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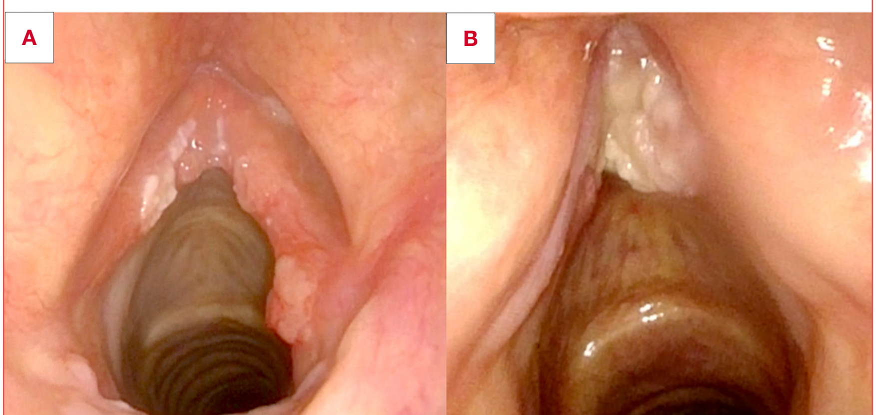
Review

Glottic tumours involving the anterior commissure in a horizontal *vs* vertical mode have different prognosis. Opportunity for refinement of the TNM 8th Edition



Cover figure. A) Horizontal spread of a glottic tumour from the right vocal cord to the contralateral one passing through the anterior commissure (AC), at a purely glottic level, without supra- and/or sub-AC extension. This tumour is presently categorised by the 8th Edition of the TNM Staging System (8TNM) as cT1b while, according to the present proposal, it should be upstaged to cT2a; B) Vertical trans-AC invasion of a tumour originating within the AC and extending downward to the subglottis. This tumour is presently categorised as cT2 by the 8TNM, while we propose to upstage it to cT2b.

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Summary

The anterior commissure (AC) represents a unique subsite of the glottic plane due to its peculiar embryological development and 3-dimensional anatomical microstructure. More than the simple junction between 2 vocal cords, in fact, the AC should be viewed as the confluence between the petiolar region and pre-epiglottic space superiorly, the anterior thirds of the false and true vocal cords and related paraglottic spaces laterally, and the conoid ligament inferiorly. These anatomical features have profound impact on the behaviour of laryngeal cancer at the level of the AC. In particular, the neoplastic patterns of growth (on the horizontal plane from one vocal fold to the contralateral one remaining on a purely glottic plane *vs* a vertical trans-AC extension from the supra- to the subglottis or vice versa) have distinct oncologic implications when treating these lesions by both surgical and non-surgical strategies. Therefore, the aim of this manuscript is to collect all the existing evidence in favour of the necessity to review the 8th Edition of the TNM Staging System by distinguishing tumours that involve the glottic plane without AC extension (cT1a of one and cT1b of 2 vocal cords without AC involvement) from those that encompass the AC. Based on available evidence, the prognostic implication of AC involvement should be considered in upstaging these tumours to T2, subclassifying them into T2a (horizontal involvement of the AC) and T2b (vertical trans-AC extension above and/or below the AC).

Keywords: larynx, cancer, glottis, anterior commissure, TNM staging system

Introduction

The anterior commissure (AC) should not be considered as a simple subsite of the glottis but rather as a complex 3-dimensional space, sharing part of its characteristics with the vocal cords, but also having special features that make it a unique site within the larynx. In fact, it is entirely filled with dense homogeneous connective tissue with a low density vascular and lymphatic network, in close relationship with the adjacent visceral compartments, i.e. the pre-epiglottic space (PES) superiorly, the superior (sPGS) and inferior paraglottic spaces (iPGS) laterally, and the loose vessel- and minor salivary and mucous gland-rich subglottic tissue inferiorly. It encompasses different anatomical structures such as the anterior maculae flavae of the 2 vocal ligaments and the thyroid cartilage insertions of the thyroarytenoid muscles (TAM) at the glottic level, the thyro-epiglottic ligament and the anterior portions of the quadrangular membranes at the supraglottic level, the conoid ligament in the subglottis, with part of the inner thyroid perichondrium and thyroid laminae anteriorly (Fig. 1) [1-3].

To date, for cancer staging purposes, the AC has been always considered an integral part of the glottic plane and, therefore, its neoplastic involvement in both the horizontal as well as in the vertical directions has been defined in a rather ambiguous way. For example, while T1a specifically indicates a glottic tumour restricted to one vocal cord without extension to the AC, T1b can be represented by any one of 4 different scenarios: 1) 2 discrete lesions affecting the right and left vocal folds without AC involvement; 2) a tumour originating within the AC without significant extension to the vocal cords; 3) a tumour of one vocal cord extending to the AC; or 4) a horseshoe tumour involving the AC and both vocal cords. The distinct potential prognostic implications associated with these 4 different lesions can cause inhomogeneity in definition and recording of oncologic outcomes. More importantly, a tumour growing cranially and/or caudally from the AC to the supra- and/or subglottis is designated as T2 similar to a laterally located T2 extending superiorly from the middle third of the true vocal cord to the superficial part of the false vocal cord and/or inferiorly to the subglottis. Indeed, each of these lesions present very different biologic behaviours and oncologic outcomes when treated by either surgical or non-surgical modalities.

