3D-Conformal versus Intensity modulated radiation therapy in the treatment of early stage glottic squamous cell carcinoma: A dosimetrical analysis

Mashhour K[1], Abdelghany H[2], Saad E[1], Mounir A[1]

[1] Department of Clinical Oncology, Kasr Al-Ainy school of medicine, Cairo University, Egypt
[2] Department of Medical Physics, Kasr Al-Ainy school of medicine, Cairo University, Egypt

Abstract:

Background: The objective of this study is to dosimetrically compare and contrast both techniques in the treatment of early stage glottic squamous cell carcinoma as regards the planning dose volume (PTV) dose coverage and the doses perceived by the organs at risk particularly the thyroid gland, carotid arteries and spinal cord.

Methods: Twenty patients with the pathological diagnosis of early glottic SCC (T1-T2/N0) were enrolled in the study design during the period October 2022 till January 2023. All patients were treated in Kasr Elainy center of clinical oncology using 3D-CRT radiotherapy technique. A dose of 66Gy in 33 fractions was the prescribed dose to the planning target volume (PTV). An intensity modulated radiotherapy (IMRT) plan was done for each patient and the dosimetric parameters were contrasted to the 3D-CRT plan

Results: The homogeneity index (HI) for PTV66Gy was higher for the IMRT plans with a value of 0.1± 0.005 as contrasted to 0.08 ± 0.006 for the 3D-CRT plans with a statistically significant p-value of 0.002. The IMRT plans showed z significantly superior PTV95% coverage with values of 98.3 ± 14.7 as opposed to 94.5 ± 30.7 for the 3D-CRT plans (p-value of 0.003). The dose received by the thyroid gland was lower in the IMRT group with a value of 14.9Gy ± 5.39 compared to 51.2Gy ± 8.62 for the 3D-CRT plans with a statistically significant p-value of 0.004. Mean doses to the right and left carotid artery were lower in the IMRT plans compared to the 3D-CRT plans (p-value of 0.201& 0.266).

Conclusion: In early glottic cancer, the plans generated by IMRT showed a better PTV coverage and more homogeneous dose distribution when compared to the plans achieved by 3D-CRT. The IMRT plans showed better OAR sparing with respect to the thyroid gland and carotid arteries.

Keywords: 3D-CRT, IMRT, Glottic, Carotid arteries

Received: 18 May 2023
Accepted: 21 May 2023

Authors Information:

Karim Mashhour
Department of Clinical Oncology, Kasr Al-Ainy school of medicine, Cairo University, Egypt
email: Karim.mashhour.81@gmail.com

Hoda Abdelghany
Department of Medical Physics, Kasr Al-Ainy school of medicine, Cairo University, Egypt
email: hodaghany@gmail.com

Ehab Saad
Department of Clinical Oncology, Kasr Al-Ainy school of medicine, Cairo University, Egypt
email: Ehab.saad239@gmail.com

Ashraf Mounir
Department of Clinical Oncology, Kasr Al-Ainy school of medicine, Cairo University, Egypt
email: achrafmounir@icloud.com

Corresponding Author:
Karim Mashhour
Department of Clinical Oncology, Kasr Al-Ainy school of medicine, Cairo University, Egypt
email: Karim.mashhour.81@gmail.com

Introduction:

In the head and neck region, laryngeal squamous cell carcinoma (SCC) is the commonest type of cancer accounting to 2% of all cases worldwide with an incidence in Egypt of 2.5% [1]. Laryngeal cancer ranks in the top ten of malignancies in male patients due to higher prevalence of alcohol and tobacco use. In the latter, former smokers also carry an increased risk of developing laryngeal cancer [2].

Anatomically, the larynx is sub-divided into three regions: the glottis, supraglottis and subglottic regions [3]. Patients diagnosed with laryngeal glottic SCC commonly present at an early stage of their disease (T1N0M0, T2N0M0). Glottic SCC carries a very good prognosis in view of the pattern of lymphatic and hematogenous spread is exceedingly rare in this disease as the glottic area is deficient in vascular vessels and lymphatics [4,5].

