



Time between Diagnosis and Treatment of Hypopharynx and Larynx Cancer: Are Longer Delays Associated with Higher Discrepancy between Clinical and Pathological Staging?

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Abstract

Introduction At the time of diagnosis, treatment strategies for cancer are largely based upon clinical staging. However, discrepancy between clinical and pathological staging has been reported.

Objective To assess the rate of staging discrepancy in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma (LHSCC), the potential influence of higher interval of time from diagnosis to primary surgical treatment, and whether this has any impact on survival outcomes.

Methods Retrospective study of patients with LHSCC proposed for primary surgical treatment.

Results The study population included 125 Caucasian patients with LHSCC. The level of agreement between clinical and pathological tumor staging was moderate (Cohen's Kappa: 0.400; $p < 0.001$) and similar result was found for node staging (Cohen' Kappa: 0.520; $p < 0.001$). The mean time between diagnosis and surgical treatment was 26.66 days and no statistically significant influence was found with staging discrepancy. The sample presented a 5-year Overall Survival (OS) of 58.2% and a Disease-specific survival (DSS) of 72.6%. No statistically significant impact of staging discrepancy on survival was found.

Conclusion For advanced LHSCC, based on the findings of physical examination, endoscopy and imaging, is possible to achieve a moderate accuracy between clinical and pathological staging which allows a reliable counselling and treatment planning. Interval of time under 3–4 weeks between diagnosis and surgical treatment does not influence the rate of discrepancy. However, almost 30% of staging discrepancy is expected due to false negatives of imaging and limitations of physical exams.

Keywords

- ▶ survival
- ▶ laryngeal cancer
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- ▶ cancer staging

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Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for ~6% of all cancers worldwide, and most patients present with locally advanced diseases.¹ For locally advanced resectable laryngeal and hypopharyngeal squamous cell carcinoma (LHSCC), organ-preservation strategies using combined chemotherapy and radiotherapy as induction, concurrent, sequential, or alternating therapies have been studied in recent decades.²⁻⁶ In more advanced LHSCC with cartilage invasion, extralaryngeal soft tissue invasion, or high-volume tumor, primary surgery with postoperative adjuvant therapy has remained the recommended therapy.⁴⁻⁸ Thus, for patient counselling, treatment planning and prognostication, an accurate clinical staging is important.

The Tumor, Node, Metastasis (TNM) classification is considered to be the most reliable system defining the extent of the primary tumor and its regional and distant metastases.⁹ Clinical TMN (cTMN) classification is based on the findings of physical examination, endoscopy and imaging. To determine pathological TMN (pTMN), a detailed histopathological analysis of surgically removed tissue is necessary.¹⁰ At the time of diagnosis, treatment strategies are largely based upon clinical staging.¹¹ However, in HNSCC, discrepancy between clinical and pathological staging has been reported.¹¹ To our knowledge, the rate at which overall staging discrepancy occurs in LHSCC and if it is influenced by the interval of time from diagnosis to treatment have not been addressed. We therefore performed a retrospective cohort study to assess the rate of staging discrepancy, the potential influence of higher interval of time from diagnosis to treatment and whether this has any impact on survival outcomes.

Materials and Methods

Patients

We obtained an information database containing 211 patients with hypopharynx and/or larynx carcinoma diagnosed and treated in the otolaryngology department of an oncological tertiary center between 2012 and 2016. Approval of the Medical Ethics Committee was obtained (CES.155/015). This database was refined to include solely patients with a primary diagnosis of hypopharynx or larynx carcinoma proposed by the Head and Neck Interdisciplinary Tumor Board for primary surgical treatment (laryngectomy or pharyngolaryngectomy and neck dissection). Therefore, pathological staging information could be obtained.

The number of institutional affiliation, age, gender, tobacco and alcohol abuse, histopathologic tumor classification according to the WHO International Classification of Diseases for Oncology (ICD-0-3), tumor localization, cTNM and pTMN classification were registered (► **Table 1**).

