± 0.12	n	n	0.011	n	0.000	0.006
Right submandibular										
D_{mean}	8.20 ± 5.44	5.08 ± 4.04	6.08 ± 4.77	11.65 ± 6.33	0.019^x	n	n	n	0.0001	0.0001
Left submandibular										
D_{mean}	5.88 ± 4.68	3.00 ± 2.71	4.11 ± 3.88	7.28 ± 6.08	0.004^x	n	n	n	0.0001	0.001
Thyroid										
D_{mean}	14.74 ± 5.45	10.24 ± 4.16	13.00 ± 5.45	27.00 ± 10.08	0.019^x	n	n	n	0.0001	0.006
V_{30} (%)	0.22 ± 0.10	0.15 ± 0.08	0.20 ± 0.10	0.41 ± 0.17	n	n	n	n	0.0001	0.011
V_{50} (%)	0.10 ± 0.07	0.04 ± 0.04	0.09 ± 0.07	0.32 ± 0.16	n	n	n	n	0.0001	0.034
Spinal cord										
D_{max}	29.57 ± 1.45	28.27 ± 2.02	25.24 ± 4.13	4.63 ± 0.48	n	n	0.000^x	n	0.002	N

X = second one is better than first one; n = statistically not significant.

Thyroid

The average mean dose values to the thyroid glands were 14.74, 10.24, 13.00, and 27.00 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. Statistically significant differences were found in mean doses when 3D-CRT compared with VMAT and IMRT plans. Also, significant differences were found in mean dose values when VMAT plans were compared HT plans for thyroid glands. Similar results were found for carotid arteries in volume-based criteria (V_{30} and V_{50}).

Spinal cord

The average maximum doses to the spinal cords were 29.57, 28.27, 25.24, and 4.63 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. Statistically significant differences for 3D-CRT *vs* VMAT and 3D-CRT *vs* HT plans were observed for maximum doses to the spinal cord.

Discussion

Early-stage glottic cancer is a highly curable malignancy, which can be treated with either larynx-sparing surgery (laser excision, cordectomy, or hemilaryngectomy) or radiotherapy. Many past researches have regarded radiotherapy as the mainstay of treatment for such patients. Because both treatment modalities offer similar rates of cure, decisions regarding which therapy to pursue often lie on the anticipated toxicity profile of a particular regimen. Other factors such as tumor location and extent of disease, comorbid illnesses, and physician and patient preference also affect the final treatment decision.[2,10]

Technological advancements continue to provide us with new treatment approaches that result in dose reduction to uninvolved nontarget tissues. In this study, we compared 4 common radiotherapy modalities for T1N0 larynx cancer for a randomly selected cohort of 10 patients. Our primary objective was to determine the capability of each modality to provide PTV coverage and simultaneously evaluate nontarget organ dose limitations.

The treatment plans evaluated were successful in providing > 95% of V_{95} dose coverage for the PTV. For HT and 3D-CRT plans, the coverage was > 99%, though for some IMRT and VMAT plans, the coverage was < 99%. Statistically significant differences for HT *vs* VMAT, HT *vs* 3D-CRT, and IMRT *vs* 3D-CRT plans were observed for mean and maximum doses. Also, significant differences were observed for HT *vs* 3D-CRT plans for minimum doses also.

IMRT treatment plans were the most consistent in allowing the lowest mean dose to the carotid arteries compared with 3D-CRT treatment plan in our study. A lower mean dose to the whole organ would potentially improve possible late cerebrovascular complications. There are sufficient data that high-dose radiation to the carotid arteries can lead to vascular disease. Several reports have shown that head and neck radiation using conventional techniques can cause carotid artery stenosis and increase the risk of ischemic stroke.[2,11] Dorresteijn *et al.* assessed 367 patients treated with radiotherapy for head and neck tumors, including 162 patients with larynx carcinomas, and examined the risk of ischemic stroke. The authors found that the relative risk of developing an ischemic stroke in the patients treated for larynx cancer was 5.1, which reached statistical significance.[12]

