Discrepâncias entre o estadiamento clínico e patológico nos tumores da laringe: Avaliação das causas prováveis e influência na sobrevida global

Discrepancies between clinical and pathologic staging in tumors of the larynx: Evaluation of the probable causes and influence in overall survival

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RESUMO

Introdução: o estadiamento TNM é fundamental para a decisão terapêutica, sendo também utilizado para estimar o prognóstico. O estadiamento clínico (cTNM) é baseado nos achados ao exame físico, exames endoscópicos, e exames imagiológicos. Por outro lado, o estadiamento patológico (pTNM) baseia-se na análise histopatológica das peças excisadas por cirurgia. Discordâncias importantes no estadiamento do carcinoma da laringe têm sido descritas na literatura, mas algumas controvérsias ainda se mantêm.

Métodos e metodologia: foi realizado um estudo retrospetivo dos doentes submetidos a cirurgia por carcinoma da laringe (CL) no hospital de Braga entre os anos de 2013 e 2017. Foram selecionados os doentes submetidos a laringectomia total (LT) ou laringectomia parcial (LP) associados a esvaziamento ganglionar cervical. Foram recolhidos os seguintes dados: idade, sexo, localização, cTNM e pTNM, tempo entre o primeiro diagnóstico histopatológico e o tratamento cirúrgico, sobrevida (SBV) global aos 5 anos, recidiva e óbito. Os doentes foram agrupados em estadios de acordo com os estadios definidos pela *American Joint Committee on Cancer* 8ª edição, 2017.

Resultados: dos 72 doentes diagnosticados com CL, 47 foram incluídos na análise. 17% (n=8) foram submetidos a LP; 83% (n=39) a LT. 66% mostraram um cTNM diferente do pTNM: um T diferente em 44,7%, com um coeficiente de concordância baixo, com um Kappa de Cohen de 0,310 (p = 0,01), e um N diferente em 29,8%, com um coeficiente de concordância substancial (Kappa de Cohen de 0,688, p < 0,001). A causa mais comum de subida do T foi a invasão do córtex externo da cartilagem tiróide, e a razão mais frequente de descida de T foi a aparente fixação da corda vocal na avaliação pré-operatória. A mediana de dias entre o diagnóstico e a cirurgia dos pacientes no qual o T subiu foi estatisticamente diferente (superior) dos restantes doentes. Os tumores que se localizavam na glote estevam associados a descida no T (p = 0,020). Não se verificaram diferenças estatisticamente significativas nas curvas de sobrevida em doentes nos quais se verificaram diferença entre o cTNM e pTNM.

Discussão e conclusões: os nossos resultados mostram taxas de re-estadiamento um pouco superiores à literatura, as quais variam entre 20 e 55%. Novos métodos de avaliação, nomeadamente o uso de exames de imagem com maior acuidade diagnóstica e, por outro lado, a redução do tempo entre o diagnóstico inicial e o tratamento cirúrgico poderão ser importantes para reduzir as taxas de discordância entre o cTNM e pTNM. Apesar disso, e de acordo com os nossos resultados, o re-estadiamento não parece estar associado a piores taxas de sobrevida.

Palavras-chave: carcinoma da laringe; estadiamento;

ABSTRACT

Introduction: TNM staging plays a central role in therapeutic decision-making, being also useful for estimating prognosis. Clinical staging (cTNM) is based on physical examination, endoscopy e imaging studies. Pathological staging (pTNM) is based on histopathological analysis after the surgical procedure. Discrepancies between cTNM and pTNM in

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larynx cancer have been reported in the literature, but some controversies remain.

Material and methods: a retrospective analysis of the patients who underwent surgery for larynx cancer (LC) in Hospital de Braga between January of 2013 and December of 2017 was performed. Patients who underwent total laryngectomy (TL) and partial laryngectomy (PL) associated with neck dissection. The following data were retrieved: age, gender, location, cTNM, and pTNM, time between first histopathological diagnosis and surgery, 5-year overall survival (OS), relapse, and death. For analysis purposes, the staging was performed according to American Joint Committee on Cancer 8th Edition, 2017.

