Article

A Critical Reappraisal of Primary and Recurrent Advanced Laryngeal Cancer Staging

Annals of Otology, Rhinology & Laryngology
1–8

DOI: 10.1177/0003489418806915
journals.sagepub.com/home/aor
SAGE

Luca Giovanni Locatello, MD[1], Michele Pietragalla, MD[2], Cecilia Taverna, MD[3], Luigi Bonasera, MD[2], Daniela Massi, MD, PhD[3], and Giuditta Mannelli, MD[1]

Abstract

Objectives: Laryngeal squamous cell carcinoma (LSCC) can involve different anatomic subunits with peculiar surgical and prognostic implications. Despite conflicting outcomes for the same stage of disease, the current staging system considers different lesions in a single cluster. The aim of this study was to critically discuss clinical and pathologic staging of primary and recurrent advanced LSCC in order to define current staging pitfalls that impede a precise and tailored treatment strategy.

Methods: Thirty patients who underwent total laryngectomy in the past 3 years for primary and recurrent advanced squamous cell LSCC were analyzed, comparing endoscopic, imaging, and pathologic findings. Involvement of the different laryngeal subunits, vocal-fold motility, and spreading pattern of the tumor were blindly analyzed. The diagnostic accuracy and differences between clinicoradiologic and pathologic findings were studied with standard statistical analysis.

Results: Discordant staging was performed in 10% of patients, and thyroid and arytenoid cartilage were the major diagnostic pitfalls. Microscopic arytenoid involvement was significantly more present in case of vocal-fold fixation ($P = .028$). Upstaging was influenced by paraglottic and pre-epiglottic space cancer involvement, posterior commissure, subglottic region, arytenoid cartilage, and penetration of thyroid cartilage; on the contrary, involvement of the inner cortex or extralaryngeal spread tended to be down-staged. Radiation-failed tumors less frequently involved the posterior third of the paraglottic space ($P = .022$) and showed a significantly worse pattern of invasion ($P < .001$).

Conclusions: Even with the most recent technologies, 1 in 10 patients with advanced LSCC in this case series was differently staged on clinical examination, with cartilage involvement representing the main diagnostic pitfall.

Keywords

laryngology, laryngeal cancer, cancer staging, head and neck cancer, TNM

Introduction

Treatment of laryngeal squamous cell carcinoma (LSCC) is complex, involving a multidisciplinary team of head and neck surgeons, oncologists, radiologists, and pathologists.[1,2] When discovered at an advanced stage (stage III or IV), the prognosis is often dismal, with 5-year disease-free and overall survival of only 50% or lower.[3] The management of such a complex disease starts with an accurate clinical and radiologic evaluation of the tumor and node stage that will be ultimately confirmed by the final pathologic report if upfront or salvage surgery is performed.[4] The latest TNM staging system considers largely different laryngeal lesions in the same cluster, such as T3 carcinomas.[5] Involvement of different subunits such as the paraglottic, pre-epiglottic, inner cortex of the thyroid gland, and vocal-fold fixation is the expression of diseases that might behave differently, as shown by conflicting results from the studies analyzing locally advanced laryngeal cancer.[6,7] Nowadays, even with current technological advances, precisely defining the extension of LSCC remains very challenging.[8] In the era of tailored organ preservation strategies, such workup becomes even more critical given the different impact of different stages on a single treatment response rate.[7,9] We sought to

[1]Division of Otorhinolaryngology, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy
[2]Division of Radiology, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy
[3]Institute of Pathology, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

Corresponding Author:
Luca Giovanni Locatello, MD, Careggi University Hospital, Division of Otorhinolaryngology, Largo Brambilla, 3, Florence, 50134, Italy.
Email: locatello.lucagiovanni@gmail.com

analyze and critically discuss current pitfalls of the pretreatment staging of primary and recurrent advanced LSCC.

Methods

We collected all patients who had undergone primary or salvage total laryngectomy (TL) at our Institution in the past 3 years. Thirty patients (22 men, 8 women) with a mean age at the time of TL of 69 years, were retrospectively included in the present study after institutional review board approval was obtained. All had histopathologically proven diagnoses of LSCC. Patients requiring TL for oropharyngeal or hypopharyngeal cancer or non-neoplastic reasons were excluded. All patients underwent at least contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI) for staging purposes. We then retrospectively reviewed the clinical (in-office and intraoperative) and radiologic (CT or MRI) pretreatment data. A clinical and radiologic evaluation helped in staging the tumor accordingly to the eighth edition of TNM staging system (clinical TNM and recurrent TNM) and guided the multidisciplinary treatment decision, while the final histopathologic report described the pathologic stage that served for adjuvant therapeutic indications.[1,5]