Therefore, several reasons support modification of the current 8th Edition of the TNM Staging System (8TNM) [4] for tumours involving the AC: 1) these lesions do not seem to be inherently more aggressive from a biological point of view, but are more prone to progression due to specific anatomical features of the AC itself; 2) AC tumours require more aggressive treatments compared to lesions not involving this structure in order to achieve comparable outcomes; 3) incorporating AC involvement into T staging could help resolve the above mentioned ambiguous classification of primary tumours involving this anatomical structure.

The aim of this manuscript is to examine the rationale for a revision of the 8TNM of the larynx, specifically addressing the AC as a distinct anatomic region with unique features derived from its embryological development, and its horizontal *vs* vertical mode of neoplastic invasion which have important prognostic implications that should be acknowledged by a modern staging system.

Anatomy and embryology of the anterior commissure

The embryological development of the AC is important as a basis for understanding the prognostic implications of its neoplastic involvement. The AC becomes identifiable as a discrete structure around the eighth week of gestation, when the 2 hemilarynges fuse to form a 3-dimensional structure known as the intermediate lamina, or developmental AC, which is rich in elastic fibres and contains blood vessels, the median process, and connective tissue of the conoid ligament. The median process evolves into Broyles' ligament, which connects deeply with the intermediate lamina and functions as a perichondrium for its dorsal surface, located just above the glottic plane. This ligament is integral to the commissural region, providing structural support [2,5]. By the eleventh week of gestation, TAM fibres connect with the median process, reinforced by Broyles' ligament, integrating them into the commissural region [2,3]. By the end of development, the so-called "AC ligament tendon" is composed of a dense network of fibres interwoven in both horizontal and vertical directions, originating from the vocal ligament, conus elasticus, and quadrangular membrane. The tendon fibres insert directly into the hyaline cartilage, with no perichondrium at the insertion site, and chondroid cells are embedded among the collagen fibres. The characteristics acquired by the commissure at the end of development define it as a distinct 3-dimensional region, extending approximately 8.5 mm above and below the glottic plane (Fig. 1). This differentiates it from the classical topographic definition of the glottis, which is delimited by 2 axial planes parallel to the free edge of the true vocal folds, positioned approximately 3 mm above and below the glottic plane (Fig. 2).

Unlike all other laryngeal subsites, where muscle tissue, fat of the PGS, and/or perichondrium are situated between the mucosa and the cartilage, the embryological development of AC results in the mucosa being closer to the cartilaginous framework in this region than in any other part of the larynx, with a separation of only 2-3 mm. This close association, combined with mechanical stress at this site, often leads to focal ossification of the thyroid cartilage, which further compromises resistance to neoplastic invasion. Ossification typically begins in the early fourth decade of life at the level of the AC median process and progresses laterally with aging. At this level, ossification occurs through a Haversian system, which is characterised by the formation of Volkmann's canals (horizontal, running from inside outward) and Haversian canals (vertically oriented in a craniocaudal direction). These canals are traversed by blood and lymphatic vessels, forming an anastomotic lympho-vascular network – which is absent in cartilage – that connects the endolaryngeal lumen at the level of the pericommissural region with the prelaryngeal tissues. Therefore, the implication of cartilage ossification is that it facilitates tumour invasion, increasing the risk of tumour spread beyond this natural barrier [6,7].

Evaluation of the anterior commissure and its neoplastic involvement by endoscopy and imaging

Endoscopic evaluation of laryngeal cancer plays a pivotal role before any type of surgical or non-surgical treatment, and this is especially true in the AC where the precise bidimensional extent of the lesion may greatly impact the choice of therapeutic approach. The need for a major AC resection, for example, may direct treatment of a given tumour towards a non-surgical approach in patients with a high priority for optimal vocal outcomes. In this sense, office-based videoendoscopy under local anaesthesia is rarely precise enough to clearly map the local extent of AC tumours. Rigid endoscopy using angled telescopes under general anaesthesia is there-

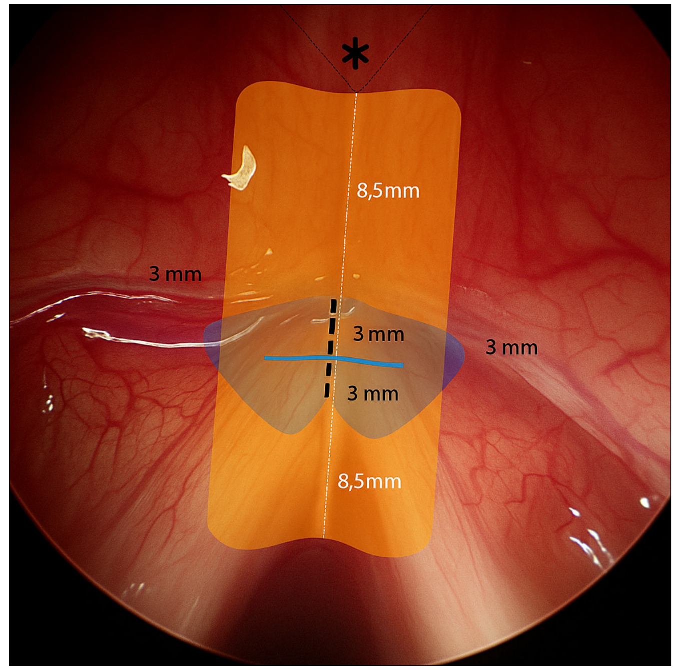

Figure 1. Endoscopic vision of the AC. Blue area, horizontal (glottic) plane of the AC, extending 3 mm up- and downward from the insertion of ligaments (represented by the blue line). Yellow area, vertical (supra- and subglottic) plane of the AC, extending 8.5 mm upward (to the thyroid notch, asterisk) and 8.5 mm downward (to the inferior margin of the thyroid cartilage) from the glottic AC plane.

