

## Similarities and Differences Between cTNM and pTNM

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### ABSTRACT

**AIM:** TNM staging system aims to classify tumour extension in a uniform, simple, homogenous and reproducible manner. The objective of this study is to evaluate the correlation between the cTNM pTNM and in tumors of the larynx and hypopharynx and the prognostic impact of the subdivision of T4 tumors in T4a and T4b in these locations.

**METHODS:** A retrospective study involving 144 patients undergoing total laryngectomy or pharyngolaryngectomy associated with cervical lymph node dissection treated in the Oporto Oncologic Institute (IPOP-EPE) between 2007 and 2011.

**RESULTS:** 81 patients were staged as cT3, of which 49 (60.5%) were restaged as pT4. 63 patients were staged as cT4 of which 7 (11.1%) were restaged as cT3. 80 patients were staged as cN0, of which 32 (40%) had metastatic cervical nodes upon pathological examination. 64 patients were staged as cN+, of which 4 (6.2%) did not have metastases upon pathological examination. We discuss the current TNM staging model compared to the previous staging systems.

**DISCUSSION:** This article compares the various categories in the TNM system in an attempt to understand the main difficulties in larynx/hypopharynx cancer staging.

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**Key words:** Laryngeal Neoplasms; Hypopharyngeal Neoplasms; Neoplasm Staging

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### INTRODUCTION

Laryngeal tumours represent 25% of malignant tumours of the head and neck. About 95% of larynx/hypopharynx tumours are squamous cell carcinomas<sup>[1,2]</sup>.

Between 1943 and 1952, Pierre Denoix began the development of the TNM system at the Institute Gustave-Roussy in Paris and in 1953 he proposed his concept to the Union Internationale Contre le Cancer (UICC) and these parameters were formally integrated into a TNM staging system. AJCC and UICC versions were unified in 1987 and, since then, the two entities have collaborated in updating the TNM system. TNM staging system allows a uniform classification of head and neck tumours, and is utilized to evaluate the extent of disease, select treatment options, define patients prognoses, facilitate the exchange of information between clinicians and researchers and support the evaluation of different treatment outcomes.

TNM system staging aims to classify the extent of each tumour in a simple and reproducible manner, taking into account three variables: the extent of the primary tumour (T) the presence or absence of metastatic cervical lymph nodes (N), the presence or absence of distant metastases (M). The various possible combinations are further grouped into TNM stages from I to IV.

TNM system has undergone successive revisions since the first edition. The latest version is the 7<sup>th</sup>, created in 2009 for implementation in 2010. With regard to the changes undergone in recent issues, specifically in respect to cancers of the larynx and hypopharynx, changes between the 5<sup>th</sup> (1997) and the 6<sup>th</sup> (2002) editions focused on the subdivision of T4 tumours into T4a (resectable) and T4b (unresectable) and on changes relating to the subdivision by stage, with T4b tumours (regardless of nodal staging) newly included in stage IVb. In the 7<sup>th</sup> edition the terms resectable/unresectable, as applied to T4, were abandoned, with T4a and T4b now applied to moderately advanced and very advanced disease, respectively.

In the staging of patients with tumours of the larynx/hypopharynx, clinical and endoscopic evaluations have obvious limitations in terms of assessing the extent of the disease, namely with regard to disease extension to the thyroid cartilage and extralaryngeal structures; imaging modalities, namely CT (Computed Axial Tomography) allows for a more objective assessment of tumour extension and nodal involvement<sup>[3,4,5]</sup>.

Staging of the primary lesion, coupled with the presence or absence of nodal neck metastases, is important in the selection of treatment options and assessing the prognosis of patients with larynx and hypopharynx tumours<sup>[6]</sup>.

The objective of this study is to evaluate the correlation between the cTNM pTNM and the prognostic impact of the subdivision of T4 tumors T4a and T4b in tumors of the larynx and hypopharynx

## METHODS

We conducted a retrospective study that included a total of 144 patients who underwent total laryngectomy or pharyngolaryngectomy associated with cervical lymph node dissection treated at IPOP-EPE between January 1<sup>st</sup> 2007 to December 31<sup>st</sup> 2011. All patients were classified according to the latest 2010 version of the AJCC and UICC TNM system, although the majority had been previously classified according to the 1997 version.