Clinical Endoscopic Evaluation

A preoperative clinical examination was conducted in the outpatient clinic, where every patient included in the present study underwent a full clinical evaluation using fiberoptic endoscopy. All oncology patients at our institution undergo a preoperative full endoscopic examination with the aid of narrow-band imaging using an Olympus CLV-S190 Visera Elite (Olympus Corporation, Tokyo, Japan). Vocal-fold mobility was retrieved from the examiner's description and video registration of the endoscopic examination and was classified using a 3-tiered system (normal, reduced, or no movement). Arytenoid involvement was deemed clinically positive or not. Extension of the disease was classified according to the glottic, supraglottic, and subglottic region, and the term *transglottic* was used when the region of origin was not certainly established and the cancer involved multiple regions.[10]

Radiologic Imaging Assessment

Imaging was collected and reviewed by our expert head and neck radiologists. In case of a recurrent tumor, the last radiologic evaluation before TL was chosen. Computed tomographic examinations were performed with a 128-slice dual-source Somatom Definition Flash (Siemens Healthcare, Erlangen, Germany) helicoidal volumetric technique scanning with a field of view from the orbital floor to the superior thoracic narrow at 100 kV with a 0.6-mm acquired slice thickness. Patients underwent a preliminary noncontrast scan; then axial computed tomographic scans in arterial (40 seconds) and venous (70-80 seconds) phases were performed after intravenous injection of iodine contrast media (iopromide 1.2 mg/kg, flow rate 3 mL/s) and a 40-mL saline bolus. Postprocessing of 1.25-mm reconstructed images in the axial, sagittal, and coronal planes oriented on the glottic plane and axial bone window images was performed. MRI examinations were performed using a 1.5-T Magnetom Aera (Siemens Healthcare) and a neck MRI coil with a field of view from the mandible to the superior thoracic narrow. MRI precontrast sequences included axial T2 turbo spin echo (TSE), axial and coronal short-tau inversion recovery, sagittal T1 TSE, T1 TSE FatSat, axial volume-interpolated breath-hold examination T1 Dixon with multiplanar reconstruction, and diffusion-weighted imaging. After the intravenous injection of gadolinium contrast media (gadobenate dimeglumine 2 mL/kg, flow rate 3 mL/s) followed by a 40-mL saline bolus, axial T1 TSE FatSat, axial volume-interpolated breath-hold examination T1 Dixon with coronal and sagittal multiplanar reconstruction, sagittal T1 TSE, and perfusion-weighted imaging sequences were performed.

Histopathologic Analysis

Histopathologic analysis was undertaken by pathologists with expertise in the head and neck field. All laryngectomy specimens were subjected to a whole-organ study. Paraffin preparations and hematoxylin and eosin stains were used. For endolaryngeal tumors, the larynx was opened through a median vertical dorsal incision. The superior epiglottic margin was cut in a vertical section for the pre-epiglottic space analysis, and the inferior tracheal margin was cut in a horizontal section. The paraglottic and subglottic spaces were studied using horizontal slices. Macrosections (3- to 4-mm slice thickness) were used to study the endolaryngeal space for a better identification of the anatomic structures and their relation with the tumor.[11] Tumor primary site, contralateral invasion and vertical extension, invasion of pre-epiglottic space, invasion of paraglottic spaces and axial extension (anterior and posterior), invasion of anterior and posterior commissures, invasion, site, and grade of erosion and of thyroid cartilage, invasion of cricoid and arytenoid cartilages and extralaryngeal extension on endoscopic, and imaging and histologic examination were systematically evaluated. All of the examiners were blinded to one another and were required to express their evaluations in a binary fashion (present or absent). When there was no agreement between the clinical and radiologic findings (eg, arytenoid fixed at laryngoscopy but no clear signs of invasion on CT or MRI), the clinical evaluation prevailed. Moreover, vascular and perineural invasion, presence of multiple foci, dissociated

Table 1. Clinical Staging, at the Time of Total Laryngectomy, for Primary and Recurrent Advanced Laryngeal Carcinoma in the Present Series.

Clinical TNM	Primary (n = 16 [53.4%])	Recurrence After RT (n = 11 [36.6%])	Recurrence After CLS (n = 3 [10%])	Total
T3N0M0	6	5	—	11
T3N1M0	1	—	—	1
T3N2bM0	1	—	—	1
T3N2cM0	1	1	—	2
T4N0M0	4	3	2	9
T4N1M0	—	1	—	1
T4N2aM0	1	1	—	2
T4N2bM0	1	—	1	2
T4N2cM0	1	—	—	1

Abbreviations: CLS, conservative laryngeal surgery; RT, radiotherapy.