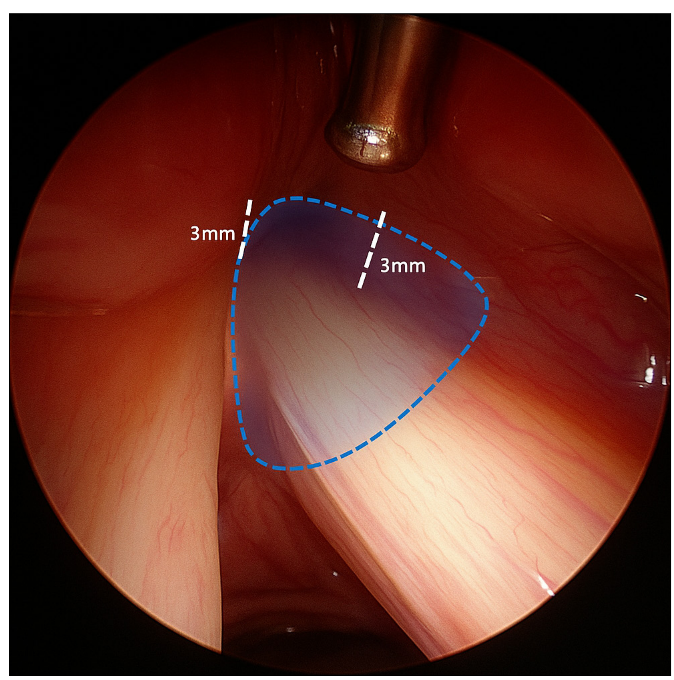

Figure 2. Endoscopic vision of the AC with particular emphasis to its lateral extension toward the anterior part of the floor and bottom of the ventricle.

fore considered the state-of-the-art clinical assessment tool for staging these tumours [8]. Even though unfavourable laryngeal exposure may negatively impact AC visualisation [9-12], every technical effort should be made to distinguish at least 3 different scenarios: 1) tumours growing from one or both vocal cords towards the AC, without reaching it; 2) tumours growing from one vocal cord across to the contralateral one, involving the AC in a purely horizontal fashion (Cover figure A); 3) tumours passing through the AC in a vertical direction, involving the petiole of the epiglottis, the anterior portions of the false and true vocal cords, and/or the crico-thyroid membrane inferiorly (Cover figure B). Narrow band imaging and other bioendoscopic in vivo imaging tools may be of help in fine-tuning superficial detection of neoplastic spread along one or more of these pathways [13-17].

AC assessment on computed tomography (CT) and magnetic resonance imaging (MRI) is heavily dependent on a correct and optimised scanning protocol and on accurate post-processing. Most studies consider CT as the reference modality [18-27]: CT protocols are in fact relatively standardised, typically involving image acquisition approximately 80 seconds after intravenous administration of iodinated contrast medium, either during quiet breathing or with dynamic manoeuvres such as deep inspiration or phonation. CT generates volumetric datasets that must be properly reconstructed. For AC assessment, axial reconstructions parallel to the glottic plane and sagittal reconstructions to evaluate the vertical extension of tumours infiltrating the AC are particularly important [25]. Some studies have proposed dual-energy CT to enhance contrast resolution, especially for the detection of cartilage infiltration [28,29] and compared it with MRI with promising results [30].

Conversely, MRI protocols reported in the literature are highly heterogeneous and often not described in sufficient detail [31]. Both 1.5 and 3 Tesla systems are employed, and a pilot study has investigated the use of a 7 Tesla scanner [32]. Van Egmond, in a systematic review, emphasised that currently available MRI protocols are suboptimal for the staging of early laryngeal cancer, without, however, addressing specific technical details [33]. Both neck and surface coils can be used: the latter allow acquisition of images with high spatial resolution and excellent signal-to-noise ratio and are therefore extremely useful for AC assessment [34]. High matrix and motion-correction sequences should be used [31,34]. The most useful acquisition planes are axial and sagittal. Diffusion-weighted sequences improve the ability to differentiate tumour from inflammatory changes; however, the spatial resolution is limited, and direct acquisition in the sagittal plane is problematic [34].

According to the literature, the normal radiologic thickness of the AC is approximately 1 mm [27], although some variability is accepted (± 0.56 mm). Only one study has described the vertical position of the AC, measuring its distance from the inferior margin of the thyroid cartilage (approximately 11 mm), a parameter relevant for assessing tumour extension toward the cricothyroid space [23].