Clinical preoperative Node (N) classification was determined by neck palpation and by computed tomography (CT) and/or magnetic resonance imaging (MRI), supplemented by a positron emission tomography (PET) in advanced or suspected locoregional disease. A clinical positive neck (cN+) indicates the presence of metastatic nodal disease, and

Table 1 Demographic characteristics of the study population

	Total Sample (%)
Age (years old), mean (standard deviation)	60.6 (9.1)
Gender	
Male	121 (96.8)
Female	4 (3.2)
Tobacco	
Never smoker	4 (3.2)
Quit	21 (16.8)
Current smoker	100 (80.0)
Alcohol	
No drinking habits	37 (29.6)
Quit heavy consumption	3 (2.4)
Heavy consumption	85 (68.0)
Primary location of the tumor	
Hypopharynx	52 (41.6)
Larynx	73 (58.4)
Supraglottic	23 (18.4)
Glottis	50 (40.0)
Subglottis	0 (0.0)

clinical negative neck (cN0) indicates the absence of any of these findings. When postoperative histology proved nodal metastases, the neck was classified as pathological positive neck (pN+), and the opposite were classified as pathological negative necks (pN0).

Overall clinical and pathological TNM staging was compared and tabulated to determine upstaging, downstaging or cases in which no stage discrepancy occurred (► **Tables 2-7**).

The database was cross-referenced to patient charts or electronic medical records to verify the integrity of the data, particularly for information involving staging, treatment, follow-up period (FU) and last known alive dates.

Time between Diagnosis and Treatment

It was considered the number of days from the first multidisciplinary decision (FMD), by the Head and Neck Interdisciplinary Tumor Board, and the date of primary surgical treatment.

Survival Outcome

During the FU, patients were considered as being alive with and without oncologic disease; dead with local, regional or distant disease; dead without oncologic disease; and finally, lost to FU. The cutoff point for statistical analysis was August 2018, encompassing a minimum FU of 24 months.

For overall survival (OS), the FU was considered as the time between diagnosis and death with or without disease (event of interest). Patients alive with disease, patients alive without disease and patients lost to follow-up were excluded.

Table 2 Accuracy between clinical and pathological tumor staging. All patients ($n = 125$)

	All (%)					Stage discrepancy		
	pT1	pT2	pT3	pT4	Total	Upstaged	Unchanged	Downstaged
cT1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
cT2	0 (0.0)	2 (25.0)	3 (37.5)	3 (37.5)	8	6 (75.0)	2 (25.0)	0 (0.0)
cT3	0 (0.0)	0 (0.0)	22 (46.8)	25 (53.2)	47	25 (53.2)	22 (46.8)	0 (0.0)
cT4	1 (1.4)	0 (0.0)	5 (7.2)	63 (91.3)	69	–	63 (91.3)	6 (8.7)
Total	1(0.8)	3(2.4)	30(24.0)	91(72.8)	125	32(25.6)	87(69.6)	6(4.8)

Cohen Kappa: 0.400 ($p < 0.001$).

Table 3 Accuracy between clinical and pathological tumor staging. Hypopharynx patients ($n = 52$)

	Hypopharynx					Stage discrepancy		
	pT1	pT2	pT3	pT4	Total	Upstaged	Unchanged	Downstaged
cT1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1	1 (100.0)	0 (0.0)	–
cT2	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0 (0.0)
cT3	0 (0.0)	0 (0.0)	10 (66.7)	5 (33.3)	15	5 (33.3)	10 (66.7)	0 (0.0)
cT4	1 (2.9)	0 (0.0)	3 (8.6)	31 (88.6)	35	–	31 (88.6)	4 (11.4)
Total	1(1.9)	2(3.9)	13(25.0)	36(69.2)	52	6(11.5)	42(80.8)	4(7.7)

Cohen Kappa: 0.583 ($p < 0.001$).

