Standardization of target volume delineation for carotid-sparing intensity-modulated radiotherapy in early glottis cancer

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Conflict of Interest Notification

We declare no conflicts of interest

ABSTRACT

Purpose

Recently, carotid-sparing intensity-modulated radiotherapy (CS-IMRT) for early laryngeal glottis (T1/T2N0M0) cancer has generated interest in the hope of avoiding long-term carotid toxicity, as well as concerns relating to geographical misses and long-term normal tissue toxicity. The aim of this review was to summarise the current literature on CS-IMRT for early glottis cancer, with particular focus on definitions of target volumes and the carotid arteries as organs at risk. In addition, we make suggestions for standardization of these structures, dose constraints, and dose reporting.

Materials and methods

From 73 references, 16 articles met the criteria for inclusion in this systematic review. These papers described 2 case reports, 11 planning studies, and 3 prospective studies.

Results

There was variation in all target volume definitions with no clear consensus. The greatest variability was in clinical target volume definition. Carotid artery and spinal cord delineation were not always defined and most studies did not utilize a carotid artery constraint. Of the 8 studies that reported carotid artery delineation, no two studies delineated the same length of carotid artery, yet most studies reported mean doses. Most studies utilized intensity-modulated radiotherapy with 3 – 7 fields. Five studies used arc therapy and 2 studies used tomotherapy.

Conclusion

This review highlights a lack of consensus in target volume definitions in CS-IMRT. Ultimately, long-term prospective data are required to show the benefit of CS-IMRT. Pooled data will prove useful as most studies will report on small numbers of patients. Therefore,

adopting a consensus now on target volume definition, dose constraints and dose reporting will be crucial.

Keywords: carotid-sparing, radiotherapy, glottic cancer

INTRODUCTION

The treatment of early laryngeal glottis (T1/T2N0M0) cancer involves the use of primary radiotherapy (RT), typically using two parallel-opposed lateral radiotherapy beams. Consequently, the carotid arteries are usually included in the treatment field as collateral structures, exposing them to endothelial injury and subsequent risk of stroke or transient ischaemic attack (1). Treating the entire larynx allows for an adequate margin (planning target volume (PTV)) to account for movement during swallowing, which can be up to 3.5 cm in the superior-inferior direction (2). Vocal cord motion during regular breathing (3) should also be accounted for when treatment volumes are significantly reduced.

Recently, carotid-sparing intensity-modulated radiotherapy (IMRT) has generated interest in the hope of avoiding long-term carotid toxicity, as well as concerns relating to geographical misses and long-term normal tissue toxicity (4). This technique requires the larynx clinical target volume (CTV) and PTV margins to be redefined to address the balance between local control and late normal tissue toxicity. Adequate allowance for laryngeal movement during swallowing and breathing is crucial in determining a PTV that balances vocal cord displacement and sparing the carotid arteries.

The aim of this review was to summarise the current literature on carotid-sparing RT for early glottis cancer, with particular focus on definitions of target volumes and the carotid arteries as organs at risk (OARs), and suggestions for standardization of these structures, dose constraints, and dose reporting.

Materials and methods

Search strategy and selection criteria

We performed a systematic search of Pubmed (1st January 2000 to 31st December 2015) for English language articles using the search terms: “carotid”, “radiotherapy”, “larynx”. The

abstracts or available data of this search were reviewed to include or exclude references for full text review. Articles reporting on patients treated with IMRT for early glottis cancer or planning studies investigating carotid-sparing IMRT in this population were eligible for inclusion, as were case reports. Studies that did not investigate or report radiation doses to the carotid arteries were excluded from this review.

Relevant references not clearly identifying patient populations or study design were included in the initial review to avoid erroneous exclusion. The full text articles from the selected references were scrutinized to select the final set of articles for review and analysis. The reference lists of these articles were also reviewed, and references from relevant titles were obtained and reviewed according to the above selection criteria.

Data abstraction and analysis

The outcomes of interest were: target volume (gross tumour volume (GTV), CTV, PTV) definitions, carotid and spinal cord OAR definition, carotid and spinal cord OAR dose constraint and reporting. Field set-up, planning technique and dose prescription were also recorded. Each parameter was considered and reported separately.