The laryngeal integrity and function are preserved with the usage of conventional radiotherapy but the carotid arteries are at risk of injury from the prescribed radiation doses being hypothesized that radiotherapy causes disruption of the endothelial barrier of the blood vessels [6,7]. Patients who receive radiotherapy to the

neck area have a higher risk for thyroid dysfunction and cerebrovascular events (CVE) such as transient ischemic attacks (TIA) or ischemic strokes likely due to radiation doses perceived by the thyroid gland and the carotid arteries [8-11].

Patients having a diagnosis of early glottic SCC are rendered highly curable when treated with parallel opposing conventional 3D conformal radiotherapy (CRT) fields with an excellent local control rates [12-22]. Recent radiotherapy technology such as intensity-modulated radiation therapy (IMRT) aids to concentrate the dose delivered to the target volume while aiming at the reducing the dose to the surrounding critical structure through inverse planning. Therefore, using IMRT may reduce to the dose to the thyroid gland and bilateral carotid arteries while maintaining an equivalent therapeutic radiotherapy effect to the conventional 3D-CRT treatment technique. Limiting the dose to these organs at risk (OAR) may allow for re-irradiation when clinically necessary. Many reports on IMRT delivery in early glottic SCC has been published [23-29].

Randomized clinical data are lacking regarding the differences in treatment toxicities and cancer outcomes between 3D-CRT and IMRT. While IMRT has clearly changed the practice of how radiation oncologists treat most head and neck SCC primary sites, its role in early stage Glottic SCC remains questionable and controversial. The objective of this present study is to dosimetrically compare and contrast both techniques as regards the planning dose volume (PTV) dose coverage and the doses perceived by the organs at risk particularly the thyroid gland, carotid arteries and spinal cord.

Patients and Methods:

An approval on the study design was obtained from our department as well as from the ethical committee (N128-2022) was obtained on the study design. A detailed written consent was received from all participants prior to their recruitment in our study.

Patient selection and preparation

Twenty patients with the pathological diagnosis of early glottic SCC (T1-T2/N0) were enrolled in the study design during the period October 2022 till January 2023. All patients were treated in Kasr Elainy center of clinical oncology using 3D-CRT (conformal) radiotherapy technique (Table 1). Patients underwent a thorough pre-treatment assessment including a detailed history and clinical examination, magnetic resonance imaging (MRI) and/or computed tomography (CT) of head and neck region, chest X-ray or thoracic CT and flexible direct fibro-optic examination.

Table 1 illustrates the patient and tumoral characteristics of both arms.

Patients included in this present study had a biopsy proven glottic squamous cell carcinoma, Karnofsky Performance status was more than 60 %, age range was between 18-70 years, adequate marrow function with white blood cell counts of ≥ 4000/cmm, platelet counts of ≥ 100,000/cmm and hemoglobin levels of ≥ 10 gm/dl were required and patients should have a normal kidney and liver functions profile. Evidence of metastatic disease, previous treatment for glottic cancer, patients with previous malignancy elsewhere, major medical or psychological illness, which would interfere with treatment were the exclusion criteria

Table 1: Patient and tumoral characteristics

	No	**%**
Age		
< 50 years	3	15%
>50 years	17	85%
Sex		
Male	18	90%
Female	2	10%
Smoking history		
Yes	18	90
No	2	10
Tumor grade		
Well differentiated	4	20%
Moderately differentiated	10	50%
Poorly differentiated	6	30%
T staging		
T1	12	60%
T2	8	40%
Commissural involvement		
Yes	14	70%
No	6	30%

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The patients were immobilized and aligned in a supine position on a head support type C pad for adequate neck extension with the aid of a head-and-shoulder shell (S- type, Aquaplast, USA) thermoplastic mask. The planning CT scans was performed using a 16-slice CT scanner (Brilliance CT Big Bore; Philips Medical Systems, Cleveland, OH, USA) with a 2.5 mm slice thickness. The patients were scanned starting from skull vertex till upper chest region. The CT data was then transferred to the Eclipse treatment planning system (Eclipse ver. 8.6; Varian Medical Systems Inc., Palo Alto, CA, USA) via DICOM network.

