Clinical versus pathological staging in laryngectomized patients

Review Article

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Abstract

Aim: To assess the accuracy of clinical staging in laryngeal and hypopharyngeal cancer, as well as its impact on the choice of treatment and associated factors
Study Design: Retrospective.
Material and Methods: We reviewed patients who underwent total laryngectomy between 2013 and 2021.
Results: This study evaluated 54 patients, almost all were men with a mean age of 61 years. There was a discrepancy between clinical and pathological overall staging in 17 cases. There was greater accuracy in the diagnosis of invasion of the pre-epiglottic space, anterior commissure, cricoid cartilage, and contralateral and extra-laryngeal invasion, as opposed to invasion of the paraglottic space and thyroid cartilage.
Conclusions: The correct characterization of this tumor requires greater accuracy in the diagnostic evaluation of invasion of the paraglottic space and thyroid cartilage.

Keywords: Laryngeal cancer, total laryngectomy, clinical stage, pathological stage

Introduction

Cancer of the larynx is the third most common head and neck neoplasm and squamous cell carcinoma is the most frequent histological subtype.[1] About half of the cases are diagnosed in the advanced stages of the disease (III and IV), resulting in a 5-year disease-free survival rate of less than 50%.[2,3]

The TNM classification is thought to be reliable for the evaluation of tumor extension (T) and metastasis, both regional (N) and distant (M), and is considered essential for adequate therapeutic decision-making and prognostic assessment.[2] Pathological staging is the gold-standard; however, it involves the surgical removal of the larynx and neck lymph nodes.[1] Because of the effects of the disease and its treatment on swallowing, breathing, and speaking, there has been a paradigmatic

shift in the treatment of this type of tumors, focusing not only on survival but also on the functional outcomes and quality of life. Thus, the number of patients undergoing organ-preserving treatments has increased.[4] In these patients, because there is no surgical specimen, staging is solely clinical and based on the clinical and imaging findings.[1] Currently, there is no diagnostic method that evaluates with total precision the extension of the primary tumor or presence of regional metastases, which can lead to discordance between the clinical and pathological staging.[5] Although the anatomic preservation of the larynx does not equal its functioning, clinical overstaging is typically associated with worse functional outcomes (because of the loss of voice and presence of a definitive tracheostoma)[6], whereas understaging is associated with an increase in the recurrence and mortality rates.[1]

The objective of the present study was to evaluate the accuracy of clinical staging of the cancer of the larynx and hypopharynx, as well as its impact on the choice of treatment and associated factors.

Material and Methods

This retrospective cohort study evaluated patients who underwent total laryngectomy in the Department of Otorhinolaryngology of the *Centro Hospitalar Vila Nova de Gaia/Espinho* between January 1, 2013 and December 31, 2021. Only patients who had the histological subtype of squamous cell carcinoma were selected. Staging of cancer of the larynx and hypopharynx was based on the 8th edition of the TNM classification.

The medical records were reviewed and the following clinical variables were analyzed and grouped: a) demographic – age and sex, location of the primary tumor, adjuvant treatment, relapse, and death; b) clinical staging based on the combination of clinical and imaging findings; c) pathological staging and margins of the surgical specimen (analyzed by different pathologists of the Anatomic Pathology department); and d) difference between the clinical and pathological staging for the subcategories of T and N.

Differences between the categories of T and N and the final overall staging were only considered when there was a change in the category (but not in the subcategory). Downstaging occurred in cases in which the pathological stage was lower than the clinical stage, while upstaging occurred in cases in which the pathological stage was higher than the clinical stage.

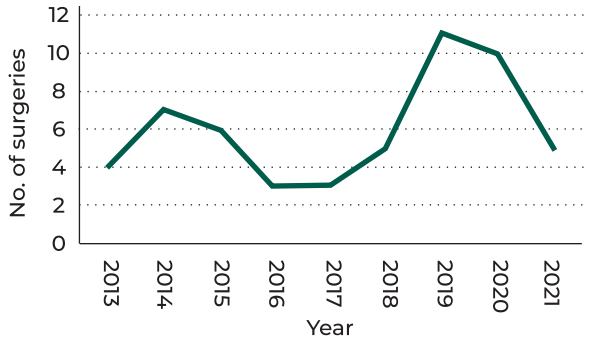
Data analysis was performed using the SPSS® software, version 27 .0. Discrete variables were expressed as frequencies and percentages and continuous variables as means and standard deviations (SD) in the case of normally distributed data, and medians and interquartile ranges in the case of a non-normal distribution. The chi-square test or Fisher's exact test were used to compare the categorical variables between the groups. Statistical significance was set at $p<0.05$.

Results

The median prevalence of total laryngectomy over the study period was five cases per year , with a peak in 2019 (Figure 1).