Results

The search revealed 73 references (Fig 1). Of these, 43 were published after 1st January 2000, and confirmed the concept of carotid-sparing RT is a recent one. Fifteen references met the inclusion criteria from the initial search. Two studies were based on the same patient cohort and reported twice – the reference not related to carotid-sparing RT was excluded in each case (15 – 2 = 13). Full text review of these articles revealed a further three references that met the inclusion criteria. Therefore, a total of 16 references met the inclusion criteria for this review (5-20). These included 2 case reports, 11 planning studies, and 3 prospective studies (one published in abstract from only).

Outlining (Table 1)

Gross tumour volume (GTV)

The gross tumour volume (GTV) definition varied from none (N = 5) (7, 9, 11, 17, 19) to bilateral true vocal cords (5, 8). This was defined based on endoscopy findings and any diagnostic imaging for some studies (6, 20). Gomez et al (5) defined the GTV on CT findings only. Some studies did not delineate a GTV (7, 9, 11, 17, 19). Mourad et al (13) did not report any target volume delineation for any structures.

Clinical target volume (CTV)

There was considerable variation in clinical target volume (CTV) delineation. Most studies included the cartilaginous framework of the larynx (vocal cords, arytenoids, 1.5 cm of subglottis), whilst others restricted the CTV to a 0.3 - 0.5 cm margin on the true vocal cords (8, 20) or the whole involved vocal cord (11). In general, the major modification to the CTV was to bring the posterior border forward to cover the arytenoids and cricoid cartilage and exclude the hypopharynx.

Planning target volume (PTV)

Planning target volume (PTV) was constructed by expanding the CTV in the following range of ways: from no expansion (6, 10) to a uniform 1 cm expansion (5, 18). Some studies (12, 15) applied standard field borders instead of a defined PTV. Prescribed doses varied – the most common prescribed dose (N = 9) was 63 Gy/28 fractions.

Organs at risk (OARs)

Spinal cord

Most studies did not define spinal cord delineation or spinal cord planning at risk volume (PRV). Two studies (7, 9) defined the spinal cord 1 cm superior and inferior to the PTV and a 3 mm.PRV Riegel et al (12) delineated the spinal cord to cover the superior and inferior

extent of the CTV. Most studies did not report the spinal cord constraints. Those that did report constraints varied from a maximum dose of < 20 Gy (6) to a maximum dose of < 45 Gy (7, 9, 10, 17).

Carotid arteries

Some studies contoured both carotid arteries as a single organ at risk (see Table 1). Others defined a left and right carotid OAR. The superior and inferior extent of the carotid arteries varied, and often not reported. Only 3 studies (7, 9, 19) applied a 3-5 mm PRV. Carotid artery constraints were applied in only 2 studies: Riegel et al (12) (mean dose as low as possible), and Zumsteg et al (mean dose <52 Gy) (18).

Planning techniques (Table 2)

Most studies utilized IMRT with a 3 to 9-field technique. Four studies (10, 12, 19, 20) used arc therapy. Two studies developed tomotherapy plans to deliver RT (14, 17). The study by Matthiesen et al also developed RT plans using proton therapy and utilized 3 uniform scanning beams (19).

Image-guided radiotherapy (IGRT)

Five studies used daily image guidance (6, 8, 14, 16, 20). The CTVs and PTVs in these studies were smaller than conventional fields and did not include all the cartilaginous structures of the larynx. Chatterjee et al was the only study to maintain the traditional larynx CTV, but did edit the PTV away from the carotid arteries (14).

Kinematics

Two studies (17, 20) advised patients not to swallow during treatment in order to try and minimize the displacement that occurs during swallowing. Neither study described whether patient compliance during treatment was assessed. Single vocal cord irradiation was

investigated in 2 studies (13, 16), but only one study utilized daily image guidance with cone beam CT (CBCT) (16).

DISCUSSION

This review highlights a lack of consensus in target volume definitions. As field sizes get smaller with carotid-sparing techniques, it is even more important to ensure the tumour is always encompassed within the treated volume. GTV delineation is, therefore, crucial and endoscopy and diagnostic imaging findings should be incorporated in this process and reported in studies. Four-dimensional CT scanning (3) and magnetic resonance imaging co-registration (21) may improve GTV localization and, perhaps more importantly, quantify vocal cord motion during breathing and allow for adaptation of treatment to account for this. It is also clear that CTV definition is variable and should be clarified before this technique becomes standard clinical practice and studies begin to report outcome data. Risk of microscopic spread to the cartilaginous structures of the larynx is low in correctly staged early glottis cancers (hence, some of these patients may be adequately treated with laser resection), yet these are often included in the CTV. CTV definitions also appear to have been defined according to laryngeal motion and, strictly speaking, should be reclassified as PTV definitions as they refer to the internal target volume. We believe PTV delineation should be dependent on whether or not centres have access to daily IGRT. We advocate more generous PTV margins that include both vocal cords and other cartilaginous structures of the larynx for those centres without an IGRT programme.