Target volume definition and dose prescription

The clinical target volume (CTV) delineation included the true and false vocal cords, the arytenoids, both the anterior and posterior commissures. Superiorly, starting from the superior thyroid notch till the bottom of the cricoid cartilage inferiorly. The CTV was laterally limited by the edge of the thyroid cartilage. The posterior boundary of the contouring included the anterior margin of the vertebral bodies. The superior border will be a bit higher for glottic T2 tumors (up to the inferior margin of the hyoid bone while the inferior border will be slightly lower for glottic T2 tumors (0.3 cm below the inferior margin of the cricoid cartilage). The field size was ranging between 5cm to 6 cm in

superior-inferior direction. An approximately fall off of 1 cm for the anterior border was allowed for the 3D-CRT. A uniform expansion from the CTV by 0.3 cm created the planning target volume (PTV) margin.

The organs at risk (OARs) contoured included the spinal cord, thyroid gland and bilateral carotid arteries. The spinal cord and carotid arteries volumes had a 1 cm cranio-caudal extension to account for the planning at risk volume (PRV). The CTVs and PTVs were contoured by the same radiation oncologist. The treatment was directed to the whole larynx without including elective nodal irradiation. The dose prescribed to the PTV was 66Gy/33F/6 and a half weeks (2Gy/F). Another PTV2 was contoured in the IMRT group with a margin of 0.3 cm around the gross target volume (GTV). The dose prescribed to PTV2 was 59.4Gy/33F/ 6 and a half weeks (1.8Gy/F). The treatment delivery was conducted and performed using a linear accelerator with the facility of Millennium 120-leaf multi-leaf collimators (MLCs) system (Clinac DBX; Varian Medical Systems Inc.). The patient set-up was verified on weekly basis by kV portal imaging system using the built in On-Board Imager system prior to delivering the radiotherapy session.

Treatment planning and plan evaluation parameters

All patients had two radiotherapy plans done for each case individually, one using 3D-conformal radiotherapy and the other using Intensity modulated radiation therapy technique. The 3D-CRT plan consisted of three fields (two lateral parallel opposing fields of equal weighting in addition to an anterior field with optimal weighting to provide adequate PTV coverage. A combination of wedges (30° and 45°) was used for beam modification in the lateral portals.

For the IMRT plans, seven fields of similar spacing was run on the Eclipse Planning System (Varian Medical Systems version 8.6.15). The energy of the beam used was 6MV photons for both plans. Treatment was delivered using sliding-window technique

The ultimate goal of all plans was to cover at least 95% of the PTV with the prescribed dose. All plans were normalized to 66 Gy (100% of the dose). We prescribed the dose constraints to the OAR as follows: a mean dose of less than 30Gy for the thyroid gland, a maximum point dose of 45Gy for the spinal cord. For the carotid arteries, the aim was to push and restrict the dose as low as possible with no specific constraints due to the lack of data of accurately defined dose thresholds related with carotid artery toxicity.

The organs at risk (OAR) and PTV coverage dose volume histogram (DVH) were generated individually. The ratio of the covered target volume by 95% isodose line divided by the whole volume of the PTV was used for calculation of PTV coverage. Maximum and minimum doses within the PTV, D2% and D98% were also obtained (the dose received by 2% and 98% of the PTV). The homogeneity index (HI) was calculated as per the ICRU 83: (D2% −D98%)/D50% which resembles the difference between the radiotherapy dose covering 2% and 98% to the dose prescribed received by 50% of the PTV target volume. The conformity index (CI95%) was calculated using the ratio between the volume of the patient receiving at least 95% of the dose prescribed and the PTV volume.