Fourteen patients who had undergone previous treatment with chemotherapy or chemo/radiotherapy were excluded from the study. Another 5 patients were also excluded because of insufficient data in their clinical processes.

cTNM staging was based on physical examination and CT of the neck, and pTNM staging was based on histopathological analysis of surgical neck dissection specimens.

Statistical analysis was performed using SPSS 20.0 (SPSS Inc. Chicago, IL). We calculated the kappa coefficient for the level of agreement between cTNM and pTNM beyond that expected by chance. Specificity, sensitivity, positive and negative predictive values were calculated assuming the histopathological records as gold standard. Statistical analysis was performed using Chi Square ( $\chi^2$ ) and Mann-Whitney tests. Curves for overall survival and disease-free survival were calculated using the Kaplan-Meier method and statistical significance was determined by log-Rank test. Multivariate analysis was performed by Cox regression. Results were considered statistically significant when  $p < 0.05$ .

## RESULTS

Out of a total of 144 patients included in the study, 140 (97.2%) were male and 4 (2.8%) female, with a mean age of 59.0 years. 109 patients (75.7%) had laryngeal tumours, 26 (18.1%) pharyngolaryngeal disease and 9 patients (6.2%) had disease localized in the hypopharynx.

The mean interval between the onset of complaints and diagnosis was 6.3 months, the mean interval between diagnosis and surgery was 2.3 months and the mean interval time between surgery and complementary treatment was 2.1 months.

97 (67.4%) patients underwent total laryngectomy and 47 (32.6%) total pharyngolaryngectomy, both associated with cervical lymph node dissection.

72 (50.0%) patients underwent additional chemoradiotherapy and 37 (25.7%) only radiotherapy. 35 patients did not undergo any additional treatment modality (24.3%).

140 patients (97.2%) had squamous cell carcinomas and the remaining 4 patients had other histological types (1

lymphoepithelioma, 1 spindle cell carcinoma, 1 leiomyosarcoma and 1 adenoid cystic carcinoma).

At the time of analysis (February 2013) 95 patients (66.0%) were alive and 48 (34%) had died.

81 patients were initially staged as cT3 and 63 as cT4. Following surgery, 39 patients were staged as pT3 and 105 as pT4.

Of the 81 patients staged as cT3, 49 (60.5%) were restaged as pT4. 63 patients were staged as cT4, 7 (11.1%) of which were restaged as cT3 (Table 1).

Out of the 105 pT4 patients, CT scans showed no cartilage or extra-laryngeal invasion in 49 (46.7%), from which we may infer that this exam modality showed a sensitivity of 53.3%, specificity of 82% and positive and negative predictive values of 88.9% and 39.5%, respectively, for T4 larynx and hypopharynx tumours.

The kappa coefficient for the clinical and pathological tumour staging (T) was 0.26 ( $p < 0.05$ ).

With respect to cervical lymph node staging, 80 patients were staged as cN0 and 64 as cN+. Following surgery, 52 patients were staged as pN0 and 92 as pN+.

Out of the 80 cN0 patients, 32 (40%) had lymph node metastasis after pathological examination. Out of the 64 patients staged as cN+, 4 patients (6.2%) had no metastases in cervical dissection specimens (Table 1).

**Table 1** Primary and Cervical lymph node Clinical and Pathological Staging.

	pT3	pT4	Total	pN0	pN+	Total	
cT3	32	49	81	cN0	48	32	80
cT4	7	56	63	cN+	4	60	64
<b>Total</b>	39	105	144	<b>Total</b>	52	92	144

The sensitivity and specificity of CT in detecting cervical metastases were 60.9% and 92.3% respectively. Positive and negative predictive values were 93.0% and 58.5% respectively.

The kappa coefficient for pathological and clinical lymph node staging (N) was 0.28 ( $p < 0.05$ ).

17 patients were classified as Stage III, 112 as Stage IVa and 15 as Stage IVb.

One year post- surgery, 97.4% of pT3, 76.3% of pT4, 85.9% of pT4a and 66.7% of pT4b patients were alive ( $p < 0.05$ ). 2 years after surgery 85.7% of pT3, 61.7% of pT4, 73.5% of pT4a and 50% of pT4b patients were still alive ( $p > 0.05$ ). 3 years post-surgery 74.2% of pT3, 42.3% of pT4, 59.7% of pT4a and 25.0% of pT4b were alive ( $p > 0.05$ ).