The larynx PTVs in most studies were similar to a standard larynx field except in the posterior direction, where the field is reduced to allow for carotid-sparing. This PTV did not differ dramatically from standard practice and would be relatively easy to introduce into clinical practice. Image-guided radiotherapy and 4-dimensional CT-planning to account for motion during breathing, as well as swallowing, would potentially allow for further reduction in PTV margins (22).

It is important to remember that the time spent swallowing during a patient's treatment has been calculated to be less than 1% (23, 24). One study reported maximum anterior and superior displacements of 6.3 mm and 11.5 mm, respectively (23), and the other reported maximum displacements of 25 mm (superior) and 8.3 mm (anterior) (24). The obvious question is the need to account for swallowing if this accounts for only 1% of a patient's time on treatment. We would argue that, in the absence of an advanced IGRT programme with daily imaging, a dramatic shrinkage in treatment volumes is not advisable. It is also important to account for the vocal cord displacement that occurs during breathing. In the context of a multi-centre clinical trial, the use of PTV margins and treatment volumes that are easy to implement for most centres and which do not differ dramatically from current standard of care seems a sensible approach.

It would perhaps be better to label carotid OARs as ipsilateral and contralateral carotid arteries, rather than left and right carotid OARs, to reflect their proximity to the GTV, as some investigators chose to spare the contralateral vocal cord or arytenoid. In addition, a single carotid OAR that incorporates both carotid arteries will underestimate the mean carotid dose in this setting. It is important to standardize delineation of the carotid OAR and PRV in order to determine mean doses as accurately as possible and realistically account for expansion and contraction during the cardiac cycle. Previous studies (5, 6, 16) have reported mean carotid doses of between 18 to 29 Gy, but none of these studies defined the carotid OAR or applied PRV margins. Chera et al (7) contoured carotid OARs 1 cm superior and inferior to the PTV and applied 3 mm PRV margins. Most studies reported carotid artery mean doses yet there is no consensus as to the length of carotid artery included in the OAR. Variability will result in significant differences in mean carotid artery doses and may not be comparable from study to study.

We recommend defining the carotid OAR as the extra-cranial extent of the carotid artery (inferiorly from the aortic arch on the left and brachiocephalic trunk on the right and extended

superiorly to at least 2.5 cm superior to the hyoid bone). We believe this carotid OAR is reasonable to calculate realistic mean doses to a defined, reproducible length of carotid artery. The average diameter of the common carotid artery is around 6.1 (SD 0.8) mm for females and 6.5 (SD 1.0) mm in males (25). During the cardiac cycle, the carotid artery luminal diameter can change by up to 15% (26). A 15% increase in 6.5 mm is 0.98 mm, so a further 1 mm margin (before applying the PRV) adequately accounts for carotid diameter changes during the cardiac cycle.

The lack of a carotid OAR dose constraint for most of these studies is a weakness and should be more clearly defined in future prospective studies. The length/volume/diameter of carotid artery does not appear to be important. Rather, the carotid artery behaves as a serial organ and it is the dose of RT to a particular section of artery that is important (1). It would be reasonable to set a stringent constraint of a maximum dose of <35 Gy (27, 28) to demonstrate a positive impact of carotid-sparing RT on future neurological events.

The spinal cord should be contoured (from the foramen magnum superiorly to at least 2.5 cm below the PTV) and a spinal cord PRV created by a 3 - 5 mm expansion (depending on institutional policy) in all directions of the spinal cord OAR. It is important to note that reported spinal cord constraints are derived based on standard fractionation (2 Gy per fraction) and some studies used hypofractionated regimens (14, 15). This becomes important when spinal cord dose constraints are set at 45 Gy for IMRT or arc therapy. Spinal cord constraints should be stringent and reported when treating patients with IMRT.

Newer radiation techniques such as proton therapy may provide incremental benefits for carotid-sparing (19). The use of MRI for RT planning may further enhance tumour localization and quantification of motion during treatment (29). These techniques, however, are only useful and comparable with other techniques and studies if accepted definitions of target volume delineation are applied.