Statistical analysis

The Computer programs SPSS (Statistical Package for Social Science; SPSS Inc., Chicago, IL, USA version 19 for Microsoft Windows) was used for all statistical calculations. Independent Student t test was used for comparisons and was studied to evaluate the difference between both techniques. P-values less than 0.05 were considered statistically significant.

Results:

3D-CRT and IMRT plans were performed for each individual patient by a senior medical physicist (a total number of forty plans. All plans were clinically acceptable and fulfilled the required dose volume coverage. All plans were approved by a single radiation oncologist. Tables (2 and 3) illustrates the dosimetric outcomes obtained from the Dose-volume histogram (DVH) regarding parameters of the target volume coverage (Table 2) and doses received by the risk organs (Table 3) compared in both group plans, respectively. The dosimetric data outcomes were reported in the form of mean values ± Standard Deviation (SD).

Table 2: shows the dosimetric parameters for the coverage of the planning target volume.

Table 3: illustrates the dosimetric parameters for the organs at risk.

Target volume coverage

The V95% covering the PTV was significantly superior in the IMRT plans with accurate values of 98.3 ± 14.7 as compared to 94.5 ± 30.7 for the 3D-CRT plans (with a p-value of 0.003). Adequate coverage of the target volume was fulfilled in both plans. The HI for PTV66Gy was superior in the IMRT plans with a value of 0.1± 0.005 as opposed to 0.08 ± 0.006 for the 3D-CRT plans with a statistically significant p-value of 0.002. Having a close look at the CI95% representing the dose conformity within the target volume, it was found to be lower in the 3D-CRT plans (0.87 ± 0.19) as contrasted to the IMRT plans (0.9 ± 0.002) However, the difference between both groups was not statistically significant (p-value of 0.206)

Figure 2 highlights the difference in the coverage of the target volume for the same case with a 3D-CRT plan

Regarding other parameters compared in both arms for the target volume coverage which were the Dmean, Dmin and Dmax; all of the three parameters did not reach statistical significance between the two groups. The mean dose within the PTV (Dmean) was closely similar between the two plans with a value of 66.4Gy ± 30.1 versus 66.6Gy ± 40.1 for the 3D-CRT and IMRT plans, respectively (p-value of 0.464). The Dmin parameter was found to be lower in the IMRT plan (53.7Gy ± 80.1) as compared to the 3D-CRT plan (60.6Gy ± 67.2) with an insignificant p-value of 0.323.

The Dmax was of higher value for the plans created for IMRT with a value of 72.1Gy ± 40.1 as compared to 70.1Gy ±76.4 for the 3D-CRT plans with a corresponding p-value of 0.026.

Sparing of the Organs at risk

Organs at risks sparing was achieved in both arms, the aim was to always keep the dose perceived by each organ to the lowest level (Table 3). The spinal cord maximum point dose was kept below 45Gy in both plans. The maximum dose to the spinal cord was higher in the 3D-CRT plans (20.3Gy ± 2.84) when contrasted to the IMRT plans (15.1Gy ± 5.67) with an insignificant p-value of 0.258. The dose received by the thyroid gland was lower in the IMRT group with a value of 14.9Gy ± 5.39 compared to 51.2Gy ± 8.62 for the 3D-CRT plans with a p-value of statistical significance (0.004).

In our study, the evaluation was carried out for the right and left carotid arteries separately. With respect the right carotid artery, the mean dose was 53.3Gy ± 371 in the 3D-CRT plans compared to 26.4Gy ± 271 in the IMRT plans (p-value of 0.201) while the mean dose for the left carotid artery was 56.2Gy ± 421 in the 3D-CRT plans as opposed to 26.3Gy ± 274 for the IMRT plans with an insignificant p-value of 0.266.