Table 2. Subsites Clinically and Pathologically Involved by Advanced Stage Laryngeal Carcinoma in the Present Series.[a]

Subsite	Clinicoradiologic	Histopathologic
Paraglottic spaces	30/30 (100)	28/30 (93.3)
Paraglottic space, anterior third	30/30 (100)	28/30 (93.3)
Paraglottic space, middle third	26/30 (86.6)	26/30 (86.6)
Paraglottic space, posterior third	20/30 (66.6)	17/30 (56.6)
Pre-epiglottic space	9/30 (30)	6/30 (20)
Anterior commissure	25/30 (83.3)	25/30 (83.3)
Posterior commissure	9/30 (30)	7/26 (26.9)
Subglottis	11/30 (36.6)	7/22 (31.81)
Thyroid cartilage, inner cortex	16/30 (53.3)	23/30 (76.6)
Thyroid cartilage, full thickness	10/30 (33.3)	7/30 (23.3)
Cricoid cartilage	6/30 (20)	5/25 (20)
Arytenoid cartilages	10/30 (33.3)	6/26 (23.0)
Contralateral extension	25/30 (83.3)	24/30 (80)
Extralaryngeal extension	9/30 (30)	10/30 (33.3)

[a]Data are expressed as positive/evaluable (percentage).

cells, and infiltration pattern (according to the 5-tier model proposed by Brandwein-Gensler et al.[12]) were recorded.

Statistical Analysis

The Fisher exact test, χ^2 test, and Student *t* test were used as appropriate. On the basis of true and false positives and negatives, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. All of the tests were 2 tailed, and *P* values $< .05$ were considered to indicate statistical significance. Data were analyzed using Graph Pad Quick Calcs (GraphPad Software, Inc, La Jolla, California, USA) and SPSS version 21 for Windows (IBM, Armonk, New York, USA).

Results

There were 16 (53.4%) primary TLs, 11 (36.6%) after failure of chemoradiotherapy and 3 (10%) salvage TLs after transoral laser microsurgery. At preoperative endoscopic assessment, vocal-fold motility was considered normal in 7 (23.3%), impaired in 16 (53.4%), and absent in 7 (23.3%) patients. Arytenoid was deemed clinically involved by the tumor in 10 and radiologically in 12 cases. Twenty-three patients (76.6%) underwent only contrast-enhanced CT before surgery, 1 patient underwent only MRI, and the remaining 6 (20%) underwent both imaging techniques. In terms of TNM staging for both recurrent and primary tumors, there were 7 rT3, 7 rT4a, 9 cT3, and 7 cT4a laryngeal cancers (Table 1). Table 2 shows the clinical and pathologic involvement of various laryngeal subsites in our series. Dissimilar clinical staging was found in 3 of 30 patients (10%). Such cases involved down-staging 1 patient missing cartilage penetration (cT3-pT4a; Figure 1) and up-staging 2 patients in terms of paraglottic space (cT3-pT2; Figure 2) and thyroid cartilage involvement (cT4a-pT3; Figure 3); all of these patients had received no previous treatment. The

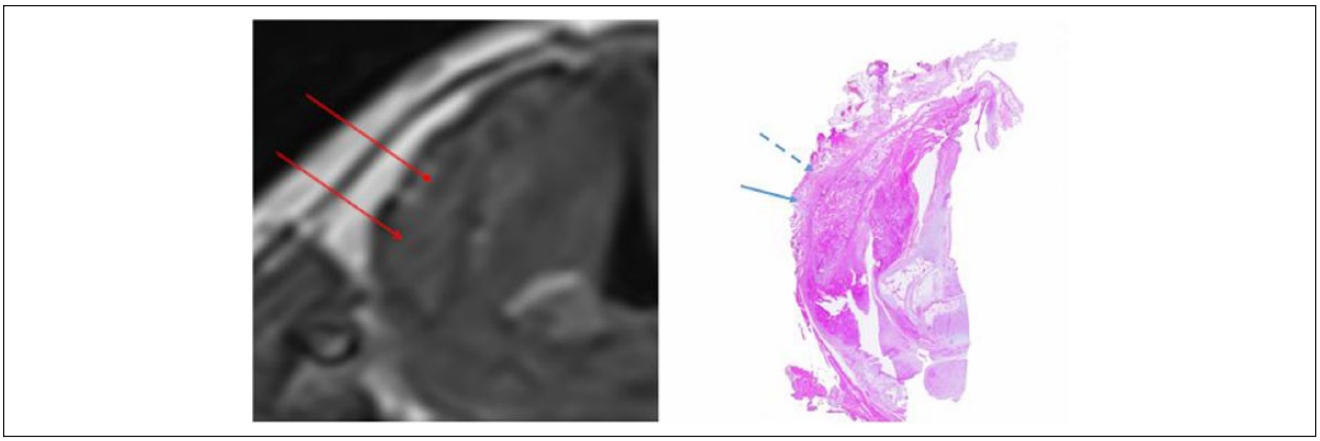

Figure 1. A case of clinically understaged advanced laryngeal cancer (cT3, pT4). Magnetic resonance imaging axial T1 sequences show the lesion to be confined to the cartilaginous skeleton (red arrows), whereas histopathologic analysis reveals thyroid shield penetration (dashed blue line) and initial extralaryngeal extension (continue blue arrow).
Note: The color version of this figure is available online.