Table 4 Accuracy between clinical and pathological tumor staging. Larynx patients ($n = 73$)

	Larynx					Stage discrepancy		
	pT1	pT2	pT3	pT4	Total	Upstaged	Unchanged	Downstaged
cT1	–	–	–	–	–	–	–	–
cT2	–	1 (14.3)	3 (42.9)	3 (42.9)	7	6 (85.7)	1 (14.3)	–
cT3	–	0 (0.0)	12 (37.5)	20 (62.5)	32	20 (62.5)	12 (37.5)	0 (0.0)
cT4	–	0 (0.0)	2 (5.9)	32 (94.1)	34	–	32 (94.1)	2 (5.9)
Total	–	1(1.4)	17(23.3)	55(75.3)	73	26(35.7)	45(61.6)	2(2.7)

Cohen Kappa: 0.297 ($p = 0.001$).

Table 5 Accuracy between clinical and pathological nodal staging. All patients ($n = 125$)

	All (%)					Stage discrepancy		
	pN0	pN1	pN2	pN3	Total	Upstaged	Unchanged	Downstaged
cN0	36 (65.5)	10 (18.2)	9 (16.4)	0 (0.0)	55	19 (34.5)	36 (65.5)	–
cN1	1 (5.9)	7 (41.2)	9 (52.9)	0 (0.0)	17	9 (52.9)	7 (41.2)	1 (5.9)
cN2	2 (3.9)	1 (2.0)	41 (80.4)	7 (13.7)	51	7 (13.7)	41 (80.4)	3 (5.9)
cN3	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	2	–	2 (100.0)	0 (0.0)
Total	39(31.2)	18(14.4)	59(47.2)	9(7.2)	125	35(28.0)	86(68.8)	4(3.2)

Cohen Kappa: 0.520 ($p < 0.001$).

For disease-specific survival (DSS), the FU was considered as the time between diagnosis and death with disease (event of interest). Patients alive with disease, patients alive without disease, patients that died without disease and patients lost to follow-up were excluded.

Statistical Analysis

A descriptive analysis of the characteristics of the patients was performed considering absolute and relative frequencies

(for categorical variables) and mean and standard deviation (SD) (for continuous variables).

To assess the accuracy between clinical and pathological staging, the Cohen Kappa coefficient was estimated.

Overall survival and DSS curves were calculated using the Kaplan-Meier method, and statistical significance was determined by the Log-Rank test.

Evaluation of time between diagnosis and surgery according to staging discrepancy (factors Tumor [T]; Node [N]) was

Table 6 Accuracy between clinical and pathological nodal staging. Hypopharynx patients ($n = 52$)

	Hypopharynx					Stage discrepancy		
	pN0	pN1	pN2	pN3	Total	Upstaged	Unchanged	Downstaged
cN0	2 (28.6)	1 (14.3)	4 (57.1)	0 (0.0)	7	5 (71.4)	2 (28.6)	–
cN1	1 (14.3)	0 (0.0)	6 (85.7)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)
cN2	1 (2.8)	0 (0.0)	29 (80.6)	6 (16.7)	36	6 (16.7)	29 (80.6)	1 (2.8)
cN3	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	2	–	2 (100.0)	0 (0.0)
Total	4(7.7)	1(1.9)	39(75.0)	8(15.4)	52	17(32.7)	33(63.5)	2(3.8)

Cohen Kappa: 0.209 ($p = 0.011$).