According to the prior classification of 1997, the estimated median overall survival was 47.7 months for pT3 and 39.5 months for pT4 tumours; regarding the division into pT4a and pT4b, the estimated median overall survival was 40.5 months for pT4a and 25.1 months for pT4b ( $p < 0.05$ ) (Table 2). It was impossible to calculate the survival rate at 5 years post-surgery due to the short follow-up time for some of these patients. The overall survival curve for this population of patients is displayed in figure 1.

Median disease-free survival was 28.4 months for pT3 and 20.5 months for pT4, according to the TNM classification of 1997. Regarding the latter classifications of 2002 and 2012, the pT4a

**Table 2** Overall Survival and Disease-free Survival.

	Overall Survival (months)		Disease-free Survival (months)	
	Mean	Median	Mean	Median
<b>T4a</b>	40.5	53.0	21.0	15.0
<b>T4b</b>	25.1	10.0	13.0	8.0
<b>All T4</b>	39.5	48.0	20.5	15.0

population had a median of 21.0 months and the pT4b a median of 13.0 months of disease-free survival ( $p>0.05$ ) (Table 2). It was impossible to calculate the disease-free survival at 5 years. The curve of disease-free survival is shown in figure 2.

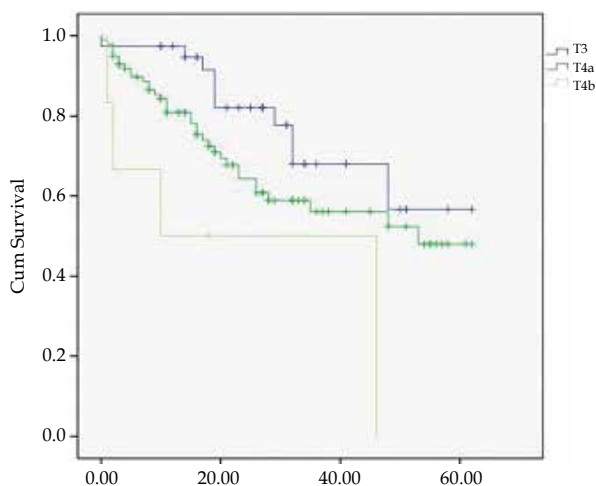


Figure 1 Overall survival curve.

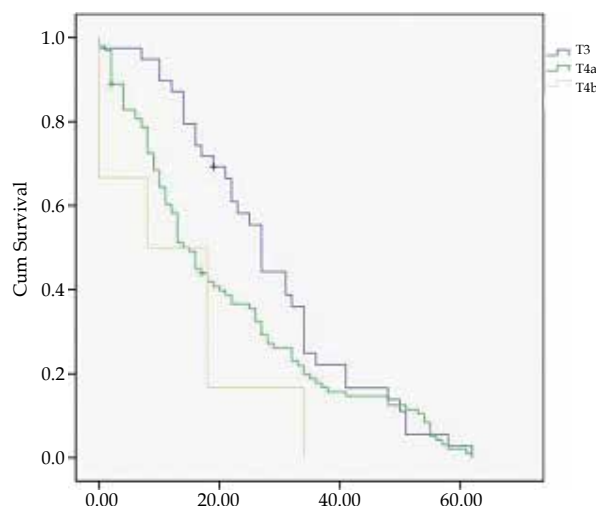


Figure 2 Disease-free survival curve.

Median overall survival was lower in patients with hypopharynx and pharyngolaryngeal tumours (28.1 months for pharyngolarynx tumours vs 36.7 months for hypopharynx, vs 45.0 months for larynx,  $p<0.05$ ), in patients with cervical lymph node metastasis (54, 5 in N0 vs 30.9 in N1 vs 38.9 in N2 vs 16.1 months in N3,  $p<0.05$ ), in patients with vascular invasion according to histological criteria (48.5 vs 27.7 months,  $p<0.05$ ), with capsular rupture in invaded cervical lymph nodes (48.3 vs 34.1,  $p<0.05$ ) and in patients with margins of less than 0.5 cm (30.5 vs. 53 months,  $p<0.05$ ).