Most studies address AC neoplastic invasion in a non-specific manner, without further subclassification and with limited description of imaging criteria. The study by Benazzo et al. [22] represents the only attempt to radiologically stage AC infiltration, proposing a detailed mapping system that distinguishes presence of tumour, superficial involvement, thyroid cartilage invasion, and extra-laryngeal spread. The reported sensitivity and specificity were, respectively, 73% and 77% for tumour detection, 25% and 96% for superficial involvement, 59% and 82% for thyroid cartilage invasion, and 100% and 88% for extra-laryngeal spread. This study highlighted the considerable underestimation of AC involvement by CT, and the authors suggested that MRI may be useful in equivocal cases. Notably, vertical tumour extension was not included in their proposed mapping system; in addition, no cut-off thickness value was reported for the superficial involvement of the AC. According to Cristalli et al. [26], the cut-off thickness value on axial scans to discriminate the presence of cancer at histological examination of the AC is 3.6 mm (positive and negative predictive values were 93% and 87%, respectively). Hartl et al. [20] found that CT had the lowest sensitivity for cartilage invasion (10%); this result must be however interpreted with caution, as the study included 236 patients, of whom only 8% had inner cortex thyroid cartilage involvement. Nonetheless, it is generally accepted that CT is not reliable for staging T3 tumours with inner thyroid cartilage infiltration: in fact, the most specific radiological sign for thyroid involvement is complete replacement of the cartilage by tissue exhibiting the same imaging characteristics as the tumour, whereas the least specific sign is cartilage sclerosis.

Barbosa et al. [19] reported that CT had an overall accuracy of 75%, and when stratified by T category was 62% for T2, 74% for T3, and 88% for T4 lesions. However, they did not specify whether extra-laryngeal extension occurred through the cartilage or via the cricothyroid space.

Taha et al. [35] found a good performance of diffusion-weighted MRI sequences in detecting infiltration of the inner cortex (sensitivity 93%, specificity 88%) and outer cortex (sensitivity 85%, specificity 85%) of the thyroid cartilage. Additional studies highlighting the superiority of MRI over CT in this context are those from Beitler et al. [36], Li et al. [37], and Adolphs et al. [38].

Some authors have investigated the potential of ultrasound (US) for staging laryngeal lesions since the AC may represent an appropriate target for this technique owing to its superficial location [39,40]. However, US is highly operator-dependent and far from being a routine standard.

New proposal for staging of glottic tumours involving the anterior commissure

Our proposal for updating the cT classification of glottic tumours involving the AC is based on the distinct embryologic and anatomic issues that influence clinical behaviour and prognosis of these tumours, and include the following:

- cT1a of one vocal cord behaves in a similar way as cT1b of 2 vocal cords without AC involvement. The latter should be, however, maintained as cT1b since, from the probabilistic point of view and considering the field of cancerisation phenomenon, these lesions have a slightly higher tendency to recur compared to unilateral cT1a;
- cT1b of both vocal cords with horizontal involvement of the AC purely in the glottic plane behaves worse than cT1a and cT1b without AC involvement and should be therefore upstaged to cT2a (Cover figure A, Fig. 3);
- cT2 of the AC extending vertically above and below the glottic plane (trans-AC tumours) (Cover figure B, Figs. 4A and B) behaves far worse than actual cT1b and superficial lateral cT2 of the mid-cord not involving the TAM and with normal vocal fold mobility. Additionally, in trans-AC tumours, minimal involvement of the thyro-epiglottic ligament and petiole of the epiglottis, PES and/or inner portion of the thyroid cartilage and loose subglottic tissue cannot be easily ruled out even by state-of-the-art imaging, with the need for targeted (and invasive) biopsies under general anaesthesia. These tumours should therefore be upstaged, according to our proposal, at least to the cT2b category and specifically need extra scrutiny in the diagnostic phase. In fact, if involvement of PES and/or inner thyroid cartilage can be clearly demonstrated, these elements will upstage such tumours to cT3, while through and through extension to the extra-laryngeal tissues will be designated cT4a, as per current criteria (Fig. 5).

Evidence supporting the new proposal for anterior commissure staging from the surgical and non-surgical perspectives

The above mentioned anatomical and embryological principles explain why the inner cortex of the thyroid cartilage at the AC level may be microscopically infiltrated more often than expected [41]. Consequently, an early-stage carcinoma involving the AC has the potential to penetrate the cartilage, with significant implications in upstaging a T1-T2 lesion to a T3 or even a T4a tumour [42] (Fig. 5). Therefore, patients affected by cT2-T3 glottic tumours involving the AC are, among all laryngeal cancers, those most frequently understaged (in approximately 16-18% of cases) [43]. Following surgical resection, this understaging is clearly associated with a higher risk of positive surgical margins and a consequent decrease of disease-free and disease-specific survivals [44,45]. Moreover, the complex anatomical structure of the AC is likely to significantly impact on tumour spread in a number of ways that should be taken into account by a modern TNM staging system of laryngeal cancer. In fact, involvement of the AC by a glottic tumour has the potential to open up pathways of spread in at least 3 major directions: horizontally (from one vocal cord to the other, along the glottic plane), vertically (from cranial to caudal or vice versa, to the supra- and/or subglottis), and postero-anteriorly (from inside to outside, involving the cartilaginous framework of the thyroid cartilage, or at the thyro-hyoid and/or crico-thyroid membrane levels cranially and caudally).