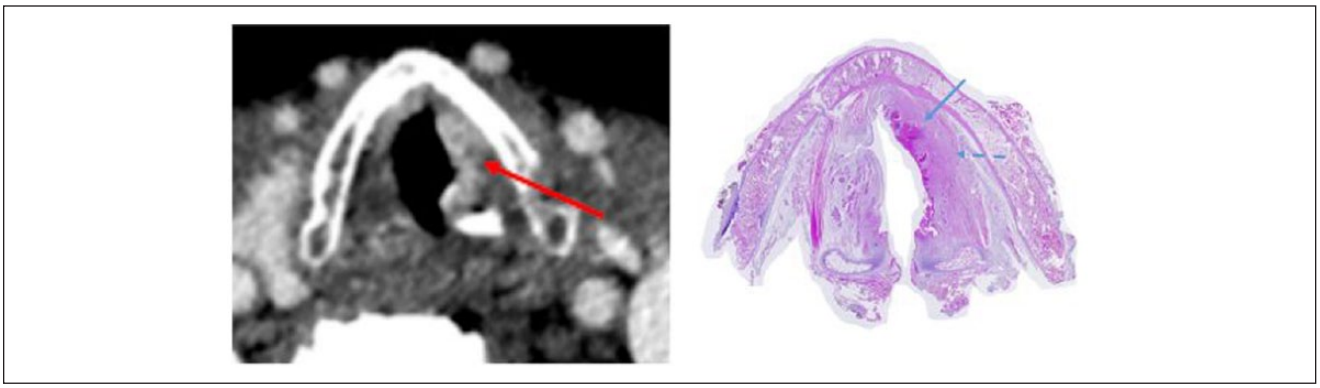

Figure 2. A cT3 laryngeal cancer pathologically understaged as pT2 because no paraglottic space involvement was apparent in this patient. Contrast-enhanced computed tomography shows only an apparent involvement of the anterior paraglottic space (red arrow) that on histology proved to be only an inflammatory reaction (dashed blue arrow) created by the infiltrating tumor (continuous blue arrow).
Note: The color version of this figure is available online.

first patient was studied with both MRI and CT, while the 2 up-staged cases underwent only CT before surgery. In these 3 patients, mean time elapsed from latest radiologic examination to TL was 12.4 days.

Table 3 shows sensitivity, specificity, and accuracy for clinicoradiologic staging according to different subsites. In our series, arytenoid and thyroid cartilages were the subsites most at risk for upstaging. In addition, imaging studies tended to overestimate the tumor invasion of paraglottic and pre-epiglottic spaces, posterior commissure, and subglottis. On the contrary, the inner cortex of the thyroid cartilage and extralaryngeal extension were prone to be underestimated. Considering the arytenoid cartilages, it is of note that had we considered the imaging evaluation only, we would have obtained far lower specificity and accuracy (65% and 65.3%, respectively).

Table 4 shows the pathologic involvement of different subsites considering vocal-fold motility. Of interest, when vocal fold was clinically judged to be fixed, there was significantly more frequent microscopic involvement of the ipsilateral arytenoid compared with cases with normal or impaired motility ($P = .028$). We also analyzed LSCC spreading according to previous radiation therapy, but no statistically significant differences were found. Finally, in Table 5, we present the different microscopic features of primary and recurrent advanced LSCC, showing the latter to present more frequently dissociated tumor cells ($P = .027$) and multiple foci ($P < .001$). When we considered the worst pattern of invasion, as described by Brandwein-Gensler et al.,[12] previously irradiated carcinomas showed significantly worse results ($P < .001$; Table 5).

