

The incidence of thyroid cartilage invasion through the anterior commissure in clinically early-staged laryngeal cancer

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Abstract In this study, the incidence of thyroid cartilage invasion in early-stage laryngeal tumors involving anterior commissure was assessed. Medical charts and pathology reports of 62 patients who underwent supracricoid partial laryngectomy as the primary treatment of early-staged laryngeal squamous cell carcinoma were retrospectively reviewed. Patients were divided into two groups according to the macroscopic examination of the surgical specimen: tumors limited to the glottis with the involvement of anterior commissure (TLG); tumors invading both supraglottis and glottis with the involvement of anterior commissure (TISG). Thirty-seven of the cases were classified as TLG group (59.7 %) and the remaining 25 of them were classified as TISG group (40.3 %). Thyroid cartilage invasion was observed totally in ten patients (16.1 %), as macroscopic invasion in two cases and microinvasion in eight patients. Only two were in the TLG group (cartilage invasion rate of 5.4 %), the remaining eight were in the TISG group (cartilage invasion rate of 32 %). Thyroid cartilage invasion rate of TISG group was significantly higher than that of TLG group ($p = 0.011$, $p < 0.05$). Tumors limited to the glottis with AC involvement may be more suitable for endoscopic resection; on the contrary, tumors with vertical extension invading both AC and supraglottis should be evaluated more suspiciously due to high rate of thyroid cartilage invasion, which may still necessitate external laryngectomy techniques.

Keywords Laryngeal cancer · Anterior commissure · Thyroid cartilage · Invasion

Introduction

The junction of the vocal folds anteriorly in the larynx is defined as the anterior commissure (AC). Carcinoma of the larynx is the second most common site of head and neck cancer and AC is involved in nearly 20 % of the glottic and supraglottic cancers [1–3]. A well-established consensus does not exist about the treatment of early-stage glottic tumors involving the AC (T1a, T1b, T2) since the tumors of this region still tend to recur more frequently than other glottic tumors, following either surgery or radiotherapy (RT) [3–5]. The high rate of recurrence can be attributed to the difficulty of clinical evaluation and staging of the tumors involving the region and the higher frequency of subtle thyroid cartilage invasion.

Anatomically, the AC is different from other parts of the glottis. Thyroid cartilage is covered, respectively, by mucosa, muscle tissue, connective tissue and perichondrium at the glottic level. However, upon the AC the thyroid cartilage is covered only by mucosa and the AC tendon, which is formed by the confluence of the vocal ligament, the thyroepiglottic ligament, and conus elasticus. As a result, the muscle and the perichondrium, which works as a barrier against tumor invasion, are absent in this region where the tendon inserts into the cartilage.

Tumors involving other sites of the glottis usually present with advanced-stage findings like vocal fold fixation before they invade the thyroid cartilage. On the contrary, tumors involving the AC are able to invade the cartilage earlier without presenting significant findings, thus it is difficult to stage them before final histopathologic

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analysis. A tumor evaluated as early staged during physical examination due to normal vocal fold mobility according to TNM classification may actually be at an advanced stage when analyzed with pathological examination. Thus, a small-limited cT1 lesion may actually be a pT3 lesion.

Treatment of the glottic tumors extending to the AC is controversial: The local control rates of RT in AC carcinoma are not reliable, with a high rate of recurrence and increased risk for radiochondronecrosis [4–6]. In most of the related articles, it is reported that even small volume tumors of the AC have a more aggressive clinical course and are more resistant to RT. The higher rate of understaging due to the anatomical properties mentioned above may be one of the reasons for resistance to treatment. Furthermore, the greater thickness of the thyroid cartilage at the anterior junction and the variable amount of ossification are the possible factors that may hinder effective irradiation of the region. Likewise, if surgical treatment is preferred, some authors proclaim the necessity of cartilage resection due to the potential predisposition to cartilage invasion even in early stages, either partially as done in frontal–anterior laryngectomy, or totally as in supracricoid partial laryngectomy [7–11]. However, the current trend in the surgical treatment of early-stage laryngeal cancer has changed in favor of transoral laser microsurgery (TLM) due to its lower surgical morbidity compared with traditional external partial laryngeal surgery techniques. Thus, TLM is often favored for the treatment of tumors involving AC despite its contentious oncologic outcomes [12–14].