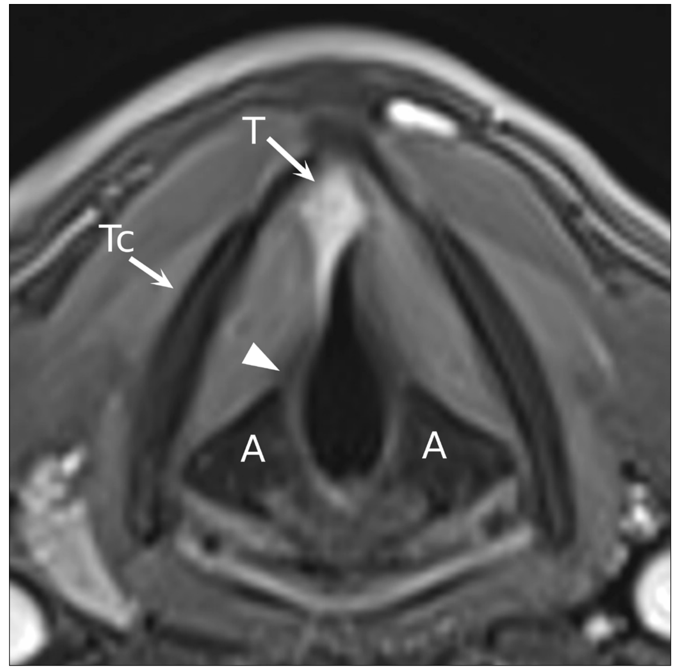

Figure 3. MRI of a small-volume cT1b confined to the horizontal plane of the AC, without cartilage invasion and no trans-AC vertical extension. T: tumour; Tc: thyroid cartilage; A: arytenoids; white arrowhead, vocal process of the right arytenoid.

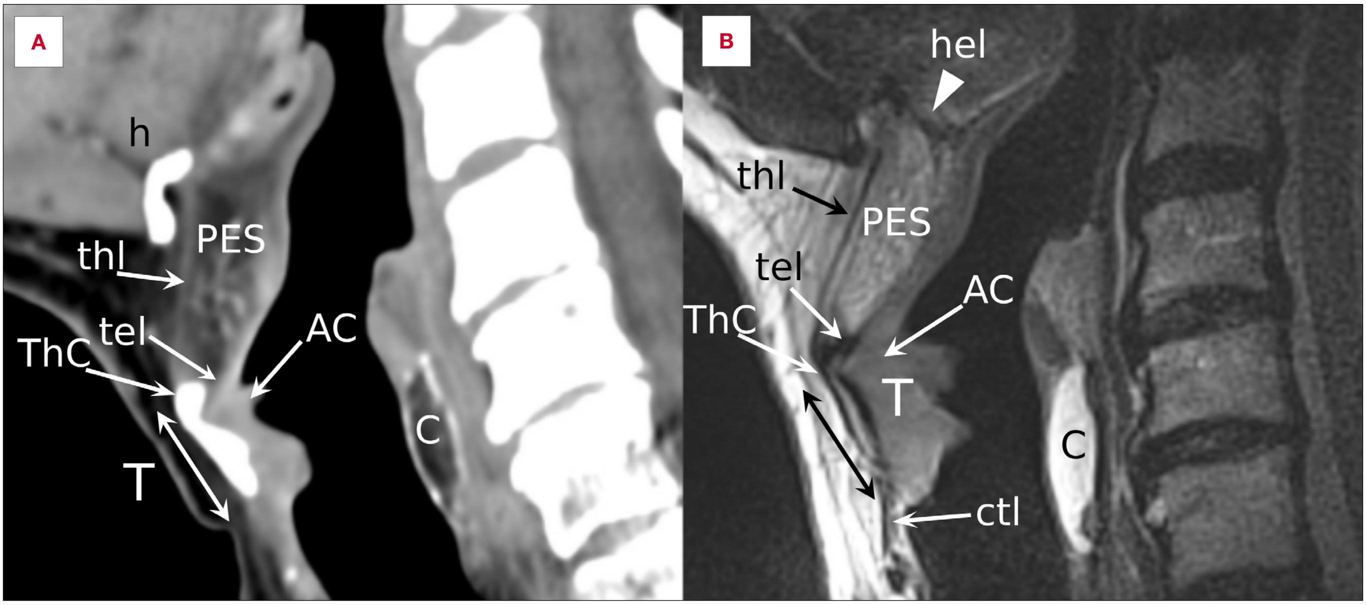

Figure 4. Comparison between sagittal CT (**A**) and MRI (**B**) of a cT2 of the AC with vertical extension to the subcommissural area. h: hyoid bone; PES: pre-epiglottic space; thl: thyro-hyoid ligament; tel: thyro-epiglottic ligament; hel: hyo-epiglottic ligament; ThC: thyroid cartilage; AC: anterior commissure; T: tumour (double arrows show its vertical extent); C: cricoid lamina; ctl: crico-thyroid ligament.