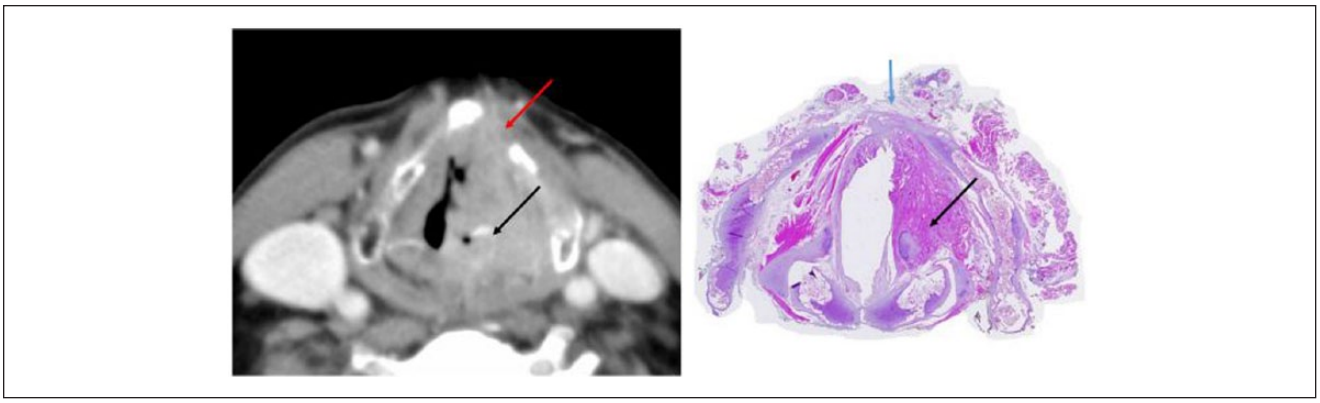

Figure 3. A pT3 laryngeal cancer overstaged as cT4a for penetration of thyroid cartilage (red arrow) and for left arytenoid infiltration (black arrow). The first was not apparent in the final pathologic report with malignant cells only eroding the inner cortex (blue arrow), whereas the arytenoid appeared to be only partially eroded (black arrow).
Note: The color version of this figure is available online.

Table 3. Accuracy of Clinical and Radiologic Evaluation Compared With Pathologic Diagnosis.

Subsite	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
PSs	28	2	0	0	100	0	93.3	93.3	0
PS, anterior third	27	2	0	0	100	0	93.1	93.1	0
PS, middle third	23	1	2	3	92	75	89.6	95.8	60
PS, posterior third	16	4	1	9	94.1	69.2	83.3	80	90
Pre-epiglottic space	6	3	0	21	100	87.5	90	66.6	100
Anterior commissure	23	2	2	2	92	50	86.2	92	50
Posterior commissure	5	2	2	17	71.4	89.4	84.6	71.4	89.4
Subglottis	7	0	1	14	87.5	100	95.4	100	93.3
TC, inner cortex	15	0	8	7	65.2	100	73.3	100	46.6
TC, full thickness	6	4	1	19	85.7	82.6	83.3	60	95
Cricoid cartilage	5	0	0	20	100	100	100	100	100
Arytenoid cartilages	4	4	2	16	66.6	80	76.9	50	88.8
Contralateral extension	24	1	0	5	100	83.3	96.6	96	100
Extralaryngeal extension	8	1	2	19	80	95	90	88.8	90.4

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; PS, paraglottic space; TC, thyroid cartilage; TN, true negative; TP, true positive.

Discussion

There are several options to treat advanced LSCC, and pretreatment staging, along with patient preference,[13] is essential because the TNM system predicts prognosis along with the chance of a defined surgical or chemoradiotherapy success.[14] In particular, both transoral and open surgical procedures must rely on radiologic and endoscopic findings which, along with intraoperative frozen sections, are crucial to evaluate the extent of the disease.[14] When a surgical conservative strategy is considered for advanced LSCC, precise boundaries must be set to perform a tailored resection while remaining oncologically sound.[2] In this regard, massive infiltration of the pre-epiglottic space, invasion in a caudocranial sense of the anterior commissure, and posterior paraglottic space involvement with vocal-fold fixation are considered to be the current limit of transoral laser microsurgery.[15-18] In this light, our positive predictive value for pre-epiglottic space involvement of 66.6%, although in agreement with another recently published series, seems to be quite unsatisfactory.[19] New surgical techniques, such as open partial horizontal laryngectomy, type III with tracheohyoidopexy has expanded the treatment of cT3 LSCC even when spreading in the subglottis or posteriorly involving one cricoarytenoid unit.[20,21] On the other hand, all of the organ-sparing protocols based on chemoradiotherapy, although more than 20 years have passed since their first report,[22] still consider cT4 tumors penetrating beyond the cartilaginous skeleton a major indication for TL.[7]

Table 4. Pathologic Involvement of Various Subsites According to Vocal-Fold Mobility.[a]

Subsite	Normal Mobility (n = 7)	Impaired Mobility (n = 16)	Vocal-Fold Fixation (n = 7)	*P*
PSs	6/7	15/16	7/7	.724
PS, anterior third	6/7	14/16	7/7	1.000
PS, middle third	5/7	13/16	7/7	.381
PS, posterior third	3/7	9/16	5/7	.561
Pre-epiglottic space	2/6	2/16	2/7	.486
Anterior commissure	6/7	13/16	6/7	1.000
Posterior commissure	0/4	4/15	3/7	.331
Subglottis	0/6	4/11	3/5	.114
TC, inner cortex	6/7	13/16	4/7	.511
TC, full thickness	2/7	4/16	1/7	1.000
Cricoid cartilage	2/7	3/13	0/5	.657
Arytenoid cartilages	0/6	2/14	4/6	.028
Contralateral extension	4/7	14/16	6/7	.252
Extralaryngeal extension	4/7	5/16	1/6	.285

Abbreviations: PS, paraglottic space; TC, thyroid cartilage.
[a]Data are expressed as positive/evaluable.