There are some limitations to consider. Tumour location may dictate feasibility of carotid-sparing, and this technique may only be reasonable for tumours located on the anterior cord. With 4 dimensional CT planning and IGRT, vocal cord displacement can be more accurately studied in a prospective setting and potentially allow for further reduction in PTV margins. The use of magnetic resonance imaging in radiotherapy planning may allow for assessment of displacement of vocal cord tumour. These techniques, however, will be restricted to centres with the relevant experience and may not be generally applicable. Therefore, in order to address both carotid-sparing and local control, we would suggest that the technique that makes the greatest allowance for uncertainties in target volume delineation and RT planning would be applicable in most cancer centres that treat these tumours. In the context of a clinical trial, multi-centre participation will be crucial for accrual and generalizability of results.

CONCLUSION

Ultimately, long-term prospective data are required to show the benefit of carotid-sparing. Lower RT dose to carotid arteries may reduce the incidence of radiation-induced atherosclerosis and subsequent stroke risk. Pooled data will prove useful as most studies will report on small numbers of patients. Therefore, adopting a consensus now on how to define target volumes, dose constraints and dose reporting will be crucial to allow this to occur in future.

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Figure legends

Figure 1 Flow diagram of literature search

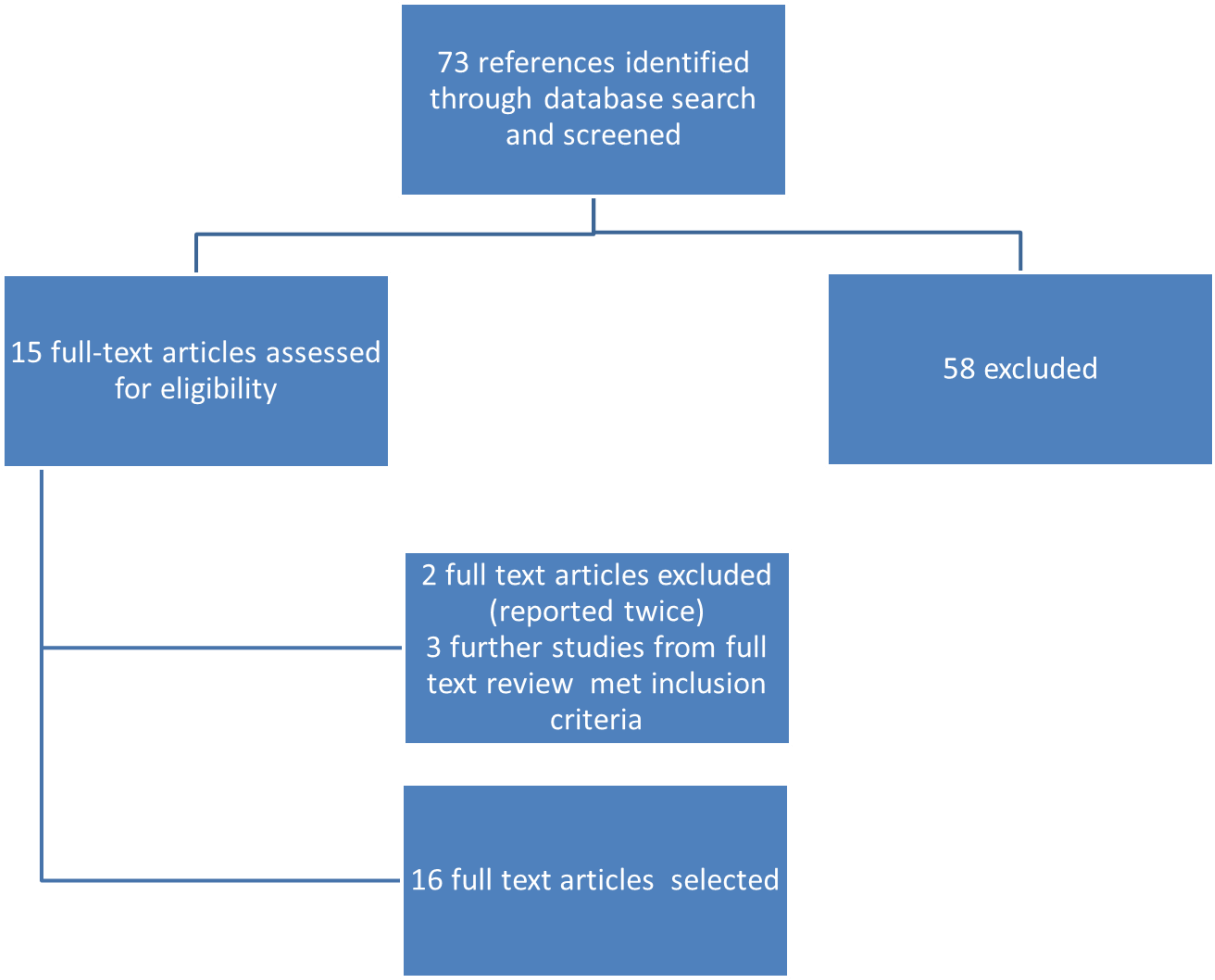

Table 1. Target volume definitions – gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OAR), planning at-risk volume (PRV)

Study	GTV	CTV	PTV	OAR
Gomez et al 2010 [5] (N = 3)	Bilateral TVC (defined on CT)	larynx (false and true VC, ant + post commissure, arytenoids and aryepiglottic folds) and subglottic region, extending from the level of hyoid bone to the bottom of cricoid	0.5 and 1 cm	Bilateral carotid OAR, not defined, no PRV Spinal cord not defined
Rosenthal et al 2010 [6] (N = 6)	Gross tumour (defined on endoscopy and CT)	Anterior limit = inside the skin as far as possible but to encompass thyroid cartilage with 5-mm margin posterior = the posterior limit of thyroid and cricoid cartilages. Minimum 4 cm x 4 cm field size used	None	Separate R and L carotid arteries, not defined. no PRV Spinal cord not defined