In the literature, most of the publications about thyroid cartilage invasion of glottic and anterior commissure tumors consist of advance-stage tumors, but reports about the rate of thyroid cartilage invasion in early-stage tumors (cT1–cT2) is scarce. Therefore, this study was intended to assess the incidence of thyroid cartilage invasion in

clinically early-stage laryngeal tumors involving the AC, to determine which tumors are more suitable for endoscopic resection, and which types of tumors are more susceptible to cartilage invasion, which would still necessitate external laryngectomy techniques.

Patients and methods

The medical charts and pathology reports of 91 patients who underwent supracricoid partial laryngectomy in a tertiary university hospital between January 2007 and December 2012, for glottic and supraglottic carcinoma extending to the glottis, were retrospectively reviewed. The patients were evaluated in the tumor board, which routinely takes place with the participation of radiation oncologists, medical oncologists, head and neck surgeons and a radiologist, and the decision of surgical treatment was made regarding the patient preferences. All patients were operated by the same surgical team. The patients were staged according to the American Joint Committee on Cancer (AJCC) 2010 staging guidelines [15]. Recurrent cases treated previously with partial laryngectomy or RT, tumor histology other than squamous cell carcinoma and primary tumors with clinically advanced stage (\geq T3 primary stage) were not included in the study. In addition to the physical examination and preoperative endoscopic records, all the patients had gone through preoperative radiologic investigations with contrasted magnetic resonance imaging (MRI) or contrasted high-resolution computed tomography (CT) or both. Patients with radiologically definite thyroid cartilage invasion findings (T3–T4) and with radiological signs of advanced-stage carcinoma (T3), like paraglottic and preepiglottic space involvement, were not included in the study. The remaining 62 patients were included in the study.

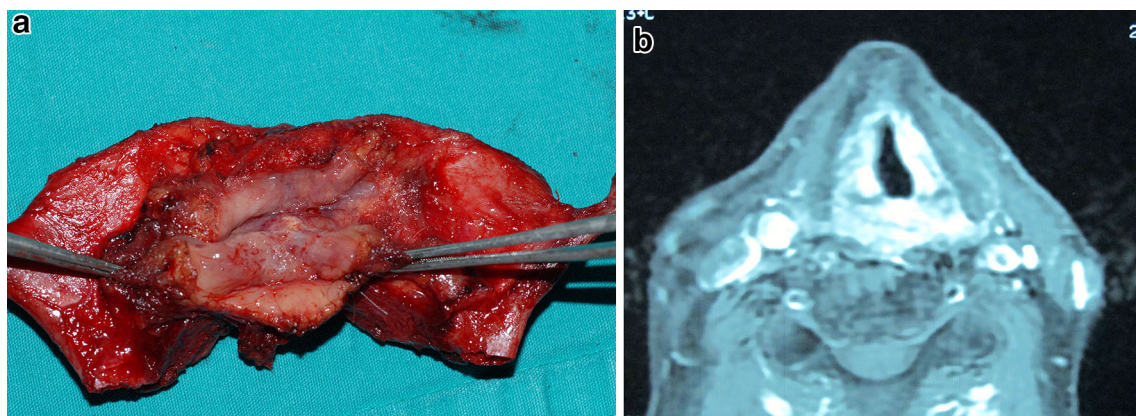


Fig. 1 a Tumor limited to the glottis with AC involvement. b T1-weighted contrasted MRI image of the same patient showing any invasion of the thyroid cartilage

According to the macroscopic examination of the surgical specimen, the tumors were divided into 2 groups: tumors limited to the glottis with the involvement of the AC (TLG); tumors invading both supraglottis and glottis with the involvement of the AC (TISG) (Figs. 1, 2).

Each supracricoid laryngectomy section was fixed in 10 % formalin solution for 24 h. During the pathologic examination, the thyroid cartilage was initially inspected macroscopically for a gross carcinoma infiltration. The next step was the decalcification of cartilage using diluted nitric acid, which alters according to the size and thickness of the material. When the softness was appropriate for cutting, the thyroid cartilage was divided into two pieces following a vertical cut from the median junction and sliced vertically into pieces with 4 mm thickness. The tissue was embedded into paraffin for routine tissue follow-