Table 5. Microscopic Features in Primary Versus Post-RT/CRT Advanced Laryngeal Cancer.

Subsite	Primary (n = 19)	Post-RT/CRT (n = 11)	*P*
Vascular invasion	3	2	.536
Perineural invasion	6	5	.695
Dissociated tumor cells	2	6	.027
Multicentric tumor foci	1	9	<.001
WPOI (average)	2.36	3.27	<.001

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; WPOI, worst pattern of invasion.

In the present work, agreement between clinical and histologic findings was found in more than 90% of cases of advanced laryngeal cancer. This result does represent an improvement of a similar study conducted in 1997 in which the authors, though analyzing some nonsquamous histologies and not specifying whether patients had been previously treated, declared concordant assessments in 80% of cases.[23] By correlating macroscopic and microscopic tumor spread in the various subsites, we have shown how the surgeon can confidently plan a tailored resection without affecting survival outcomes and, at the same time, ensure good functional results even when facing advanced LSCC according to what other authors have called a "modular approach."[20]

Thyroid cartilage involvement remains a major pitfall in LSCC staging.[8,24] It is well known that MRI has more sensitivity (more false positives given focal ossification or the frequent peritumoral inflammation), whereas CT is more specific.[8] Nevertheless, and even with the most recent imaging techniques, distinguishing between cartilage invasion through the inner cortex (cT3) and full-thickness penetration (cT4a) remains difficult, and even in other published series positive predictive value does not exceed 74%.[25,26] CT shows high accuracy for cartilage penetration but only where a concomitant extralaryngeal diffusion is identified; on the other hand, CT is of little help when a tumor shows minimal signs of erosion or a similar density to the cartilage on contrast-enhanced sequences.[8] In case of recurrent LSCC, correct staging becomes even harder, and a recent study has proposed positron emission tomography as a useful tool to discriminate between rcT3 and rcT4a.[27] In addition, the categories of cT3 and cT4 LSCC do not consider the multiple patterns of invasion in both horizontal and vertical planes, which need to be analyzed in further studies.[28,29] Even though a transoral resection of thyroid shield is technically feasible, cartilage invasion poses a great risk in terms of radicality because of difficult exposure and the difficulty of frozen section evaluation.[15] It must be stressed, however, that there is some evidence that thyroid cartilage involvement could have no impact on overall or disease-specific survival.[30]

Our results of arytenoid cartilage invasion are in agreement with the classic study by Becker et al.,[31] who suggested computed tomographic criteria with sensitivity and specificity of 68% and 79% in case of isolated sclerosis;

still, it must be kept in mind that such asymmetric mineralization can be found in up to 12.9% of healthy subjects.[32] Such findings could be explained because, where no clear demarcation line is spotted, arytenoid sclerosis can be due to an inflammatory response, real ossification, or tumor invasion.[8] Despite slightly better results with MRI, both imaging techniques show low accuracy in case of chondronecrosis after radiotherapy.[8,32]

It is well known that clinical fixation of the true vocal fold portends a poor prognosis in terms of survival and organ preservation.[32,33] We have shown that a vocal fold with no motility is highly associated with an arytenoid invasion ($P = .028$). On the contrary, thyroarytenoid muscle invasion was historically considered the main cause of impaired movement, and some authors found a direct correlation between range of motion and proportion of the vocalis muscle involved.[34,35] Although it is possible that the invasion of the posterior paraglottic space can lead to motility reduction by affecting the lateral cricoarytenoid muscle, this was not apparent from our and others' series.[36] When it comes to cricoid and subglottis involvement, in agreement with the literature and mainly thanks to coronal plane sections, our results confirm good diagnostic accuracy.[8]

Recurrent LSCC after radiation therapy is notably a more aggressive and problematic disease.[36,37] Our results confirm that radiotherapy-recurrent tumor cells tend to spread more diffusely, thus representing a potential risk for salvage partial laryngectomies.[38-40] This behavior is confirmed by the higher pattern of invasion compared with primary LSCC; worst pattern of invasion is becoming a popular tool in head and neck pathology, particularly for oral cavity cancer, and future studies are needed to assess its prognostic role in LSCC.[12]

To the best of our knowledge, this is the first work to analyze the accuracy of endoscopic and radiologic staging for each subsite in primary and recurrent advanced LSCC. However, our study does have several limits: there is an obvious observation bias given that vocal-fold and arytenoid motility are subjective and based on a single examiner's judgment; another issue is the retrospective nature of this work, as radiologists were already aware of the fact that all patients had undergone TL. In terms of pathologic analysis, because of inadequate sampling, some of the subsites were unfortunately deemed not evaluable, thereby lowering the number of patients analyzed. Last, it is worth mentioning that none of the differently staged patients would have undergone different treatments, because of their poor systemic conditions and high related surgical risk, but this aspect needs further insights in future studies.