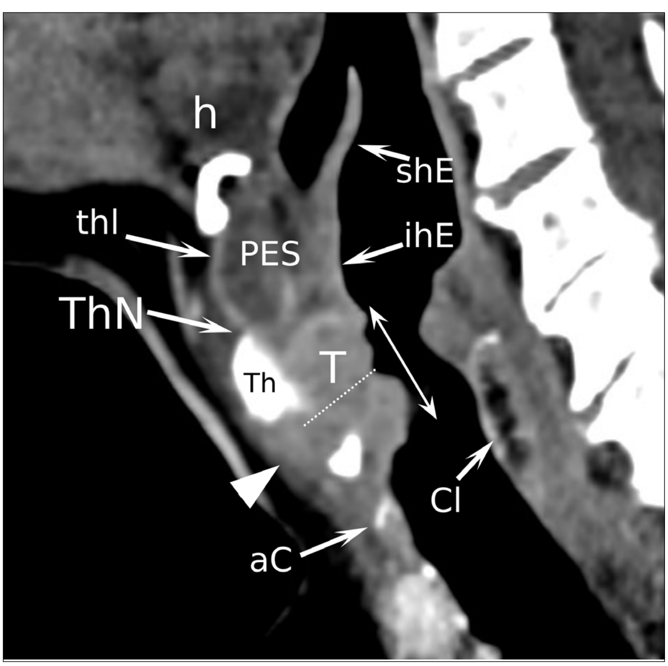

Figure 5. Sagittal CT showing a vertical trans-AC tumour (T) with cranial extension to the infrahyoid epiglottis (ihE), pre-epiglottic space (PES), and full-thickness invasion (white arrowhead) of the thyroid cartilage (Th) at the level of the AC (dotted line). h: hyoid bone; shE: suprahyoid epiglottis; thl: thyro-hyoid ligament; ThN: thyroid notch; aC: anterior arch of the cricoid; Cl: cricoid lamina.

There is general agreement, even in the early glottic cancer scenario, that AC involvement can negatively impact both oncological and functional outcomes, regardless of the therapeutic strategy adopted. Some authors have recently reported AC involvement as a factor that significantly influences the risk of local recurrence and/or the organ preservation rate (Tables I and II) [46-67]. Conversely, a limited number of other authors [68-75] have not found an independent role of AC involvement on local relapse. This variability can be explained by a number of factors like variation in the clinical definition of AC, different levels of detail in clinical, endoscopic, and radiologic evaluation in the pre-treatment setting, distinctive features and limitations related to each single therapeutic modality, different biological tumour behaviours in distinct histopathologic entities, as well as variations in the rigor of the follow-up policy.

A small number of systematic reviews and meta-analyses [76-78] have attempted to provide more concrete data on the prognostic role of AC involvement in early glottic cancer. Unfortunately, unacceptable rates (> 50%) of heterogeneity among selected studies limit the validity of results and feasibility of pooled analyses [65]. Moreover, since AC involvement may be correlated to other clinical variables (i.e. T category), its independent prognostic role can only be assessed within studies that control for other confounders, and this is usually not the case within published meta-analyses [76-78].

Table I. Review of the literature showing oncological outcomes of T1-T2 glottic cancer with or without AC involvement treated by surgery.

Author	T category	Treatment	AC	DFS	OP	LC	OS
Steiner et al., 2004 [46]	T1b	TOLMS	+			73	100
	T1b	TOLMS	-			92	70
	T2	TOLMS	+			79	80
	T2	TOLMS	-			74	56
Chone et al., 2007 [47]	T1-T2	TOLMS	+		96	79	
	T1-T2	TOLMS	-		100	96	
Rodel et al., 2009 [48]	T1b	TOLMS	+		88	68	
	T1b	TOLMS	-		100	86	
	T2	TOLMS	+		89	76	
	T2	TOLMS	-		95	76	
Sachse et al., 2009 [49]	T1	TOLMS	+			70	
	T1	TOLMS	-			88	
Hakeem et al., 2013 [50]	T1b	TOLMS	+		95	58	
	T1b	TOLMS	-		93	70	
	T2	TOLMS	+		93	65	
	T2	TOLMS	-		96	90	
Hoffman et al., 2016 [51]	T1-T2	TOLMS	+	55	92	71	77
	T1-T2	TOLMS	-	80	100	96	88
Wolber et al., 2017 [52]	T2	Open Surg	+	57		86	71
	T2	Open Surg	-	100		100	100
Carta et al., 2018 [53]	T1-T2	TOLMS	+		95	91	79
	T1-T2	TOLMS	-		99	96	89
Vilaseca et al., 2018 [54]	T1-T2	TOLMS	+			60	
	T1-T2	TOLMS	-			77	
Piazza et al., 2018 [55]	T1	TOLMS	+	68	90	89	
	T1	TOLMS	-	90	100	99	
	T2	TOLMS	+	61		72	
	T2	TOLMS	-	82		90	
Marchi et al., 2025 [56]	T2	TOLMS	+		81	71	
	T2	TOLMS	-		94	90	

TOLMS: transoral laser microsurgery; AC: anterior commissure; DFS: disease-free survival; OP: organ preservation; LC: local control; OS: overall survival.

Upon closer review of the available literature, the differences in terms of recurrence rates in tumours with horizontal *vs* vertical trans-AC extension have mostly been observed in studies that precisely address these potential different patterns of AC involvement. These studies have shown that, in particular, the cranio-caudal extension of the commissural tumours towards the infrapetiolar area and/or the crico-thyroid membrane is a significant variable affecting local control and organ preservation (Tab. III) [46,48,50,52,53,55,79,80]. This has recently prompted recommendations for a more aggressive management of these tumours [53,55,61] and a special type of endoscopic cordectomy (Type VI) has been also codified to appropriately modify transoral resection of AC tumours with vertical extension [81], in addition to the 5 previously described within the European Laryngological Society classification [82]. Notably, Type VI cordectomy is the most aggressive transoral procedure conceived for tumours located at the glottic level and encompasses the anatomical boundaries previously described as 3-dimensional limits of the AC (from the petiole of the epiglottis above, to the crico-thyroid membrane below, including the anterior thirds of both false and true vocal cords).