Over the study period, 54 patients underwent total laryngectomy along with bilateral neck lymph node dissection, of which 52 were men (96.3%) and two were women (3.7%); the age range was 40-87 years (mean age ± standard deviation [SD] 61.04±9.40 years). The primary tumor was supraglottic, glottic, and hypopharyngeal in 59.3%, 24.1%, and 16.6% of the cases, respectively. Positron emission tomography-computed tomography (PET-CT) was performed in approximately half of the cases (53.7%), and N positive (N+) clinical stage was more frequent among patients who underwent this examination. The patients were divided into four categories according to the overall staging (pathological): 66% of the patients were in stage IV, 24.1% were in stage III, 5.6% were in stage II, and 4.3% were in stage I. The margins of the surgical specimen were < 5 mm in eight cases. Adjuvant treatment with radiotherapy (RT) was necessary in 38 cases

Figure 1
Annual distribution of surgeries (total laryngectomies)



and 23 of these also received chemotherapy (CT). The patients with surgical margins < 5 mm underwent CTRT more often (p<0.001) and also had a higher rate of relapse (p=0.009) (Table 1). PET-CT, positron emission tomography-computed tomography.

There was a discrepancy between the final clinical and pathological staging in 17 cases (31.5%), which was not related to the tumor location (supraglottic [p=0.522], glottic [p=0.303], or hypopharyngeal [p=0.703]). Downstaging of the overall stage occurred in 10 cases, most often (6/10 patients) from stage IV to stage III, whereas upstaging occurred in seven cases (from stage III to stage IV in 6/7 patients). The change in final staging (downstaging and upstaging) was not associated with an increase in the rate of relapse (p=0.911 and p=0.859, respectively) or death (p=0.805 and p=0.775, respectively). There was a discordance regarding the T category in 35.1% (19/54) cases, with it being more often clinically overestimated, which was reflected in a higher percentage of cases of downstaging (68.4%; 13/19 cases) than of upstaging (31.6%; 6/19 cases). Discordance regarding the N category occurred in 44% (24/54) cases and it was more often clinically underestimated, resulting into a higher percentage of cases of upstaging (75%; 18/24 cases) than of downstaging (25%; 6/24 cases) (Table 2).

With regard to the T category, there was greater clinico-pathological agreement for the invasion of the preepiglottic space (p=0.017), anterior commissure (p=0.003), cricoid

Table 1
Characteristics of the patients undergoing total laryngectomy

Variable	Frequency	%
Sex		
Male	52	96,3%
Female	2	3,7%
Location of the primary tumor		
Supraglottic	32	59,3%
Glottic	13	24,1%
Hypopharyngeal	9	16,6%
Clinical stage (cT cN)		
cT2 cN0	2	3,7%
cT2 cN1	2	3,7%
cT3 cN0	17	31,5%
cT3 cN1	2	3,7%
cT3 cN2	7	12,9%
cT3 cN3	3	5,6%
cT4 cN0	7	12,9%
cT4 cN1	4	7,4%
cT4 cN2	10	18,6%
Pathological stage (pT pN)		
pT1 pN0	2	3,7%
pT1 pN1	1	1,9%
pT2 pN0	3	5,6%
pT2 pN3	2	3,7%
pT3 pN0	11	20,3%
pT3 pN1	1	1,9%
pT3 pN2	9	16,7%
pT3 pN3	4	7,4%
pT4 pN0	7	12,9%
pT4 pN1	2	3,7%
pT4 pN2	6	11,1%
pT4 pN3	6	11,1%
Overall stage (pathological)		
I	2	4,3%
II	3	5,6%
III	13	24,1%
IV	36	66%
PET-CT		
Yes	29	53,7%
No	25	46,3%
Surgical margin		
<5mm	8	14,8%
>5mm	46	85,2%
Complementary treatment	38	70,4%
Radiotherapy	15	39,5%
Chemotherapy + Radiotherapy	23	60,5%
Relapse		
Yes	17	31,5%
No	37	68,5%
Death		
Yes	18	33,3%
No	36	66,7%

cartilage (p=0.039), and contralateral (p=0.022) and extralaryngeal involvement (p=0.05), than for the invasion of the paraglottic space (only eight in 19 cases) and thyroid cartilage (six in 18 cases for the internal surface and 10 in 18 cases for the external surface). A complementary magnetic resonance imagin g (MRI) study was performed in five of the 19 patients. With regard to the invasion of the thyroid cartilage, the findings of CT-MRI were only consistent in two cases, increasing to four cases when assessing the MRI/pathology agreement (Table 3).