Figure 3 demonstrates comparative DVHs for PTV coverage and doses to OAR for 3D-CRT (triangles) and IMRT (squares), respectively**.**

Table 2: Dosimetric outcomes for the PTV66Gy

Parameter	**3D-CRT plan**	**IMRT plan**	***P*-value** (Independent Student t test)
V95%	94.5 ± 30.7	98.3 ± 14.7	0.003
Dmax(Gy)	70.1 ±76.4	72.1 ± 40.1	0.026
Dmin (Gy)	60.6 ± 67.2	53.7 ± 80.1	0.323
Dmean(Gy)	66.4 ± 30.1	66.6 ± 40.1	0.464
CI95%	0.87 ± 0.19	0.9 ± 0.002	0.206
HI	0.08 ± 0.006	0.1± 0.005	*0.002*

Dmax: maximum dose, Dmin: minimum dose, Dmean: mean dose, VXGy volume receiving X Gy or more, CI: conformity index, HI: homogeneity index

Table 3: Dosimetric outcomes for the organs at risk

Organ	***Parameter***	***3D-CRT***	**IMRT**	***P*-value** (Independent Student t test)
Spinal Cord	*Max. Dose (Gy)*	20.3 ± 2.84	15.1 ± 5.67	0.258
Thyroid Gland	*Mean. Dose (Gy)*	51.2 ± 8.62	14.9 ± 5.39	0.004
Right Carotid artery	*Mean dose (Gy)*	53.3 ± 371	26.4 ± 271	0.201
Left Carotid artery	*Mean dose (Gy)*	56.2 ± 421	26.3 ± 274	0.266

Dmax: maximum dose Dmean: mean dose

Figure 1: IMRT plan axial view

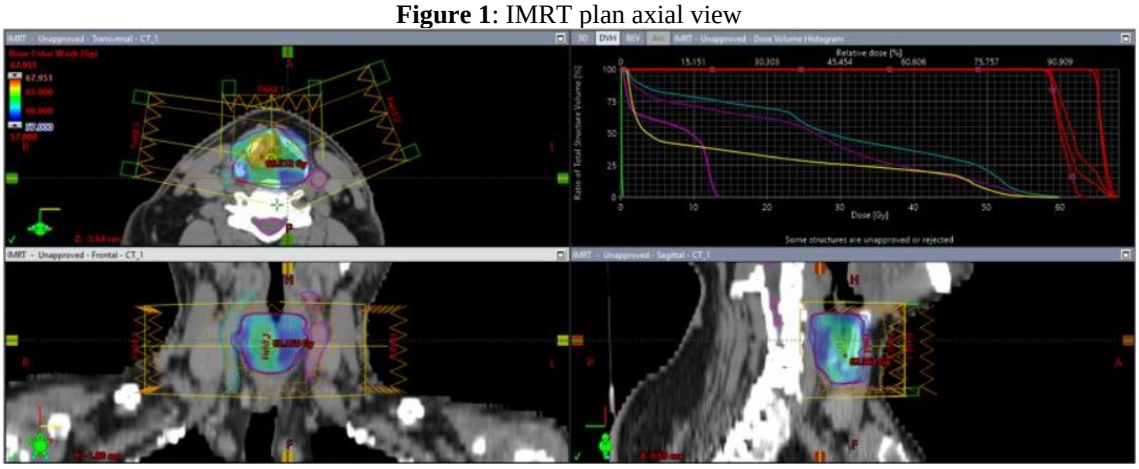


Figure 2: Difference in the coverage of the target volume for the same case with a 3D-CRT plan