Table 7 Accuracy between clinical and pathological nodal staging. Larynx patients ($n = 73$)

	Larynx					Stage discrepancy		
	pN0	pN1	pN2	pN3	Total	Upstaged	Unchanged	Downstaged
cN0	34 (70.8)	9 (18.8)	5 (10.4)	0 (0.0)	48	14 (29.2)	34 (70.8)	–
cN1	0 (0.0)	7 (70.0)	3 (30.0)	0 (0.0)	10	3 (30.0)	7 (70.0)	0 (0.0)
cN2	1 (6.7)	1 (6.7)	12 (80.0)	1 (6.7)	15	1 (6.7)	12 (80.0)	2 (13.3)
cN3	–	–	–	–	–	–	–	–
Total	35(47.9)	17(23.3)	20(27.4)	1(1.4)	73	18(24.6)	53(72.6)	2(2.8)

Cohen Kappa: 0.541 ($p < 0.001$).

performed considering the Mann-Whitney test (non-normal distribution was found for the variable time).

All of the analysis were performed in the software IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY, USA), and p -values < 0.05 were considered statistically significant.

Results

The study population included a total of 125 Caucasian patients (121 males; 4 females) with LHSCC, and the mean age at diagnosis was 60.6 years old (range: 43–83 years old) (► **Table 1**).

Accuracy between Clinical and Pathological Staging

Almost 93.0% of the patients ($n = 116$) presented a clinical local advanced disease (cT3T4), and 56.0% of the patients ($n = 70$) presented palpable nodal extension (cN+).

For each patient with an assigned clinical stage, the corresponding pathological stage is summarized in ► **Tables 2–7**, as well as the rate of upstaging, downstaging or cases equally staged. The discrepancy between clinical and pathological classification was 30.4% and 31.2%, respectively, for tumor and node staging. The highest congruence between clinical and pathological staging was seen for tumor clinical stage 4 and node clinical stage 3.

The level of agreement between clinical and pathological tumor staging was moderate for hypopharynx patients (Cohen Kappa: 0.583; $p < 0.001$) and slight for larynx patients (Cohen Kappa: 0.297; $p = 0.001$). Among patients with larynx tumor, the highest discrepancy was registered from clinical T2 for pathological T3 (► **Table 4**).

The level of agreement between clinical and pathological node staging was moderate for larynx patients (Cohen Kappa: 0.541; $p < 0.001$) and slight for hypopharynx patients (Cohen kappa: 0.209; $p = 0.011$). Among patients with hypopharynx tumor, the highest discrepancy was registered from clinical N1 for pathological N2 (► **Table 6**).

Staging Discrepancy and Time between Diagnosis and Surgical Treatment

The mean time between diagnosis and surgical treatment was 26.66 days (± 18.64 standard deviation [SD]). To evaluate a potential influence of this interval on staging discrepancy, two separate analyses were made: one for tumor staging and another for node staging.

Regarding tumor staging, 2 groups were compared: Group 0 (cT = pT; $n = 87$) and Group 1 (cT \neq pT; $n = 38$). No statistically significant difference was found in the time between diagnosis and surgical treatment among both groups ($p = 0.524$).

Regarding node staging, 2 groups were compared: Group 0 (cN = pN; $n = 86$) and Group 1 (cN \neq pN; $n = 39$). No statistically significant difference was found in the time between diagnosis and surgical treatment among both groups ($p = 0.697$).

Survival Outcomes

The sample presented a 5-year OS of 58.2% and a DSS of 72.6%.

The hypopharynx group presented a 5-year OS of 47.3%, and the larynx group presented a 5-year OS of 65.9%. No significant differences between groups were found (log-rank test $p = 0.150$).

The hypopharynx group presented a 5-year DSS of 62.9%, and the larynx group presented a 5-year DSS of 79.6%. No