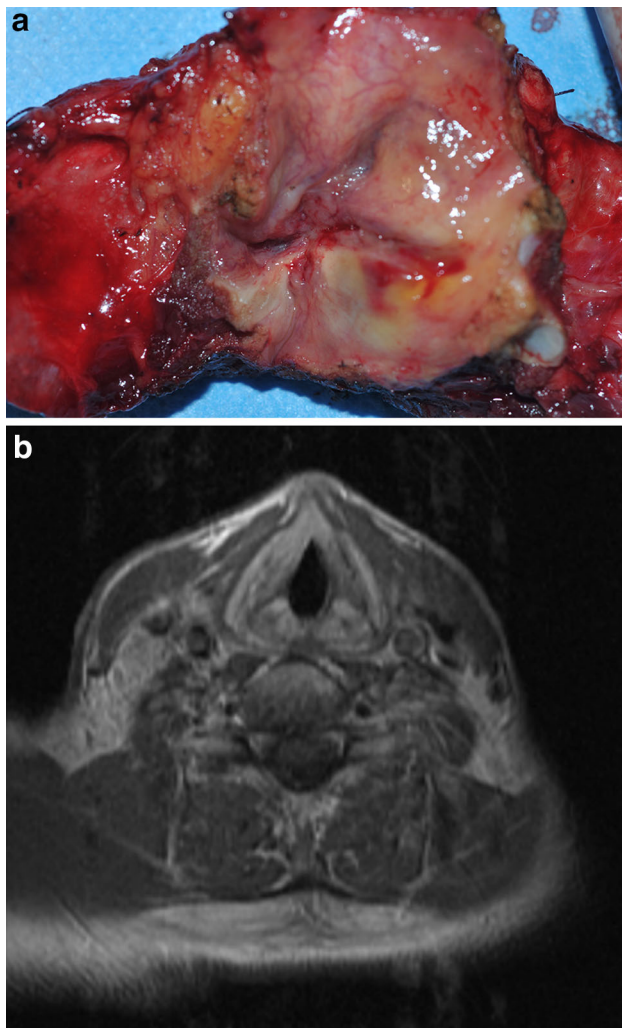


Fig. 2 **a** Tumor invading both supraglottis and glottis, which demonstrated thyroid cartilage invasion in the final pathology report. **b** T1-weighted contrasted MRI image of the same patient showing any invasion of the thyroid cartilage

up. The histologic sections were 2- μ m thick and stained with hematoxylin–eosin. Using light microscopy, the relationship between the cartilage and tumor was defined as follows: no cartilage invasion, microinvasion, and macroscopic invasion (Fig. 3).

All statistical calculations were performed with SPSS Statistics 17.0 (Polar Engineering and Consulting, 2008). Fisher's exact test was used in the assessment of parameters and statistical significance level was established as $p < 0.05$.

Results

The study consisted of 62 patients. The mean age at presentation was 59.3 years (range 45–80 years, SD ± 8.56), and except for one woman, all the patients were men.

When the tumors were grouped according to their origin, 37 patients were classified as TLG group (59.7 %), and 25 were classified as TISG group (40.3 %) (Table 1). All of the TISG tumors were staged as cT2 and their locations were as follows: in addition to AC involvement, the

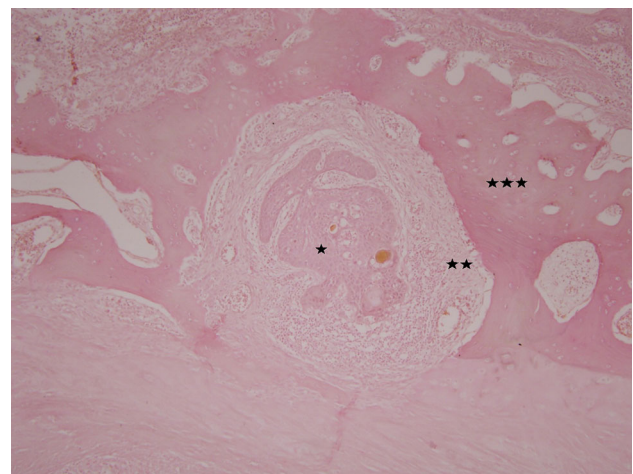


Fig. 3 Microscopic findings of a thyroid cartilage invasion (hematoxylin–eosin staining, $\times 10$). *Single asterisk* tumor foci invading the thyroid cartilage, *double asterisks* inflammation tissue surrounding the tumor, *triple asterisks* cartilage tissue

Table 1 Distribution of the tumors

	Cases (<i>n</i>)	Thyroid cartilage invasion
TLG	37 (59.7 %)	2 (5 %)
TISG	25 (40.3 %)	8 (32 %)
Total	62	10 (16.1 %)

TLG tumors limited to the glottis with the involvement of the AC, *TISG* tumors invading both supraglottis and glottis with the involvement of the AC

ventricle and vestibular folds were involved in 20 patients, and epiglottic petiole was involved in 5 patients. In the TLG group, 22 of the tumors were classified as cT1b, and 15 of them as cT2 owing to limited subglottic involvement less than 1 cm.