Conclusions

Staging and treating advanced LSCC remains a challenging task. Our comparative study has shown that up to 1 in 10 patients with advanced LSCC demonstrates a difference in terms of clinical versus pathologic extent. Among different subsites, we have confirmed that thyroid and arytenoid cartilage involvement represents the main diagnostic pitfalls and the major potential geographic miss during clinical staging. In addition, a distinction between vocal-cord and arytenoid motility does deserve independent consideration, and it should be addressed in the future revision of the TNM staging system. These points must be kept in mind by head and neck surgeons in order to offer the most radical yet conservative treatment for advanced laryngeal cancer.

Acknowledgments

This work was presented at the 12th Congress of the European Laryngological Society, London, United Kingdom, May 18, 2018, and it was a candidate for the Patrick Bradley Oncology Prize.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Luca Giovanni Locatello https://orcid.org/0000-0002-1879-5580
Michele Pietragalla https://orcid.org/0000-0003-4589-7109
Giuditta Mannelli https://orcid.org/0000-0001-7079-3964

References

1. PDQ Adult Treatment Editorial Board. PDQ Laryngeal Cancer Treatment. Bethesda, MD: National Cancer Institute. https://www.cancer.gov/types/head-and-neck/hp/laryngeal-treatment-pdq. Accessed February 1, 2018
2. Tamaki A, Miles BA, Lango M, Kowalski L, Zender CA. AHNS series: do you know your guidelines? Review of current knowledge on laryngeal cancer. *Head Neck*. 2018;40(1):170-181.
3. Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2014;140:855-860.
4. Pillsbury HR, Kirchner JA. Clinical vs histopathologic staging in laryngeal cancer. *Arch Otolaryngol*. 1979;105:157-159.
5. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
6. Mannelli G, Lazio MS, Luparello P, Gallo O. Conservative treatment for advanced T3-T4 laryngeal cancer: meta-analysis of key oncological outcomes. *Eur Arch Otorhinolaryngol*. 2018;275(1):27-38.
7. Forastiere AA, Ismaila N, Lewin JS, et al. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2018;36(11):1143-1169.