Chera et al 2010 [7] (N = 5)	None	CTV = arytenoids cartilages, false VCs, anterior and posterior commisures, TVCs, and 1 - 1.5 cm of subglottis. Two CTVs created: bilateral CTV + unilateral CTV	3mm in lat and ant directions	Bilateral carotid OAR Carotid PRV = 3 mm margin Spinal cord and carotid arteries contoured 1cm beyond superior and inferior extent of PTV
Tiong et al 2011 [8] (Abstract) (N = 50)	Bilateral TVCs (Not defined)	0.5 and 1cm margins on GTV (2 x CTVs) = CTV60 Further 0.5 to 2 cm margin = CTV50	0.5 cm	None
Sert F et al 2012 [9] (N = 5)	None	CTV = arytenoids cartilages, false VCs, anterior and posterior commisures, TVCs, and 1 - 1.5 cm of subglottis.	0.3 cm	Bilateral carotid OAR Carotid PRV = 3 mm margin Spinal cord and carotid arteries contoured 1cm beyond superior and inferior extent of PTV

Atalar et al 2012 [10] (N = 5)	Not defined	CTV - encompass thyroid with 5 mm margin ant, cricoid, arytenoid, false VCs, ant and post commissures, TVCs and 1-1.5 cm of subglottis; the borders extended to hyoid superiorly and to bottom of cricoid inferiorly	None	Left and right carotid OARs, length not defined, no PRV Spinal cord not defined
Osman et al 2012 [11] (N = 10)	None	Whole involved VC based on CT imaging – CTV66	0.2 cm	Bilateral carotid OAR Level of C2 to C6, no PRV Spinal cord not defined
Riegel et al 2013 [12] (N = 11)	Not defined	Whole larynx Sup – hyoid Inf bottom of cricoid Ant – skin Post – posterior to arytenoids	0	Left and right carotid OARs contoured 1.2 cm superior and inferior of CTV, no PRV Spinal cord to cover superior and inferior extent of CTV
Mourad et al 2013 [13] (case report) (N = 1)	Gross tumour (Not defined)	Not defined	Not recorded	R carotid OAR, not defined, no PRV
Chatterjee S et al 2013 [14] (N = 5)	Not defined	Sup = cranial border of thyroid cartilage Inf = caudal edge cricoid Ant = ant edge thyroid cartilage Post = include arytenoid Lat = include entire thyroid cartilage	0.5 cm, edited off carotid	Left and right carotid OARs, no PRV Superior = Skull base Inferior= sternoclavicular joint Spinal cord not defined
Garcez et al 2014 [15] (N = 10)	Not defined	Not defined	Not defined – standard 5.5 x 5.5 cm fields centred on VCs	8 cm length of left and right carotid, no PRV Spinal cord not defined
Janssen et al 2014 [16] (N = 77)	Gross tumour (Not defined)	10 – 15 mm	0.2 – 0.3 cm	Left and right carotid OARs, not defined, no PRV Spinal cord not defined