In the final pathologic examination, thyroid cartilage invasion was observed in ten patients (16.1 %), as macroscopic invasion in two patients, and microinvasion in eight patients (Table 2). Only two were TLG with a cartilage invasion rate of 5.4 %, the remaining eight were TISG with a cartilage invasion rate of 32 %. Of the two patients with cartilage involvement in the first group, one of them was cT1b and the other one was cT2. All thyroid cartilage invasions were observed at the attachment of the AC to the thyroid cartilage.

The thyroid cartilage invasion rates of the two groups were compared using Fisher's exact test and the invasion rate of TISG group was found significantly higher than that of TLG group ($p = 0.011$, $p < 0.05$).

When the histological subtype of the tumors was reviewed, they were as follows: TLG group comprised 11 cases of well-differentiated SCC (29.7 %), 24 cases of moderately differentiated SCC (64.9 %), 1 case of verrucous carcinoma, and 1 case of basaloid carcinoma. The two cases with cartilage invasion from the TLG group were moderately differentiated. The TISG group consisted of 4

poorly differentiated SCC (8 %), 18 moderately differentiated SCC (72 %), and 3 well-differentiated SCC (12 %). Of the 8 cases with cartilage invasion from the TISG group, 1 was poorly differentiated and 7 were moderately differentiated. It is to be noted that the cartilage invasion was observed totally in 25 % ($n = 1$) of poorly differentiated SCC cases, in 21.4 % ($n = 9$) of moderately differentiated SCC cases, but in none of the cases of well-differentiated SCC or in other variants of SCC.

Discussion

In the treatment of early-stage laryngeal cancer, management of the AC involvement is one of the most challenging points for the clinician because of the high rate of insidious thyroid cartilage invasion. The clinical evaluation of the region still remains difficult and the selection of a treatment modality is controversial. Physical examination methods like videostroboscopy or palpation via microlaryngoscopy are not sufficient to detect thyroid cartilage microinvasions and the role of radiological investigations is also controversial, whereas both CT and MRI can be used for this purpose. CT is better than MRI for the assessment of thyroid cartilage if ossified; on the contrary, MRI is more sensitive for cartilage invasion [16]. The signs of cartilage invasion

Table 2 Patients with thyroid cartilage invasion

No.	Stage	Group	Tumor description	Surgery	Postoperative pathology
1	T2	TISG	AC, left VC, left ventricle, left VF, subglottic extension (1 cm)	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, two positive LNs in left neck
2	T1b	TISG	AC, left VC, left ventricle, left VF	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, negative neck
3	T2	TLG	AC, both VC	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, negative neck
4	T2	TISG	AC, left VC, left ventricle, left VF	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, perineural invasion+, negative neck
5	T1b	TISG	AC, right VF, right ventricle, right VF	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, negative neck
6	T2	TISG	AC, right VF, epiglottic petiole	CHP	Moderately differentiated SCC comprising areas of clear cells, macroscopic cartilage invasion, negative neck
7	T2	TISG	AC, both VC, both ventricle, both VF	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, negative neck
8	T2	TLG	AC, both VC, subglottis (10 mm)	CHEP	Moderately differentiated SCC, microscopic cartilage invasion, negative neck
9	T2	TISG	AC, right VC, right ventricle, right VF	CHP	poorly differentiated SCC, microscopic cartilage invasion, negative neck
10	T2	TISG	AC, right VC, right ventricle, right VF, epiglottic petiole	CHEP	Moderately differentiated SCC comprising areas of poor differentiation, macroscopic cartilage invasion, one positive LN at right neck