8. Baugnon KL, Beitler JJ. Pitfalls in the staging of cancer of the laryngeal squamous cell carcinoma. *Neuroimaging Clin*. 2013;23(1):81-105.
9. Stokes WA, Jones BL, Bhatia S, et al. A comparison of overall survival for patients with T4 larynx cancer treated with surgical versus organ-preservation approaches: A National Cancer Data Base analysis. *Cancer*. 2017;123(4):600-608.
10. Kirchner JA, Cornog JL Jr, Holmes RE. Transglottic cancer: its growth and spread within the larynx. *Arch Otolaryngol*. 1974;99:247-251.
11. Slootweg PJ. Complex head and neck specimens and neck dissections. How to handle them. *J Clin Pathol*. 2005;58(3): 243-248.
12. Brandwein-Gensler M, Smith RV, Wang B, et al. Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol*. 2010;34(5):676-688.
13. Shuman AG, Larkin K, Thomas D, et al. Patient reflections on decision making for laryngeal cancer treatment. *Otolaryngol Head Neck Surg*. 2017;156(2):299-304.
14. Britt CJ, Gourin CG. Contemporary management of advanced laryngeal cancer. *Laryngoscope Invest Otolaryngol*. 2017;2(5):307-309.
15. Peretti G, Piazza C, Mora F, Garofolo S, Guastini L. Reasonable limits for transoral laser microsurgery in laryngeal cancer. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24(2):135-139.
16. Succo G, Crosetti E, Bertolin A, et al. Treatment for T3 to T4a laryngeal cancer by open partial horizontal laryngectomies: prognostic impact of different pathologic tumor subcategories. *Head Neck*. 2018;40(9):1897-1908.
17. Marchi F, Piazza C, Ravanelli M, et al. Role of imaging in the follow-up of T2–T3 glottic cancer treated by transoral laser microsurgery. *Eur Arch Otorhinolaryngol*. 2017;274(10):3679-3686.
18. Peretti G, Piazza C, Penco S, et al. Transoral laser microsurgery as primary treatment for selected T3 glottic and supraglottic cancers. *Head Neck*. 2016;38(7):1107-1112.
19. Bozkurt G, Ünsal Ö, Çelebi İ, et al. Does CT help in predicting preepiglottic space invasion in laryngeal carcinoma? *Auris Nasus Larynx*. 2018;45(3):546-552.
20. Succo G, Crosetti E, Bertolin A, et al. Benefits and drawbacks of open partial horizontal laryngectomies, part B: intermediate and selected advanced stage laryngeal carcinoma. *Head Neck*. 2016;38(Suppl. 1):E649-E657.
21. Succo G, Peretti G, Piazza C, et al. Open partial horizontal laryngectomies: a proposal for classification by the working committee on nomenclature of the European Laryngological Society. *Eur Arch Otorhinolaryngol*. 2014;271(9):2489-2496.
22. US Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991;324(24):1685-1690.
23. Zbären P, Becker M, Läng H. Pretherapeutic staging of laryngeal carcinoma: clinical findings, computed tomography, and magnetic resonance imaging compared with histopathology. *Cancer*. 1996;77(7):1263-1273.
24. Dankbaar JW, Oosterbroek J, Jager EA, et al. Detection of cartilage invasion in laryngeal carcinoma with dynamic contrast-enhanced CT. *Laryngoscope Invest Otolaryngol*. 2017;2(6):373-379.
25. Beitler JJ, Muller S, Grist WJ, et al. Prognostic accuracy of computed tomography findings for patients with laryngeal cancer undergoing laryngectomy. *J Clin Oncol*. 2010;28(14):2318-2322.
26. Ryu IS, Lee JH, Roh JL, et al. Clinical implication of computed tomography findings in patients with locally advanced squamous cell carcinoma of the larynx and hypopharynx. *Eur Arch Otorhinolaryngol*. 2015;272(10):2939-2945.
27. Kendi AT, Corey A, Magliocca KR, et al. Is there a role for PET/CT parameters to differentiate thyroid cartilage invasion from penetration? *Eur J Radiol*. 2016;85:319-323.
28. Nakayama M, Brandenburg JH. Clinical underestimation of laryngeal cancer: predictive indicators. *Arch Otolaryngol Head Neck Surg*. 1993;119(9):950-957.
29. Serrano MG, Moreno MC, Hernández JG, Medina LO, Villares CM, Broto JP. Cartilage invasion patterns in laryngeal cancer. *Eur Arch Otorhinolaryngol*. 2016;273(7):1863-1869.
30. Koopmann M, Weiss D, Steiger M, Elges S, Rudack C, Stenner M. Thyroid cartilage invasion in laryngeal and hypopharyngeal squamous cell carcinoma treated with total laryngectomy. *Eur Arch Otorhinolaryngol*. 2016;273(11): 3789-3794.
31. Becker M, Zbaren P, Delavelle J, et al. Neoplastic invasion of the laryngeal cartilage: reassessment of criteria for diagnosis at CT. *Radiology*. 1997;203:521-532
32. Zan E, Yousem DM, Aygun N. Asymmetric mineralization of the arytenoid cartilages in patients without laryngeal cancer. *AJNR Am J Neuroradiol*. 2011;32(6):1113-1118.
33. Vilaseca I, Bernal-Sprekelsen M, Luis Blanch J. Transoral laser microsurgery for T3 laryngeal tumors: prognostic factors. *Head Neck*. 2010;32(7):929-938.
34. Kirchner JA, Som ML. Clinical significance of fixed vocal cord. *Laryngoscope*. 1971;81(7):1029-1044.
35. Hirano M, Kurita S, Matsuoka H, Tateishi M. Vocal fold fixation in laryngeal carcinomas. *Acta Otolaryngol*. 1991;111(2):449-454.
36. Agra IM, Ferlito A, Takes RP, et al. Diagnosis and treatment of recurrent laryngeal cancer following initial nonsurgical therapy. *Head Neck*. 2012;34(5):727-735.
37. Zbären P, Nuyens M, Curschmann J, Stauffer E. Histologic characteristics and tumor spread of recurrent glottic carcinoma: analysis on whole-organ sections and comparison with tumor spread of primary glottic carcinomas. *Head Neck*. 2007;29(1):26-32.
38. Deganello A, Gallo O, De Cesare JM, et al. Supracricoid partial laryngectomy as salvage surgery for radiation therapy failure. *Head Neck*. 2008;30(8):1064-1071.
39. Chen MM, Holsinger FC, Laccourreye O. Salvage conservation laryngeal surgery after radiation therapy failure. *Otolaryngol Clin North Am*. 2015;48(4):667-675.
40. Mortuaire G, Chevalier D, Mouawad F. Open partial laryngectomy after failure of (chemo) radiation: indications, oncologic and functional outcomes. *Curr Opin Otolaryngol Head Neck Surg*. 2017;25(2):159-162.