Results: of the 72 patients diagnosed with LC, 47 were included in the analysis. 17% (n=8) underwent PL, while 83% (n=39) underwent TL. There was a discrepancy between cTNM and pTNM in 66% of the patients: a different T in 44,7%, with a low Cohen Kappa coefficient of 0,310 (p = 0,01), and a different N in 29,8%, with a substantial Cohen Kappa coefficient of 0,688 (p < 0,001). The most common reason for upstaging T was the invasion of the outer cortex of the thyroid cartilage, and the most frequent reason for downstaging was apparent vocal cord fixation in the preoperative examination. The median of the days between histopathological diagnosis and surgery in the patients whose T was upstaged was significantly different (superior) than other patients. Tumors located in the glottis were associated with a T downstaging (p = 0,020). There was no statistically significant difference in survival curves between patients with and without discrepancies in cTNM and pTNM.

Discussion and conclusions: our results show higher rates of re-staging than the ones described in the literature, that vary between 20 and 55%. New evaluation methods, such as imaging studies with better diagnostic accuracy, and, on the other hand, reducing the time between first diagnosis and surgical treatment may be important to reduce the rates of discrepancy between cTNM and pTNM. Despite re-staging being frequent, according to our data, it is not associated with worse OS.

Keywords: larynx cancer; TNM staging

INTRODUCTION

Cancer staging plays a major role in the treatment of a patient with cancer. Standardizing patients by their stage ease prognosis establishment, contributing to the treatment choosing decision.[1]

Clinical TNM (cTNM), the pretherapeutic staging, in squamous cell carcinoma (SCC) of the larynx depends on a myriad of procedures: physical examination, endoscopic exams, and imaging studies. The latter can be further subdivided in computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron-emission tomography (PET).[2] On the other hand, after the surgical approach and histopathological analysis, the pathological TNM (pTNM) is determined.

Many authors found important differences between cTNM and pTNM in larynx cancers.[2-4] As treatment choice depends on the cTNM, the search for the most accurate diagnosis has been discussed thoroughly in the literature.

While physical exam and endoscopy are useful to assess neck staging and the mucosal extent and vocal cord (VC) mobility, imaging studies are essential to determine adjacent structures invasion and to evaluate metastasis (neck and distant).[5] Nevertheless, there are some well-described limitations in cTNM assessment.

Neck palpation has a sensitivity of only 64% for N+ (with positive SCC metastasis, in contrast with N0, term which refers to a neck without SCC metastasis) considering histopathology examination the standard.[6] Complementing the patient study with ultrasonography or CT can improve neck staging accuracy, given the higher sensitivity of these exams.

Also regarding imaging studies, one of the most discussed controversies is CT and MRI capacity to determine cartilage involvement. CT has a low sensitivity for cartilage invasion and can miss early/minor involvement, being difficult to distinguish between normal irregular calcification of the cartilage or its involvement by tumor growth.[3,7] MRI, on the other hand, has proven more sensitive, with a sensitivity that can go as high as 93% for inner lamina involvement and 85% for outer lamina involvement.[7]

After proper patient investigation, diagnosis, and cTNM establishment, treatment is programmed. There is usually a time gap between the diagnosis confirmation and treatment (either surgery of systemic treatment initiation). Some authors have questioned the influence of the delay in potential discrepancies between cTNM and pTNM and in prognosis itself, although the results are quite conflicting.[4]

The objective of this study is to assess the differences in cTNM and pTNM staging between patients in whom surgery including neck dissection was performed to treat SCC of the larynx, investigate the potential reasons for the differences, and the impact of the time gap between diagnosis and treatment in these discrepancies. Another objective of this study is to evaluate the influence of these differences in prognosis, namely the outcome 5-year overall survival (OS).

MATERIAL AND METHODS

After Ethics Committee approval, a retrospective analysis of the patients who underwent surgery for SCC of the larynx treatment between January 2013 and December 2017 was performed.

Patients who underwent partial laryngectomy (PL) or total laryngectomy (TL) associated with neck dissection were selected. Patients who underwent surgery as salvage treatment and follow-up losses were excluded.