TISG tumors invading both supraglottis and glottis, TLG tumors limited to the glottis, AC anterior commissure, VC vocal fold, VF vestibular fold, CHEP supracricoid partial laryngectomy with cricohyoidoepiglottopexy, CHP supracricoid partial laryngectomy with cricohyoidopexy, SCC squamous cell carcinoma

on CT are sclerosis, lysis, erosion and extralaryngeal tumor spread [17]. However, thyroid cartilage ossification, beginning in the third decade, causes high-density areas in the cartilage, which hinders identification of the inner perichondrium on CT, so CT in the evaluation of inner perichondrium involvement and minor cartilage invasion is insufficient [18]. For this purpose, Barbosa et al. [19] published a gross radiological CT classification system for the AC involvement (GRACI), which did not provide any statistically significant benefit for early-stage tumors and failed in demonstrating thyroid cartilage invasion. Likewise, Hartl et al. [18] published a retrospective study investigating the correlation of postoperative pathologic reports and preoperative CT findings, which also demonstrates that preoperative CT was not efficient in predicting thyroid cartilage invasion in early-stage lesions and overestimated cartilage invasion for AC lesions. Similarly, other studies have found CT to have a low positive predictive value in detecting microscopic invasion of the inner cortex of the thyroid cartilage [20, 21]. On the other hand, MRI can demonstrate details of non-ossified cartilage better than CT, but also MRI has unsatisfactory and inconsistent results for the evaluation of thyroid cartilage involvement [22]. On MRI, laryngeal cartilage infiltration by tumor shows high signal intensity on T2w and low signal intensity on T1w and after contrast enhancement, the signal is similar to tumor. In the study of Banko et al. [23], the reliability of MRI in the evaluation of AC involvement in glottic tumors was 100 %, however, the cartilage invasion was overestimated; of the seven patients who were radiologically judged to have cartilage invasion, only five had pathologically proven invasion. In the study of Kinshuck et al. [24], preoperative MRI scans performed for investigating laryngeal carcinoma were retrospectively reviewed and they concluded that MRI has a false-negative rate of 27.2 % and a false-positive rate of (54.8 %) in demonstrating thyroid cartilage invasion. The authors attributed this over-predicted thyroid cartilage invasion to reactive inflammation, edema and fibrosis secondary to the underlying pathology, which can mimic minor thyroid cartilage invasion. This high false-positive cartilage invasion rate based on MRI findings might result in over-treatment for patients who are planned to have partial, function-organ sparing laryngeal surgery. This is a significant problem especially in patients who might be candidates for TLM [24]. With the guidance of these studies, it is reasonable to conclude that radiological investigation for the evaluation of thyroid cartilage is not beneficial in the presence of an early-stage AC tumor. When we consider that none of the cases in our series had gross radiologic findings indicating cartilage invasion, it was a striking result to have a positive pathological report in 32 % of the cases in the TISG group supporting the inefficiency of radiological investigation for staging tumors in the region.

Thyroid cartilage invasion by a laryngeal tumor can mostly be observed in five different zones; the thyroid angle at the attachment of the AC tendon is the most important site in glottic tumors [25]. The other risky sites are the upper margin of the thyroid ala, which is mostly invaded through the preepiglottic space; the lower margin of the thyroid ala, which is at risk when the tumor has a subglottic extension; the cricoarytenoid articulation; and lastly, the posterior border of the thyroid lamina adjacent to the pyriform sinus. All of the patients conducted in our study were early-stage tumors without preepiglottic space or cricoarytenoid joint involvement; so, the site of thyroid cartilage invasion was at the level of the AC in all of the cases, where Broyle's ligament attaches to the thyroid cartilage.

Variable rates of thyroid cartilage invasion in tumors involving the AC are reported in the literature: Hartl et al. [26] reported a rate of 8.9 % for 94 cases of cT1–cT3, which consist of patients that underwent any type of open conservation laryngeal surgery like vertical hemilaryngectomy, supraglottic laryngectomy, and SCPL (62 % of the cases). In another study by Rifai et al. [27], thyroid cartilage invasion was detected in all of the 30 patients who had undergone total laryngectomy for laryngeal carcinoma with the involvement of AC and as a conclusion the authors suggested avoiding both RT and TLM for this type of tumor. However, of the 30 patients in this study, 19 had received RT and 5 had undergone TLM as the primary treatment, but only 6 patients (4 T2 and 2 T3) had received no prior treatment. Besides, in Rifai's study, the majority of the cases was advanced-stage tumors and does not reflect the results of the target population of our study, which consist of clinically early-stage tumors. As a result of these clinical studies, there is a confusion about the thyroid cartilage invasion rate in AC tumors and none of these studies can guide to the clinician which type of AC tumors is more risky for the invasion.