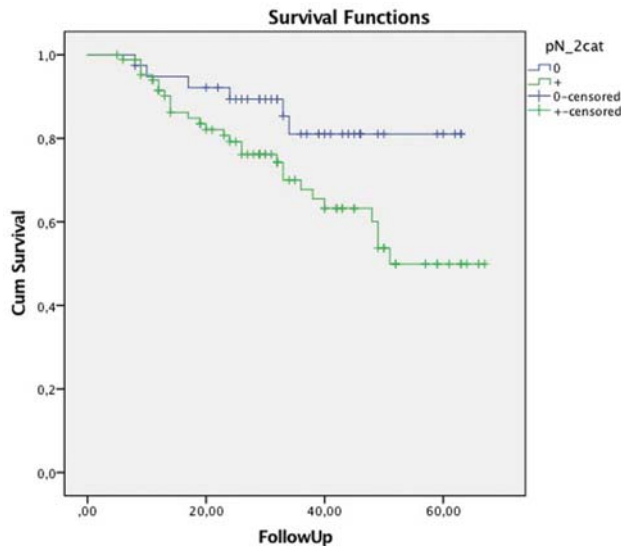


Fig. 1 Overall Survival Kaplan-Meier curves for pN0 and pN+ (log-rank $p = 0.042$).

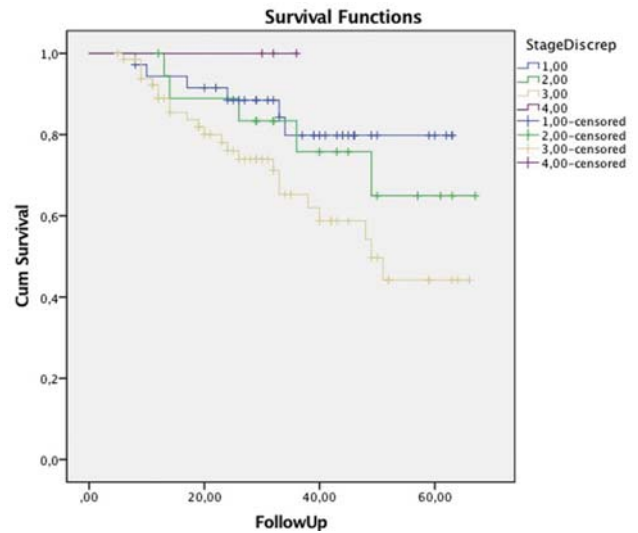


Fig. 3 Overall survival Kaplan-Meier curves according to nodal stage discrepancy (log-rank test $p = 0.094$).

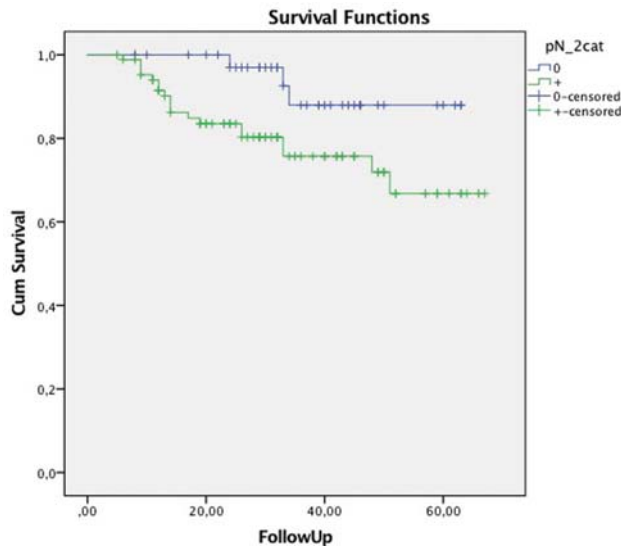


Fig. 2 Disease specific survival Kaplan-Meier curves for pN0 and pN+ (log-rank $p = 0.042$).