The following data were retrieved: demographic features; cTNM based on clinical examination and imaging (CT and/or MRI), and pTNM, based in histopathologic analysis; the time gap between first histopathologic diagnosis confirmation and surgery; the outcomes death, relapse, 5-years overall survival. For analysis purposes, we subdivided the staging process in T (cT or pT) and N (cN and pN); patients without neck

metastasis in clinical and pathological staging were considered cN- and pN-, respectively; on the other hand, patients with neck metastasis in clinical and pathological staging were considered cN+ and pN+, respectively. American Joint Committee on Cancer 8th edition (2017) was used to evaluate and stage the patients in the time frame evaluated.[1]

Statistical analysis

Continuous variables with normal distribution were described as mean ± standard deviation. Continuous variables without normal distribution were described as median and interquartile range (IQR). Non-parametric Mann-Whitney U test was used to compare medians of continuous variables without normal distribution. The Pearson Chi-square was used to evaluate the correlation between two categorical variables. Cohen kappa coefficient was used to assess the accuracy between cTNM and pTNM.

Kaplan-Meier method was used to create survival curves, and Log Rank was used to compare between them.

SPSS 24.0 for macOS was used for the statistical analysis. A p-value < 0.05 was used to reject the null hypothesis.

RESULTS

Of the 77 patients who underwent PL or TL in the designated time frame, 47 fulfilled the inclusion criteria. 21 were excluded given neck dissection was not performed; 4 patients underwent surgery as salvage treatment; 5 patients were lost to follow-up (emigrants who returned to their living country after surgery).

The analyzed population was comprised of a majority of male patients (95,7%, n=45), with a mean age of 59.8 ±9.6 year-old (range 42-79).

Regarding location, the most common were the supraglottic tumors (44,7%, n=21), followed by the transglottic (38,3%, n=18), and glottic (17%, n=8).

The median time between the first histopathological confirmation and definitive surgical treatment was 27 days (IQR=18). The surgical approach varied between PL, in 17% (n=8), and TL in 83% (n=39), always associated with neck dissection.

Most of the patients had advanced stages in the pre-operative period, with stage IVa in 61,7% of the patients (n=29), followed by stage III (19,1%, n=9). Most of the patients were cN+ (59,6%, n=28). The pathological staging was advanced for the majority of cases, with IVa in 63,8%, and stage III in 19,1%.

Regarding follow-up, there was a 5-year OS of 70,2% (n=33). Relapse was diagnosed in 17,8% of patients, in a mean time of 473,4 ± 267,2 days.

Discrepancies between cTNM and pTNM

We verified a discrepancy between cTNM and pTNM in 66% (n=31) of the cases: a different T (Table 2) was verified in 44,7% of the patients (n=21) and a different N in 29,8% of the patients (n=14). The level of agreement between cT and pT was fair (Cohen Kappa = 0,310, p = 0,01); on the other hand, there was a substantial agreement between cN and pN (Cohen Kappa = 0,688, p < 0,001).

The highest rate of discrepancy regarding cT was verified in the patients with a tumor staged as cT2, with an upstaging rate of 40% and downstaging of 20%, followed by cT3, with an upstaging rate of 37% and downstaging of 11%. The most common reasons for up and downstaging were the invasion of the outer cortex of the thyroid cartilage not visible in preoperative imaging studies and an apparent vocal cord fixation in physical examination, respectively (table 4).

Regarding cN (Table 2), there was a discrepancy in all the cN+ necks staged as cN2a and cN3b. On the other hand, the cN- necks were the ones with the highest correspondence between cN and pathological staging.

Of the analyzed factors, there were only two that were associated with a cTNM change after pathological analysis: regarding location, the glottic tumors were associated with a higher rate of discrepancy (p = 0,020); on the other hand, there was a higher median time gap between diagnosis and surgery in patients who had been upstaged (p = 0,048).