Patients with T category upstaging did not have narrow surgical margins (<5 mm) (p=0.575) or relapse (p=1.000) more frequently. Among the cases in which there was downstaging of the T category, after assessing the patients' comorbidities and characteristics, as well as the tumor characteristics, and based on the guidelines of the National Comprehensive Cancer Network, seven of the 13 patients were found to be eligible for organ-preserving treatment. Surgery was the proposed treatment for the remaining patients (Table 4).

With regard to the cases in which there was a change in the N category, clinico-imaging and clinico-pathological correlation were considered in the case of N0 or N+, and there was a clinico-imaging correlation in 15/24 cases (62.5%), especially in those who underwent a PET scan (p=0.02). The change in the N classification was not related to the tumor size (p=0.093) or side of the lymph nodes (p=0.317).

Table 2
Differences between the clinical and pathological staging

	Pathological T stage			
Clinical T stage	**T1**	**T2**	**T3**	**T4**
T1	-	-	-	-
T2	1	1	-	1
T3	2	3	19	5
T4	-	1	6	15
Downstage (n)	3	4	6	-
Upstage (n)	-	-	-	6

	Pathological N stage			
Clinical N stage	**N0**	**N1**	**N2**	**N3**
N0	19	1	6	1
N1	1	1	2	3
N2	3	2	7	5
N3	-	-	-	3
Downstage (n)	4	2	-	-
Upstage (n)	-	1	8	9

Table 3
Clinical-pathological agreement for different variables

Variable	Clinico-pathological agreement	p-value
Preepiglottic space	84,2% (16/19)	0,017
Paraglottic space	42,1% (8/19)	0,650
Anterior commissure	88,2% (15/17)	0,003
Posterior commissure	58,8% (10/17)	1,000
Subglottis	88,2% (15/17)	0,063
Internal surface of the thyroid cartilage	33,3% (6/18)	0,335
External surface of the thyroid cartilage	55,6% (10/18)	0,294
Cricoid cartilage	89,5% (17/19)	0,039
Arytenoid cartilages	66,7% (12/18)	0,326
Contralateral extension	83,3% (15/18)	0,022
Extralaryngeal extension	77,8% (14/18)	0,050

Table 4
Impact on the prognosis of patients with downstaging of the T category

Age	cT cN Stage	pT pN Stage	Karnofsky index	Conditions for conservative treatment	Location of the tumor	Tumor size (> measurement)	Invasion of the internal surface of the thyroid cartilage	Laryngeal mobility	Previous tracheostomy	Dysphagia	Proposed treatment
53	cT4cN0	pT3pN0	90%	Yes	Glottic	3,5 cm	Yes	Immobile	Yes	No	TL
80	cT4cN0	pT3pN0	80%	No	Supraglottic	2,4 cm	Yes	Immobile	Yes	Yes	TL
60	cT4cN0	pT3pN0	90%	Yes	Supraglottic	2 cm	No	Normal	No	No	Organ Preservation
51	cT4cN1	pT3pN0	80%	Yes	Supraglottic	3,6 cm	Yes	Normal	No	No	Organ Preservation
69	cT4cN2	pT3pN2	90%	No	Supraglottic	2,5 cm	Yes	Poorly mobile	No	No	TL
57	cT4cN2	pT3pN2	90%	Yes	Supraglottic	3,4 cm	No	Immobile	No	No	TL
62	cT3cN0	pT2N0	90%	Yes	Glottic	1,2 cm	No	Normal	No	No	Organ Preservation
57	cT3cN0	pT2N0	90%	Yes	Glottic	2 cm	Yes	Poorly mobile	No	No	Organ Preservation
61	cT3cN1	pT2N3	80%	Yes	Hypopharyn	3,5 cm	No	Normal	Yes	No	TL
56	cT3N0	pT2cN1	80%	Yes	Glottic	1,7 cm	No	Normal	No	No	Organ Preservation
75	cT4cN2	pT2pN3	70%	No	Supraglottic	3 cm	No	Normal	No	Yes	TL
46	cT3cN2	pT1pN0	80%	Yes	Supraglottic	4,5 cm	No	Normal	No	No	Organ Preservation
78	cT2cN1	pT1pN0	90%	Yes	Hypopharyn	2,6 cm	No	Normal	No	Yes	Organ Preservation

Discussion

In the present study, discrepancy between the clinical and pathological staging of cancer of the larynx and hypopharynx was frequently observed and was similar to that reported in the literature (between 18% and 50%); it was greater for the N category than for the T category.[1,5,7] In fact, approximately 20% of the patients who were clinically classified as N0 had positive lymph nodes (N+) in the pathological staging. Although the pN classification is usually the factor that best correlates with survival[5,7], in the present study, the change in the N classification did not have an impact on the overall outcomes.