In our study, VMAT plans had the lowest mean dose to the thyroid glands, followed by IMRT plans. The anatomical location of thyroid gland, like the carotid arteries, is such that it comes in close proximity with the PTV of T1N0 glottic cancer. The use of radiotherapy for head and neck cancer has been shown to result in adverse effects such as hypothyroidism, hyperthyroidism, Graves' disease, and thyroid malignancies on the thyroid gland.[13] It is estimated that 25% to 50% of patients receiving radiotherapy for head and neck cancer develop some diminution of thyroid function and approximately 6% to 15% experience hypothyroidism.[14] Therefore, consideration of dose received to the thyroid in T1N0 larynx cancer is of relevance. The tolerance dose of thyroid gland has not been absolutely elicited and agreed on; many investigators have suggested that the mean dose of > 30 Gy to thyroid gland is a possible predictor for the development of hypothyroidism.[15,16] Therefore, any technique other than 3D-CRT would potentially be of clinical benefit to prevent adverse effects of thyroid function by delivering a lower mean dose.[4] In our study, maximum dose values to the spinal cord by the 4 techniques employed are 30, 28, 25, and 5 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. It is well known that the tolerance dose at conventional fractionation for the spinal cord is approximately 50 Gy.[17] Doses more than 60 Gy are known to potentially result in serious conditions such as progressive radiation myelopathy,

which is followed by shocklike sensations from the flexed neck to extremities called Lhermitte sign or radiotherapy-induced cord transection.[18,19]

Near the PTV of T1N0 larynx cancer, submandibular glands are another important organ. The average mean dose received by the right submandibular glands were 8.20, 5.08, 6.08, and 11.65 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. The average mean dose received by the left submandibular glands were 5.88, 3.00, 4.11, and 7.28 Gy for HT, VMAT, IMRT, and 3D-CRT plans, respectively. Submandibular gland sparing can reduce the risk of both stimulated and unstimulated xerostomia.[20] Regarding the dose response, Murdoch-Kinch et al.[21] reported that submandibular gland–stimulated salivary function decreased significantly after a mean dose of > 40 Gy.

There are several limitations to the current study. This is a dosimetric study, and it does not consider vital aspects required for clinical use. The treatment modalities studied other than 3D-CRT radiotherapy have the potential to improve, or at least not compromise PTV dose coverage, then they are of potential clinical benefit. The number of patients used for comparison in this study was limited to 10, this may be improved in the future to obtain a better sample. To expand the sample of population for our recommendations, we attempted to select both patients with normal anatomy and those with T1N0 disease. The effect of organ motion was not assessed in this study. Clearly there is some degree of organ motion when treating the larynx, and the typical boundaries with conventional techniques account for this motion. HT, IMRT, and VMAT techniques have significant potential to limit mean dose to nearby OAR of the carotid arteries and thyroid gland. Thus, it makes sense that this coverage with the combined limitation of normal tissue exposure may be of clinical benefit to patients receiving radiotherapy. Although 3D-CRT technique approach provides the lowest dose to the spinal cord, all other techniques provide well below the established tolerance dose limit. Therefore, the allowance of increased dose to the spinal cord potentially could improve dose reduction to the carotids and thyroid gland allowing for less potential patient morbidity.

Conclusions

Based on the dosimetric findings in this study, there is a potential clinical advantage for HT, IMRT, or RA treatment modalities compared with 3D-CRT for the treatment of T1N0 laryngeal cancer. HT treatment planning was shown to be the most effective modality to maintain or improve PTV coverage with the most reduction in mean carotid, submandibular, and thyroid dose. All these 3 modalities showed superiority with less variation among themselves compared with 3D-CRT plans, with the exception of spinal cord dose. Clinical investigation is warranted to determine if these advanced treatment approaches would translate into a reduction in many radiotherapy-induced chronic toxicities and potential improvement in the quality of life in patients treated with radiotherapy for T1N0 laryngeal cancer. Based on our

experiences, the current policy at our institution is to treat all patients with nasopharyngeal carcinoma with HT or VMAT. Further studies are needed to corroborate our findings and to determine whether the improvements in isodose distribution and DVHs would indeed translate into improved clinical outcomes in the future.

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