TABLE 1
Descriptive features

	Result
Age (Mean ± SD)	59.8 ± 9.6
Minimum	42
Maximum	79
Gender	
Female	4,3% (n=2)
Male	95,7% (n=45)
Location	
Supraglottic	44,7% (n=21)
Glottic	17% (n=8)
Transglottic	38,3% (n=18)
Days between histopathological diagnosis and surgical treatment [Median (IQR)]	27 (18)
Minimum	4
Maximum	75
Staging cTNM	
Stage II	17% (n=8)
Stage III	19,1% (n=9)
Stage IVa	61,7% (n=29)
Stage IVb	2,1% (n=1)
Staging pTNM	
Stage I	4,3% (n=2)
Stage II	8,5% (n=4)
Stage III	19,1% (n=9)
Stage IVa	63,8% (n=30
Stage IVb	4,3% (n=2)

TABLE 2
Correspondence between cT and pT, rate of upstaging, downstaging, and paired stage

	pT1	pT2	pT3	pT4a	Upstaged	Downstaged	Paired stage
cT1	1	0	0	0	0%	0%	100%
cT2	2	4	4	0	40%	20%	40%
cT3	1	2	14	10	37%	11%	52%
cT4a	0	1	1	6	12,5%	12,5%	75%

TABLE 3
Correspondence between cN and pN, rate of upstaging, downstaging, and paired stage

	pN0	pN1	pN2a	pN2b	pN2c	pN3a	pN3b	Upstaged	Downstaged	Paired stage
cN0	15	2	0	2	0	0	0	21%	0%	79%
cN1	0	1	0	0	1	0	0	50%	0%	50%
cN2a	0	0	0	2	0	1	0	100%	0%	0%
cN2b	0	1	0	3	5	0	1	60%	10%	30%
cN2c	2	2	0	0	6	0	0	0%	40%	60%
cN3b	0	0	0	1	0	0	0	0%	100%	0%

TABLE 4
Reasons for the discrepancies between cTNM and pTNM

	Count
cT upstaging	
Invasion of the outer cortex of the thyroid cartilage	8
Invasion of the inner cortex of the thyroid cartilage	2
Invasion of the pre-epiglottic space	2
Invasion of the paraglottic space	1
Invasion of the first tracheal ring	1
cT downstaging	
Fixation of the vocal cord on physical examination	4
Lack of invasion of the outer cortex of the thyroid cartilage	2

FIGURE 1
Kaplan-Meier survival curves comparing patients that were upstaged and the ones that were not for cT

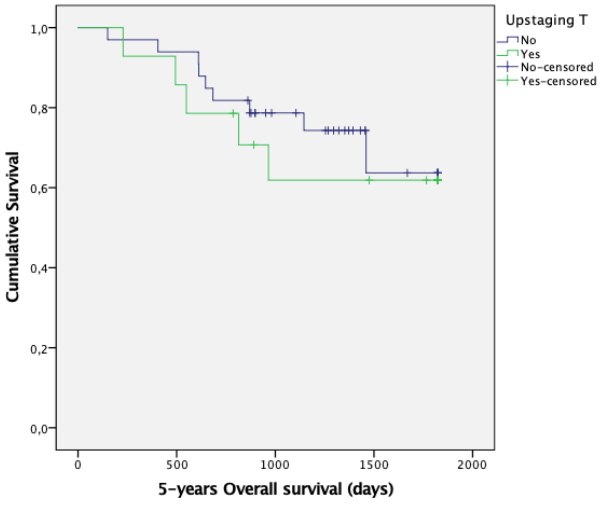
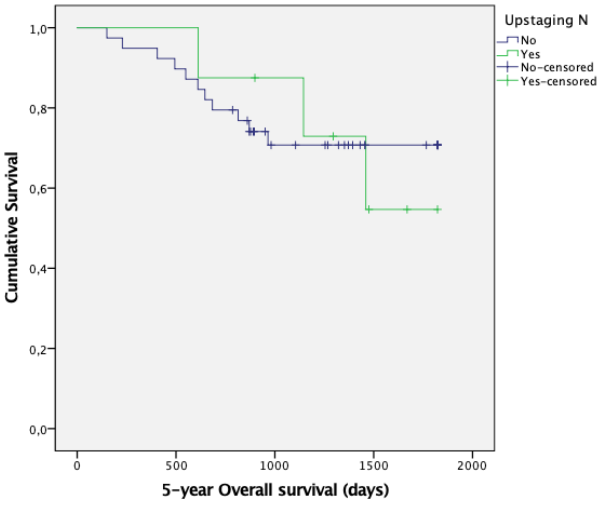


FIGURE 2
Kaplan-Meier survival curves comparing patients that were upstaged and the ones that were not for cN



Impact in 5-year OS of the discrepancies between cTNM and pTNM

Using the Kaplan-Meier method to create survival curves, and Log Rank to compare them, the estimated 5-year OS was not significantly different for patients who had been upstaged in cT and cN (Log Rank = 0,254, p = 0,614, and Log-Rank = 0,26, p = 0,871, respectively).