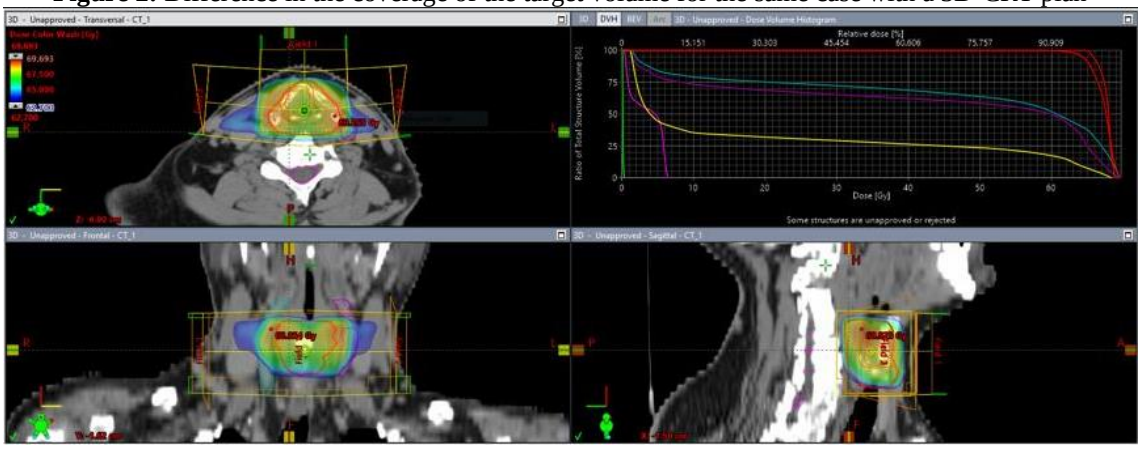
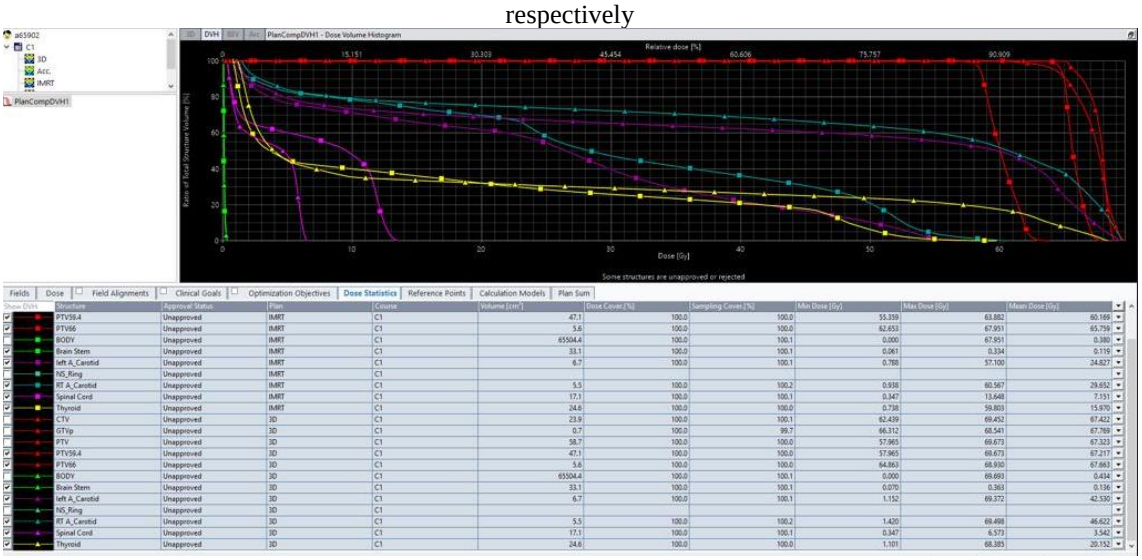


Figure 3: Comparative DVHs for PTV coverage and doses to OAR for 3D-CRT (triangles) and IMRT (squares), respectively



Discussion:

Early Glottic Squamous Cell Carcinoma (T1-2) has an excellent disease outcome when treated with radical radiotherapy achieving a 5 year local control rates of 85-95% and 5 year overall survival of 85% [1-2]. Because of the expected long term survival in these patients, late toxicities induced by radiotherapy is of real concern and measures to minimize these late effects are of utmost importance.