The T component of the 8th edition of the TNM classification included T3 tumors that exhibit distinct patterns of invasion and behavior in the same category.[3] Tumors are classified as T3 when they are associated with vocal cord fixation or invade the pre-epiglottic space, paraglottic space, and/or the internal surface of the thyroid cartilage.[3] The preepiglottic and paraglottic spaces, both rich in adipose tissue, blood, and lymphatic vessels, are important routes for the submucosal dissemination of laryngeal carcinoma.[8] Invasion of the preepiglottic space occurs through the fenestrations in the epiglottic cartilage in the case of supraglottic tumors (especially those of the epiglottis), by upward dissemination from the anterior commissure (in glottic tumors), or by invasion of the paraglottic space in cases where there is no anatomic barrier/fibrous layer separating the two spaces.[8,9] In turn, the invasion of the paraglottic space can lead to tumor dissemination that may be posterior (cricoarytenoid joint, hypopharynx, and esophagus), downward (to the subglottis), anterior (to the extra-laryngeal tissues through the hiatus between the thyroid and cricoid cartilages), or, less frequently, upward (to the preeepiglottic space).[9] It is thus essential to identify tumor invasion in these

spaces, not only for assessing the prognosis but also for therapeutic purposes.[3,8] MRI has higher sensitivity than CT in the evaluation of the paraglottic space, although it can overestimate , especially in the presence of previous submucosal biopsies.[10,11] Unlike the findings of the present study, the accuracy of evaluation of paraglottic space invasion in the studies by Jaipuria[9] and Locatello[3] was 82% and 93.3%, respectively. With regard to invasion of the thyroid cartilage, differentiating between invasion and tumor penetration through its entire thickness remains difficult and the positive predictive value does not exceed 75%, unless there is clear extralaryngeal invasion, which occurred in 55% of our study sample.[2,3] Although only a small percentage of patients underwent MRI, the latter increased the diagnostic accuracy of evaluation of invasion of the thyroid cartilage in 50% cases, validating its usefulness for evaluating tumor invasion of the thyroid cartilage. In the present study, the diagnostic accuracy for invasion of the preepiglottic space, contralateral extension, and extralaryngeal extension was higher than 78%, similar to the result reported by Locatello et al.[3]

In the present study, clinical overstaging of T-category in patients who could have been candidates for organ-preserving treatment occurred in seven patients. Retrospectively, it is difficult to predict what the patient's status could have been and whether total laryngectomy could have been avoided, but these patients would probably have achieved good disease control and laryngeal function with a regimen of organ-preserving treatment. The decision regarding the treatment of locally advanced laryngeal cancer should be made by a multidisciplinary team and individualized; in addition, the risks and benefits of the different treatment approaches should be considered, both surgical and non-surgical.[4,12] In the T4N0 or T4N+ stages, the rate of disease-free survival was reportedly higher after total laryngectomy than after organ-preserving treatment strategies.[4,12] However, in some T3N0 tumors, the two strategies resulted in similar rates of disease control.[4,12] In these patients, the choice of organ-preserving treatment strategies should be based on patient factors, such as age, occupation, comorbidities (including lung function), compliance, smoking and drinking abstinence, and tumor factors, including its size, location, and laryngeal function.[4,12] In fact, patients with lung disease, vocal cord fixation, gastrostomy and/or tracheostomy, and large tumors (supraglottic > 5.0 cm^3 or glottic > 2.5 cm^3) appear to have better outcomes when treated surgically.[4] Furthermore, factors associated with the healthcare system should be considered because regular follow-up is required to identify and treat complications associated with chemotherapy and radiotherapy (such as chronic aspiration, dysphagia, and dyspnea), as well as relapse or tumor persistence, which may require salvage surgery.[4,12] In the study by Sherman et al.,[13] the TALK score (T stage, serum albumin, drinking habits, Karnofsky index) was shown to be a good predictor for organ-preserving regimens as it correlates positively with disease control in the absence of tracheostomy and gastrostomy tube feeding.

The limitations of this study are that it was a retrospective study and the patients' clinical assessment was performed by different professionals (surgeons, radiologists, and pathologists). The decision regarding the patients' treatment was always made in a group consultation setting that included otorhinolaryngologists, radiologists, and oncologists.

Conclusion

If the clinical staging of laryngeal and hypopharyngeal cancer is inaccurate, it may lead to inadequate treatment and poor vital and functional outcomes. The correct characterization of this type of tumor, including its extension, requires an accurate diagnostic evaluation of the paraglottic space and thyroid cartilage. However, these conclusions are based on the results of an observational study with a small sample size and should be validated in a larger multicenter study.

Human and animal protection

The authors declare that the procedures followed in the study were according to the regulations established by the Ethics and Clinical Research Committee and according to the Helsinki declaration of the World Medical Association.

Data confidentiality

The authors declare that they followed the protocols in use at their working center regarding the publication of the patients' data.

Conflict of Interest

The authors declare no conflict of interest regarding this article.

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