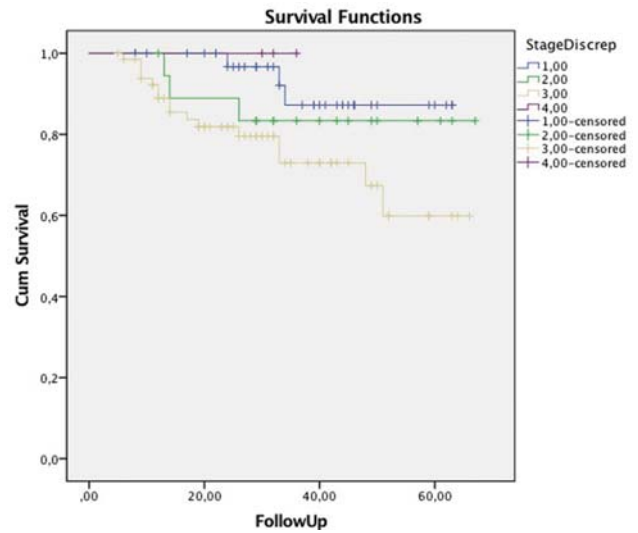


Fig. 4 Disease-specific survival Kaplan-Meier curves according to nodal stage discrepancy (log-rank test $p = 0.113$).

significant differences between groups were found (log-rank test $p = 0.118$).

The number of deaths in pT1 ($n = 0$) and pT2 ($n = 1$) groups was too small for survival analysis. The pT3 group presented a 5-year OS of 63.3% and DSS of 68.5%. The pT4 group presented a 5-year OS of 56.9% and DSS of 76.3%. No significant difference was found between OS or DSS among pT3 and pT4 ($p > 0.05$).

The pN0 group presented a 5-year OS of 81.0% and DSS of 87.9%. The pN+ group presented a 5-year OS of 49.9% and DSS of 66.8% (log-rank $p = 0.042$ for OS and log-rank $p = 0.042$ for DSS) (► Fig. 1 and 2).

Impact of Staging Discrepancy on Survival

Given the significant differences in OS and DSS between pN0 and pN+, we compared survival between these groups as a

function of staging discrepancy. Thus, OS and DSS function were calculated taking into account 4 groups: Group 1: clinical negative neck patients with no pathological stage change ($n = 36$; number of deaths = 6); Group 2: clinical negative neck patients upstaged to positive nodal disease ($n = 19$; number of deaths = 5); Group 3: clinical positive neck patients with pathological positive neck ($n = 67$; number of deaths = 23) and Group 4: clinical positive neck patients downstaged to negative nodal disease ($n = 3$; number of deaths = 0).

The 5-year OS was 79.8%, 64.9% and 44.2%, respectively, for Groups 1, 2 and 3. No differences between groups were found (log-rank test $p = 0.094$) (► Fig. 3).

The 5-year DSS was 87.2%, 83.3% and 59.9%, respectively, for Groups 1, 2 and 3. No differences between groups were found (log-rank test $p = 0.113$) (► Fig. 4).

Discussion

The clinical and demographic characteristics of the present study correlate with other series regarding the age of presentation, male predominance, as well as high tobacco and alcohol consumption.¹² However, a more advanced local (cT3T4) and regional (cN+) disease at diagnosis was presented in this cohort, probably because only patients that underwent primary laryngectomy or pharyngolaryngectomy with neck dissection were included.

The first aim of the present study was to access the accuracy between clinical and pathological staging in LHSCC and **a slight to moderate level of agreement for both** was found. A possible reason for this finding is that all the physical examinations were performed by senior ENT surgeons, all them with differentiation in head and neck oncology, supplemented by imaging exams of high resolution, such as CT or MRI. However, it was identified a disparity between clinical and pathological classification of 30.4% and 31.2%, respectively, for tumor and node staging. This values correlate with other series regarding laryngeal cancer patients and might be explained by the limitations associated to the physical exam as well as the number of false negative results of imaging exams.⁹ Physical examination details such as measurement of tumor and node size and manual palpation are relatively inaccurate.¹¹ The lower limit of node palpation has been shown to be 0.5cm in superficial areas and 1cm in deeper regions.¹³ The use of CT scanning does significantly improve the accuracy of staging; however, it does not detect micrometastasis.^{13,14} Therefore, microscopic deposits and extracapsular spread may not be clinically identified and can only be definitively assessed by neck dissection with pathological examination.¹¹ Nowadays, there is no imaging technique which would show 100% accuracy in detecting lymph node metastases.⁹ Clinical examination, including the newest imaging modalities, gives false negative results in ~ between 20 and 30% of the cases, which corroborates the rate of discrepancy found in the present study.^{15,16}