It has been clearly recognized that radiotherapy to the head and neck area can cause premature carotid arteries arteriosclerosis with consequent cerebrovascular events. The mechanism of such vascular injury is attributed to an inflammatory reaction involving macrophages, pro-inflammatory cytokines and growth factors leading to increased thickness of the intima-media of the vessel wall and consequently smooth muscle atrophy, fibrosis, necrosis and accelerated development of atherosclerosis. The complication of atherosclerosis includes arterial stenosis, occlusion, thrombosis and rupture [7-10]. Radiotherapy induced carotid artery atherosclerosis are typically longer than normal atherosclerotic lesions on angiography occurring within the limits of the radiotherapy field [11].

Dosimetric advantages of IMRT in carotid artery sparing has been emphasized in several reports, knowing the fact that carotid artery irradiation increases the risk of stroke and limiting the application of re-irradiation if necessary [13,15,24]. In a Surveillance, Epidemiology, and End Results (SEER)-Medicare study had revealed that the risk of developing cerebrovascular events at 10 years for head and neck cancer patients was 34% after receiving definitive radiotherapy versus 26% after having surgery alone [25]. In a recent series on Glottic T1 carcinomas, it demonstrated no cerebrovascular events in the cohort of patients treated with carotid artery sparing IMRT while the incidence was 3% in the conventional radiotherapy arm [17].

In a study by Gomez and his colleagues, they compared three different radiotherapy techniques in the treatment of early stage laryngeal cancer patients (two dimensional, 3D-CRT and IMRT) and they reported lower mean carotid artery doses in the IMRT arm [21]. Their results were in accordance with our data in terms of superiority of IMRT in the ability to lower the mean doses to the Ipsilateral and contralateral carotid arteries

In current literature, there is no clear consensus on delineation and definition of target volumes in IMRT technique carotid sparing. It was reported in a review that the highest variation was in the clinical target volume definition and in most of the studies, the number of fields used in IMRT delivery was three to seven fields [22]. Similar to our current study, most of the studies in literature didn't use gross target volume definitions [23, 24]. The definition of CTV in most of the studies included an area 1.5 cm below the true vocal cords, subglottic region and arytenoids. The PTV was performed with a margin range between 3-20 mm. In our study, the PTV margin was created by a uniform expansion from the CTV by 0.3 cm.

Atalar et al. [30] dosimetrically compared 3D-CRT, intensity modulated arc therapy (IMAT) and IMRT. They reported that the number of hot spots was significantly higher in the IMRT and IMAT compared to the 3D-CRT plans. This was not was not the case in our study, as we found a more homogeneous dose distribution in the IMRT plans as compared to the 3D-CRT plans which was reflected in the homogeneity index (HI) for PTV66Gy which was higher in the IMRT plans as compared to 3D-CRT plans. The conformity of the dose within the target volume was found to be lower in the 3D-CRT plans as compared to the IMRT plans. However, the difference between both groups was not statistically significant.

In a study by Rosenthal and his colleagues [31], they compared IMRT to conventional planning in early glottic cancer (T1-2). They found out that the IMRT plans had a lower median carotid doses in terms of V35, V50, and V63 compared to conventional planning. Their results were similar to ours; however, we did not use median carotid doses instead we used the mean doses and tried to keep it as low as possible in view of lacking evidence in literature regarding the exact dose tolerance for the carotid arteries.

In the evolving field of recent technologies in radiotherapy, efforts are made to try to reduce the dose perceived by the organs at risk. In this setting, we do recommend IMRT in the treatment of early glottic SCC (T1-2) as a standard of care. However, more randomized clinical studies with higher number of enrolled patients are needed to endorse the treatment accuracy.

Conclusion:

In early glottic cancer, the plans generated by IMRT showed superior PTV coverage and more homogeneous dose distribution when compared to 3D-CRT plans. The IMRT plans showed better OAR sparing with respect to the thyroid gland and carotid arteries.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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