Recently some anatomic studies were published about the invasion pathways of laryngeal carcinoma; Bagatella mentioned that supraglottic tumors tend to stop growing when they reach the fibrous connective tissue of X-space above the anterior commissure [28]. X-space is thought to behave like a barrier against further deep invasion and enables the tumor to spread only superficially and horizontally in the early stages. In another study of Bagatella, the surgical specimens of 13 patients without prior RT operated for a laryngeal carcinoma with tumors crossing the AC in a vertical direction were examined by whole-organ section, and 10 of the patients showed invasion and destruction of the thyroid cartilage [2]. The result reflects the risk of thyroid cartilage invasion at the level of the AC if a supraglottic tumor has extended to the glottis in the midline or a laryngeal tumor beginning from the glottis and

extending to the supraglottis with an atypical clinical behavior characteristic. In our series comprising 62 cases of supracricoid partial laryngectomy, thyroid cartilage invasion was observed in 10 cases (16.1 %). The rate of invasion was 5 % in the TLG group and 32 % in the TISG group and the difference between the two groups was found to be statistically significant. This result supports Bagatella's hypothesis that tumors invading the AC in a vertical direction are more likely to cause cartilage infiltration than tumors extending from one vocal fold to the other crossing the AC. Bagatella's x-space theory and the Pressman's theory of submucosal compartmentalization of the larynx both underline the importance of the anatomic barrier that hinders a supraglottic tumor from descending to the glottis at the level of the AC, and constitute the basis of the oncologic validity for horizontal supraglottic laryngectomy [28, 29]. This type of tumors tends to be limited to the supraglottis for a certain time. However, if a tumor crosses this barrier vertically and invades the AC, it is supposed to be much more aggressive than expected. This behavior character may explain why one-third of supraglottic tumors extending to the AC had caused cartilage invasion in our series as well. In contrast, glottic tumors tend to extend within the glottis with a mucosal spread pattern and not invade deeply. The AC tendon and conus elasticus might be working as a barrier for the anterior spread of cancer until the late stages owing to its fibroelastic structure as suggested by Kirchner [30]. The low rate of cartilage invasion in the TLG group in our series (5 %) also supports this hypothesis.

The less the tumor is histologically differentiated, the more likely the tumor is to have aggressive behavior and to invade the cartilages of the larynx [31, 32]. It is well known that the degree of differentiation of the supraglottic tumors is generally poorer than glottic tumors [33]. Consistently, 29.7 % of the glottic tumors were found to be well differentiated, while only 12 % of the supraglottic tumors were so in our study. This finding supports the idea that the supraglottic tumors descending to AC may be predicted to behave more aggressively than those originating from purely glottic region, and accordingly, they are more likely to invade the cartilage.

Conclusion

In our institution, in the past we routinely performed open surgical techniques for tumors involving AC because of its proved oncologic validity. However, the current worldwide trend in the declining use of open partial conservation surgical techniques and acceptance of TLM's oncologic safety changed our preference to endoscopic surgical techniques, which have lower morbidity. On the other hand,

retrospective data indicate a high cartilage invasion rate of AC tumors relative to their tumor size, so it is important to subgroup these tumors, which may have different clinical behavior. This study demonstrates that tumors with vertical extension invading both AC and supraglottis have an increased rate of thyroid cartilage invasion than those limited to the glottis with AC involvement. Despite our relatively small patient group, this could guide the surgeon when choosing a surgical technique for clinically early-stage laryngeal cancer with AC involvement. SCPL can be preferred for the previous group considering the high risk of thyroid cartilage invasion since it may be difficult to resect the cartilage during TLM in the older patient group with prominently ossified laryngeal skeleton. Instead, if a tumor is limited to the glottis, TLM should be chosen considering the high probability of overtreatment and high morbidity resulting from open surgical techniques. TLM, as today's most popular and controversial laryngeal conservation surgery technique, may be chosen with greater resection margins as the treatment modality for the tumors with minor thyroid cartilage invasion, but its oncological validity still necessitates further research.

Conflict of interest None.

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