The secondary purpose of the present paper was to determine if the interval of time between diagnosis and primary surgical treatment influences the rate of discrepancy between clinical and pathological staging. The mean time was 26.66 days and no statistically significant difference was found between higher intervals of time and higher rate of discrepancy. Further studies are needed to access potential time intervals that could serve as a cutoff reference. According to our results, an interval of time until between 3 and 4 weeks has no influence in the discrepancy between clinical and pathological staging of **advanced** LHSCC.

Another purpose of the present study was to determine survival outcomes. While different T stage, among advanced T stage tumors, did not influence survival outcomes, the existence of pN+ was associated with significantly shorter OS and DSS. The prognostic impact of nodal stage is well documented in the literature. Upstaging from cN0 to pN+ has a negative impact on OS, decreasing the 5-year survival rates

to nearly one-half.¹² A statistical significance on OS and DSS was found in the present sample, in accordance with the literature, providing that survival was reduced to a half in pN+ despite appropriate postoperative radiation or chemoradiation. The poorest survival rate was observed in cN0/pN+ and cN+/pN+ patients with a 5-year OS of 64.9% and 44.2%, respectively, which is in accordance with other series.^{3,12,17,18} In our study, survival outcomes were not influenced by discrepancies between clinical and pathological staging, provably, due to slight staging differences. Most of the upstaging cases were cT3 to pT4 and cN1 to cN2. In the current literature, only a limited number of studies focuses on the accuracy of cTNM and pTMN staging in HNSCC.⁹ Koch et al¹⁹ compared cTMN and pTMN classifications in a large group of 501 patients with HNSCC. A disparity between cTMN and pTMN staging was proven in almost 50% of the cases. According to the author, both cTMN and pTMN classifications showed a strong association between the stage and overall survival. However, the authors did not evaluate site-specific HNSCC individually and there is also no correlation of a disparity in clinical (c) and pathological (p) staging with DSS.

The present study has some limitations. First of all, it is a retrospective study and some patients exhibited a small FU that had conditioned the calculation of 5-year survival rates. Second of all, histopathological analysis was not always performed by the same pathologist. Third, the conclusions of the present study might change if the study population size was expanded. Nevertheless, to our knowledge, this is the first explorative study that accesses the accuracy between clinical and pathological staging of LHSCC, taking into account survival outcomes and potential influence of the interval of time between diagnosis and primary surgical treatment that allowed an adequate pathological staging. Our study population included an adequate ratio of hypopharyngeal/laryngeal tumors, and data was collected from one single institution with uniform processing and reporting protocols, which highlight the reliability of our results. In further studies, it would be interesting to evaluate the prognosis taking into account the specific subsite of the tumor within hypopharynx and larynx patients. We will continue to evaluate staging discrepancies, survival outcomes and potential influencing factors by increasing the sample size and time of follow-up to increase the power of the findings of the present study.

Conclusion

For advanced LHSCC, based on the findings of physical examination, endoscopy and imaging, it is possible to achieve a moderate accuracy between clinical and pathological staging, which allows a reliable counselling and treatment planning. An interval of time under between 3 and 4 weeks between diagnosis and surgical treatment does not influence the rate of discrepancy. However, almost 30% of staging discrepancy is expected due to false negatives of imaging and limitations of physical examinations.

Compliance with Ethical Standards

Ethical approval: All of the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the present study.

Financial Disclosure

The authors declare that they have no financial disclosure to declare.

Conflict of Interests

The authors declare that there are no conflict of interests.

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