DISCUSSION

Given the importance of cTNM in the clinical decision, this process must be as meticulous as possible. It has a direct impact on treatment planning and prognosis establishment.

Our rate of discrepancy in cT (44.7%) was higher than described in the literature.[3,4,8] Despite imaging studies contributing to larynx tumors staging process after clinical examination, there are some relatively common discordance motives, such as cartilage invasion, which, in our population, was the most common factor for discordance, leading both to upstaging and downstaging tumors. As stated before, despite some controversy in their sensitivity, MRI has shown greater potential than CT in detecting cartilage invasion, above all in low stages of larynx cancer.[9] Nevertheless, their specificity is compromised by some potential artifacts related to the inflammatory tumor-related changes in cartilage, which can be easily mistaken with invasion. More recent technology, such as dual-energy CT, is being investigated to surpass mostly the specificity problems of CT and MRI, to improve staging and prognosis establishment.[9]

Regarding cT discrepancies, we verified an association between discrepancies in cT and glottic tumors, which is compatible with the literature.[2] Literature relates the frequent discrepancies in glottic tumors staging predominantly with the ones involving the anterior commissure; nevertheless, authors report a higher rate of upstaging (as high as 50% of the cases) in this tumors, which is the opposite of our results, in which we found a high rate of downstaging.[10]

Another factor that might influence the rate of upstaging is the delay in the treatment after the first diagnosis. We found a statistically significant difference between the median time between diagnosis and surgery. Despite our median time to treatment (27 days) being similar to the one presented by other authors, they did not find any significant difference between patients who had discrepancies between cTNM and pTNM.[4]

On the other hand, the discrepancy in cN (29.8%) was similar to other oncology groups.[2,4] Most authors relate the discrepancies in the neck evaluation with micrometastasis and extranodular extension (ENE). Neck palpation alone may fail to identify micrometastasis besides lacking the capability of adequate dimension measurement.[4,6] CT scan is, undoubtfully, very important in these patients' evaluation and may improve diagnostic accuracy, despite low sensitivity to micrometastasis. Nevertheless, the gold standard for diagnosis micrometastasis and ENE is still histological analysis.

Regarding 5-year OS, we did not find any difference in survival curves between patients who had been upstaged. This information is contradictory in the literature. Celakovsky et al (2017) found that discordance between cTNM and pTNM was a prognostic factor, and should indicate the need for post-operative treatment (if not indicated by pTNM itself).[2]

Our study has some limitations that can directly impact results: because it is based on a retrospective analysis, it took into account physical exams performed by different Surgeons, imaging studies reported by different Radiologists, and histopathological analysis by different Pathologists; moreover, it has a limited number of patients.

CONCLUSION

Despite advances in clinical evaluation and imaging studies, discrepancies between cTNM and pTNM are still frequent, and, in our population, they reached 44.7% in cT and 29.8% in cN. The most frequent reason for this difference was the invasion of the outer cortex of the thyroid cartilage not diagnosed in the preoperative evaluation. Despite that, according to our research, there is no difference in 5-year OS between patients with and without discrepancies in TNM staging, the impact of the staging itself is well known, so improving diagnostic accuracy should be a priority among Head and Neck cancer dedicated surgeons and oncologists.

Conflito de Interesses

Os autores declaram que não têm qualquer conflito de interesse relativo a este artigo.

Confidencialidade dos dados

Os autores declaram que seguiram os protocolos do seu trabalho na publicação dos dados de pacientes.

Proteção de pessoas e animais

Os autores declaram que os procedimentos seguidos estão de acordo com os regulamentos estabelecidos pelos diretores da Comissão para Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Política de privacidade, consentimento informado e Autorização do Comité de Ética

Os autores declaram que têm o consentimento por escrito para o uso de fotografias dos pacientes neste artigo.

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Disponibilidade dos Dados científicos

Não existem conjuntos de dados disponíveis publicamente relacionados com este trabalho.

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