Multivariate analysis of overall survival, showed, that amongst pT4 tumours, differences were statistically significant for location of lesion, vascular invasion and extracapsular rupture ( $p<0.05$ ). For pT4a, in addition to these parameters, nodal staging was also statistically significant ( $p<0.05$ ) (Table 3). There was insufficient data for pT4b multivariate analysis because of the small number of patients.

Regarding the multivariate analysis of disease-free survival,

differences proved statistically significant for location of lesion and lymph node involvement ( $p<0.05$ ), both amongst the pT4 population as well as amongst the pT4a tumour subset (Table 3). There was insufficient data for pT4b multivariate analysis because of the small number of patients.

Table 3 Multivariate analysis of overall survival and disease-free survival.

	T4			T4			
	HR	IC95%	p	HR	IC95%	p	
Overall Survival	<b>Location</b>						
	Larynx vs hypopharynx/haryngolaryngeal	3.6	1.5-8.5	0.04	4.3	1.7-10.8	0.02
	<b>Cervical Status</b>						
	N0-1 vs N2-3	-	-	-	0.24	0.1-0.7	0.01
Overall Survival	<b>Perivascular</b>						
	No vs Yes	2.2	1.0-4.9	0.042	2.7	1.2-6.1	0.02
	<b>Extracapsular</b>						
No vs Yes	3.2	1.3-7.7	0.009	4.4	1.7-11.6	0.02	
Disease-free survival	<b>Location</b>						
	Larynx vs hypopharynx/haryngolaryngeal	2.9	1.6-5.3	0.00	3.2	1.7-6.0	0.00
	<b>Cervical Status</b>						
N0-1 vs N2-3	0.5	0.3-0.9	0.04	0.44	0.2-0.8	0.01	

HR: Hazard ratios; IC 95%: Confidence Interval 95%.

## DISCUSSION

Diagnostic strategies for staging head and neck tumours have evolved over time, especially with regard to the routine use of imaging modalities and considerable improvements in their quality<sup>[7]</sup>.

The development of a simple and easy staging system is fundamental, and in this sense the current TNM staging system has undergone several changes along the years.

The importance of proper characterization of tumour extent is of utmost importance for the staging, with a view to select the appropriate treatment and determining patient prognosis.

With respect to clinical and pathological staging, a large number of cT3 patients (60.5%) were restaged as pT4. Also, for nodal staging, a considerable number of cN0 tumours (40%) presented metastatic lymph nodes upon pathological evaluation.

The kappa coefficient showed a low agreement rate between clinical staging and pathological grading which suggests a low concordance when taking into account that which would be expected by chance. This low kappa coefficient, both locally and regionally, may be explained not only by the limitations inherent to physical examination and imaging exams but also by the time elapsed between diagnosis and surgery<sup>[5]</sup>. However, these data seem to indicate that, in a large number of patients, pathological staging is more advanced than clinical staging.

With regard to the TNM system in use since 2002 (updated in 2010 when the terms resectable and irresectable were abandoned and replaced with moderately advanced disease and very advanced disease), this study showed that T4b patients have a worse prognosis when compared with T4a patients, both in terms of median overall survival (40.5 months for pT4a vs 25.1 months for pT4b) and of median disease-free survival (21.0 months for pT4a vs 13.0 months for pT4b), although the differences in terms of median disease-free survival did not prove statistically significant. The short follow-up of some of the patients in this analysis has conditioned the calculation of 5-year survival rates and the small number of T4b tumours in the sample has also affected the significance of the results. The small number of T4b tumours may be due to earlier diagnosis, the greater likelihood of distant metastases at diagnosis ruling-out the option of surgery as an initial treatment option or the selection of some of these

patients for nonsurgical treatment regimens.

However, despite these limitations, the results validate the subdivision of larynx and hypopharynx tumours into T4a and T4b with regard to the prognostic impact.

However further studies will be important so that the TNM system can evolve to overcome its limitations.

In conclusion, the analysis of the data collected for this study seems to suggest that clinical staging, even when supported by imaging modalities (CT), shows a considerable tendency to understage tumours, both locally and regionally. The implications of the staging process in terms of prognosis may have been harmed, in this study, by the low calculated agreement coefficient.

The current division of T4 into T4a and T4b has been shown by this study to yield statistically significant prognostic implications, with respect to overall survival, and as such this subdivision may be considered relevant.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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