Wu et al. [83] assessed 31 glottic carcinomas with AC involvement in patients who underwent partial or total laryngectomy

Table II. Review of the literature showing oncological outcomes of T1-T2 glottic cancer with or without AC involvement treated by RT.

Author	T category	Treatment	AC	DFS	OP	LC	OS
Nozaki et al., 2000 [57]	T1	RT	+			58	
	T1	RT	-			89	
Jin et al., 2002 [58]	T1	RT	+			70.5	79.4
	T1	RT	-			87.1	86
Zouhair et al., 2004 [59]	T1-T2	RT	+			73	
	T1-T2	RT	-			94	
Cellai et al., 2005 [60]	T1	RT	+			89	
	T1	RT	-			81	
	T2	RT	+			69	
	T2	RT	-			77	
Sjogren et al., 2009 [61]	T1	RT	+			85	
	T1	RT	-			87	
Tong et al., 2011 [62]	T1	RT	+			86	
	T1	RT	-			95	
Gultekin et al., 2012 [63]	T1	RT	+	81		79	78
	T1	RT	-	92		82	92
Kitani et al., 2015 [64]	T1b	RT	+				69
	T1b	RT	-				92
	T2	RT	+			51	42
	T2	RT	-			91	91
Hendriksma et al., 2019 [65]	T2	RT	+			68.1	
	T2	RT	-			74.8	
Wang et al., 2022 [66]	T2	RT	+				
	T2	RT	-		59.2	68.1	
Seno et al., 2024 [67]	T1, T2	RT	+			88	92

RT: radiotherapy; AC: anterior commissure; DFS: disease-free survival; OP: organ preservation; LC: local control; OS: overall survival.

(TL). The specimens were studied by axial serial sections parallel to the vocal cords and analysed to explore the characteristics and potential invasion pathways of glottic carcinomas with AC involvement. In this study, the involvement of the intermediate lamina of the thyroid cartilage was significantly associated with invasion of the vocal muscle in the AC region ($p < 0.05$). Additionally, Rifai et al. [84] performed a histopathological examination of the AC using whole organ sections in 30 randomly selected specimens affected by AC tumours. They found that microscopic involvement of the thyroid cartilage without penetration was detected in all sections analysed. These findings indicate that tumours in this region have a higher risk of presenting microscopic foci of infiltration in the AC, which may be undetectable prior to surgery and ensuing histopathological examination.

Therefore, tumours originating from the AC, in contrast to those from other laryngeal subsites, necessitate more radical treatment to ensure adequate clearance of the thyroid cartilage, as seen in open partial horizontal laryngectomy (OPHL) with crico-hyoido-epiglotto-pexy (Type IIa) [85], to achieve adequate local control of the described pathways of spread [86,87].

These concepts explain why tumours involving the AC – whether cT1a reaching the commissure, cT1b affecting the glottic plane bilaterally, or trans-AC tumors – exhibit significantly lower local control rates in patients treated with carbon dioxide transoral laser microsurgery (CO_2 TOLMS) [88] compared to lesions not involving the AC. Table I shows that oncologic outcomes in patients treated with TOLMS are adversely influenced in both T1 (with AC involvement and horizontal extension) and T2 tumours (with AC involvement and vertical extension), compared to T1 or T2 glottic lesions without AC involvement. Table III demonstrates that, in the context of AC involvement, vertically extending tumours have worse outcomes compared to those

Table III. Review of the literature showing oncological outcomes of T1-T2 glottic cancer with vertical *vs* horizontal involvement of the AC.

Author	T category	Involvement of AC	DFS	OP	LC	OS
Steiner et al., 2004 [46]	T1	Horizontal	-	-	73%	100%
	T2	Vertical	-	-	79%	80%
Peretti et al., 2005 [79]	T2	Vertical	60%	90%	68.6%	-
Rodel et al., 2009 [48]	T1	Horizontal	73%	-	-	-
	T2	Vertical	76%	-	-	-
Peretti et al., 2010 [80]	T1	Horizontal	-	98%	92.8%	-
Hakeem et al., 2013 [50]	T1	Horizontal	57%	95%	-	-
	T2	Vertical	65%	95%	-	-
Wolber et al., 2017 [52]	T1	Horizontal	52%	-	-	-
	T2	Vertical	50%	-	-	-
Carta et al., 2018 [53]	T1	Horizontal	89%	96%	-	-
	T2	Vertical	74%	71%	-	-
Piazza et al., 2018 [55]	T1	Horizontal	68%	90%	-	-
	T2	Vertical	48%	75%	-	-

AC: anterior commissure; DFS: disease-free survival; OP: organ preservation; LC: local control; OS: overall survival.

Table IV. Review of the literature showing oncological outcomes of T1-T2 glottic cancer with vertical vs horizontal involvement of the AC in patients who underwent surgery *vs* RT.