Hong et al 2015 [17] (N = 10)	None	CTV = arytenoids cartilages, false VCs, anterior and posterior commisures, TVCs, and 1 - 1.5 cm of subglottis	0.3 cm lat and ant, 0.1 cm post	Bilateral carotid OAR, 2 cm superior and inferior to PTV, no PRV Spinal cord not defined
Zumsteg et al 2015 [18] (N = 48)	Gross tumour (defined on endoscopy)	Entire larynx, including ant and post commissures, and arytenoids, from top of thyroid cartilage to bottom of cricoid	1.0 cm	Left and right carotid OARs, on slices of PTV, no PRV Spinal cord not defined
Matthiesen et al 2015 [19] (N =10)	None	CTV = arytenoids cartilages, false VCs, anterior and posterior commisures, TVCs, and 1 - 1.5 cm of subglottis.	0.5 cm	Bilateral carotid OAR, 1 cm superior and inferior to PTV, 3- 5 mm PRV Spinal cord not defined
Ward et al 2015 [20] (case report) (N = 1)	Gross tumour (defined on endoscopy and CT	CTV63 = GTV CTV51.8 = CTV63 + 3mm in sup-inf direction and extended to include both TVCs and ipsilateral arytenoid	0.2 cm	Left and right carotid OARs, not defined, no PRV Spinal cord not defined

Table 2. Planning constraints, dose reporting and dose prescription

Study	Spinal cord constraint	Carotid constraint	Carotid dose reported	Field set-up	Dose prescription	Image guidance?
Gomez et al 2010 [5]	None	None	Mean	3-4 anterior fields	63 Gy/28 (2.25 Gy/fx) over 38 days	No – planning study
Rosenthal et al 2010 [6]	V90 < 10 Gy Max dose 20 Gy	None	Mean Median V35, V50	3 fields (0, 70, 290)	63 Gy/28	Yes – daily (planning study)
Chera et al 2010 [7]	Max < 45 Gy	None	Median Max median point dose	7 equispaced beams	63 Gy/28 (2.25 Gy/fx)	No – planning study
Tiong et al 2011 [8]	Not reported	None	Not reported	5 fields	60 Gy/25 50 Gy/25	Yes - CBCT
Sert F et al 2012 [9]	Max < 45 Gy	None	Median Mean V63, V50, V35	9 fields	62.25 Gy/28	No – planning study
Atalar et al 2012 [10]	Max < 45 Gy	None	Mean V35, V50	3 or 5 – fields IMAT	63 Gy/28	No – planning study
Osman et al 2012 [11]	Not reported	None	Maximum V35	5 fields	66 Gy/33	No – planning study
Riegel et al 2013 [12]	Max < 25 Gy	Mean carotid dose as low as possible	Maximum Mean V63, V50, V35	VMAT 3-field IMRT	63 Gy/28	No – planning study
Mourad et al 2013 [13]	Not reported	None	Mean	IMRT – fields not defined	63 Gy/28	No
Chatterjee S et al 2013 [14]	None	None	Mean Median	Tomotherapy (carotid-sparing)	55 Gy/20	Daily MVCT - retrospective (planning study)
Garcez et al 2014 [15]	Not reported	None	Maximum Mean	Anterior wedged pair	50 Gy/16	No – planning study
Janssen et al	Not reported	None	Mean	IMRT – 4 – 5 fields	66 – 70 Gy/33 -	Yes – KV and CBCT

2014 [16]			V63, V50, V35		35	
Hong et al 2015 [17]	Max < 45 Gy	None	Maximum V63, V50, V35	IMRT – 3 fields Tomotherapy	67.5 Gy/30	Daily (retrospective planning study) Patient asked not to swallow
Zumsteg et al 2015 [18]	Not reported	Mean carotid < 52 Gy	Median Mean V50, V40	IMRT - 4 fields	63 Gy/28	No
Matthiesen et al 2015 [19]	Not reported	None	Maximum Mean D20, D50, D90	IMRT – 5 fields RapidArc – single arc Protons	63 Gy/28	No – planning study
Ward et al 2015 [20]	Not reported	None	Maximum Mean V50	VMAT	63 Gy/28	Daily CBCT Patient asked not to swallow