Author	T category	Treatment	AC	DFS	OP	LC	OS
Mannelli et al., 2020 [89]	T1b	TOLMS, RT	+	95.7	76.6		95.7
	T1b	TOLMS, RT	-	100	80		100
Tulli et al., 2020 [77]	T1	TOLMS, RT	+			84	
	T1	TOLMS, RT	-			92	
Li et al., 2021 [90]	T1, T2	TOLMS	+		90		89.7
	T1, T2	RT	+		91.9		88.2

TOLMS: transoral laser microsurgery; RT: radiotherapy; AC: anterior commissure; DFS: disease free survival; OP: organ preservation; LC: local control; OS: overall survival.

confined to the glottic plane. Table IV summarises studies in which the outcomes of radiotherapy (RT) and TOLMS are compared according to the involvement of the AC [77,89,90]. It should be also mentioned that in TOLMS certain technicalities may at least partially explain the poorer outcomes observed when the AC is involved. Specifically, the AC represents the most challenging region within the larynx for transoral visualisation and access, even in patients with otherwise favourable overall laryngeal exposure [9]. Inadequate endoscopic exposure increases the chance of transoral incomplete excision, which is highest precisely at the AC level [10]. Furthermore, in recurrent tumors involving the AC, surgical conservative approaches such as TOLMS and OPHL are not feasible in nearly 50% of cases. In contrast, in the absence of AC involvement, TL is required in only about 30% of patients [56]. Not surprisingly, the adverse prognostic implication of any type of AC involvement disappears in patients undergoing open surgical approaches where the thyroid cartilage is removed en bloc with the tumour [86,87]. Mannelli et al. [89] proposed a new classification system for glottic T1 tumours with AC involvement. This system could serve as a starting point to address the current heterogeneity in T1a-b staging and treatment. Furthermore, a systematic review and meta-analysis highlighted that the current T1 glottic staging does not allow for accurate prognostication [77]. These data revealed that the 5-year local control rate for T1 glottic tumours with AC involvement was 12% lower compared to those without, supporting the notion that the presence of AC involvement is a negative prognostic factor even for T1 glottic tumours, irrespective of whether the treatment is RT or TOLMS.

Considering patients treated with RT, one of the most limiting factors in drawing accurate conclusions with respect to the issue of horizontal *vs* vertical trans-AC extension is related to the fact that these fine-tuned subclassifications are rarely, if ever, reported in the pertinent non-surgical literature. To the best of our knowledge, however, one study incorporating these variables, as assessed on imaging, found vertical trans-AC involvement in T2 glottic carcinoma to be a predictive factor for RT failure, suggesting that this may be a uniform adverse prognosticator across different treatment modalities [65]. Also, unlike surgical resection, non-surgical treatment does not provide histopathologic correlation with clinical endoscopic features and radiologic findings. Moreover, the use of different RT techniques (in terms of photon energy and beam arrangement) or fractionation schedules might explain the different results on the impact of AC in those series. Traditionally, AC involvement has been regarded as a negative predictive factor of local control with high energy photons in a parallel opposed beam arrangement. Especially in thin patients, where the thyroid cartilage lies close to the skin surface, the AC region may fall within the build-up region, and this along with the lack of back-scatter electrons may lead to under-dosing [91,92]. Consistently, a higher than conventional RT dose per fraction has been found to reduce the negative predictive impact of commissural involvement in cT1b patients possibly by compensating for the above mentioned underdosage. This benefit becomes apparent in a linear fashion starting from doses of 200 cGy and above [87,93]. This trend in outcomes is reported in Table II which includes studies involving the same categories of patients, but treated with RT.

A recent meta-analysis including patients treated with intensity modulated RT, where the dose to the target is more precisely controlled, failed to detect a negative impact for AC involvement [94]. Additional factors that may have limited the negative role of AC in the recent series include a more precise and reliable calculation of the delivered dose via Monte Carlo planning and more accurate tumour staging by MRI. It is noteworthy that none of the studies that found a predictive role of AC involvement in early glottic cancer included only cT2, suggesting that multicollinearity among covariates may have confounded the results. Nevertheless, AC neoplastic involvement remains the most influential tumour factor in the decision-making process for early glottic cancer even among radiation oncologists [95]. Moreover, a recent meta-analysis demonstrated that AC represents a risk factor for RT failure in early stage glottic carcinoma, thus confirming its independent prognostic value [76].

Conclusions

A modern staging system for laryngeal cancer should take into account the specific embryological characteristics of the AC as a unique glottic subsite and the potential impact of the different modes of tumour spread (horizontal *vs* vertical) that are now amenable to detection using contemporary endoscopic and imaging techniques. Based on our review of available evidence, the prognostic implication of AC involvement should be considered in upstaging T1 tumours with AC involvement to T2 and subclassify them into T2a (AC horizontal involvement) and T2b (vertical trans-AC extension above and/or below the glottic plane). Future surgical and non-surgical studies should therefore evaluate these tumours according to different patterns of growth and precisely assess their oncologic prognoses. Meta-analyses investigating the collinearity of AC involvement and other covariates are also needed in order to retrospectively assess these issues and fine-tune the most adequate therapeutic choices, tailoring them on a case-by-case basis.

Conflict of interest statement

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Author contributions

All authors contributed to the interpretation of the data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

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