ONCOLOGIA

TONSIL SQUAMOUS CELL CARCINOMA TREATMENT
132 cases retrospective study at the Portuguese Oncology Institute - Oporto

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ABSTRACT

Optimal management of palatine tonsils squamous cell carcinoma is still under debate. The authors describe a retrospective study at the Portuguese Oncology Institute of Oporto. Overall, 46 (34.8%) were treated with surgery and 86 (65.2%) were submitted to non-surgical treatment as first option. After a mean (SD) follow-up time of 24.2 (21.6) months, 49 (37.1%) patients were alive and 83 (62.9%) had died. Surgical treatment was associated with higher survival probability only among patients at early stages (p=0.028) and the risk of death in this group, after adjustment for age, was higher in the non surgical group (HR= 3.31; 95% CI 1.07-10.2). For those at later stages, we found no significant differences between the survival rates of the two treatment groups (p=0.125). There is a changing pattern in the treatment of advanced cases towards non-surgical approach based on similar survival rates.

KEY-WORDS: Palatine Tonsil; Oropharynx; Squamous cell carcinoma; Retrospective study

INTRODUCTION

The oropharynx, as described by the American Joint Committee on Cancer (AJCC) [1], can be divided in four anatomical areas: base on the tongue, soft palate, posterior oropharynx and palatine tonsils (in the following text described as tonsils).

Of all tumours on tonsils, 75% are malignant and the squamous cell carcinoma (SCC) variety represents 70 a 90% of these. The tonsil is the most common location of SCC in the oropharynx (15-20%), and the second most common in the head and neck area [2]. The tonsils are a part of Waldeyer's ring, therefore is not rare to diagnose lymphomas and lymphoepytheliomas within this organ [3]. These tumours have different origin, treatment and prognostic and will not be addressed in this paper.

It is a solid fact in literature that abusive consumption of alcohol and tobacco have a synergetic effect on carcinogenesis [4]. The diagnosis is based on biopsy's histological examination of a visible tumour and staging is mostly done using the AJCC classification [1]. A plain asymmetry of the tonsil, without clear mucosal disruption turns out to be malignant in only 5% of cases, most of them lymphomas. Nevertheless, diagnostic biopsy or tonsillectomy is mandatory in these cases [3].

The treatment of choice is still a controversial subject and target of many publications. Many treatment options are available nowadays, with many schemas, dosages and combinations possible. Usually, patients are often submitted to more than one type of treatment [5]. The multiplicity of treatment regimens performed in these patients makes it difficult for specific treatment efficacy comparison. Head and Neck surgeons, Radiotherapists and Medical Oncologists still debate, in most cases, if the best initial treatment option is surgical or non-surgical.

At the Portuguese Oncology Institute of Oporto (IPOFGP), a referral oncology hospital in the North of Portugal, this pathology represented 0.8% of all oncologic cases treated in the unit during 2005 [6]. This article describes a retrospective study on a significant number of tonsil SCC cases treated during a 13 years period. The study aims to assess the effect of initial surgical or non-surgical treatments option on survival of patients with tonsil squamous cell carcinoma, and compare it to previously published data.

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METHODS

It was designed a retrospective study of all the cases that have been coded (according to ICD-10) with pathologic code "Carcinoma" (M.8070.3) and clinical code "Tonsil neoplasm" (T.146.0) or "Non-specified oropharynx neoplasm" (T.146.9), coding, at the IPOFGP from 1995 to 2007 (13 years). Information on social and behavioural characteristics of the patients, clinical presentation, treatment and outcome was recorded. The disease was considered initial when found on stage I or II and advanced when classified on stage III or IV (according to AJCC classification). Due to numerous treatment options found, first treatment options were aggregated in surgical, which included all surgical procedures that addressed the primary tumour with a curative intention regardless of the cervical lymph nodes treatment, and nonsurgical that included radiotherapy, quimiotherapy or radio-quimiotherapy as the inicial treatment protocol. Treatment response was evaluated by clinical persistence of disease at 3 months follow-up visit.

Drinking habits were stratified in as light/moderate when there was a consumption < 40g of alcohol per day and as heavy when ≥ 40g/day. Ex-smokers who had quitted smoking more than 10 years ago were considered non-smokers.

The statistic analysis was performed using the statistical software SPSS version 16.0 (SPSS Inc, Chicago, USA). Means were compared using independent-sample t-student tests and the X^2 test was used to compare proportions when all expected frequencies in contingency tables were greater than 5. When this criterion was not fulfilled, Fisher's exact test was used for comparison between the two treatment groups.

Cumulative survival probabilities were estimated by the Kaplan-Meier method and the comparison of survival curves by the log-rank test. The outcome under study was all-cause death. The follow-up period was the time, expressed in months, between the date of the first clinical encounter and the patient's death or the latest date when the patients were known to be alive, censored at 72 months. The 5% level of significance was used for all statistical tests.

To estimate the magnitude of the association between treatment and survival, hazard ratios (HR) and 95% confidence intervals (95% CI) were computed using multivariate Cox regression analysis.

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RESULTS

Initially, a list of 187 patients was obtained. Six cases were excluded because the records charts were missing or were too incomplete (no end-points). After review, 31 cases were discarded because they were SCC primarily located in other oropharynx sites. Eighteen cases were directly sent to palliative care, therefore were not considered for treatment analysis in this study. Therefore, a total of 132 cases of tonsil neoplasm were evaluated.

Among these, 123 (93.2%) were men and 9 (6.8%) were women. Overall, the participant's ages ranged from 31 to 87 years, with a mean (standard deviation (SD)) age of 55.7 (11.5) years. Most patients were smokers (86.2%) and heavy alcohol drinkers (75.4%). Approximately half (56.1%) were observed within three months after appearance of the first symptom. Only 7% presented at first consultation with a neoplasm limited to the tonsil (excluding pillars). Fifty-nine point one percent (59.1%) did not have cervical adenopathies at initial image study, however 78.0% were classified in stages III or IV. Distant organ dissemination was only seen in 2.7% of the patients. Four point six percent had other synchronous malignant tumours and 4% revealed metachronous tumours.

The distribution of social, behavioural and clinical characteristics in the study sample is summarized in Table 1, was well as their comparison by treatment groups. Patients with adenopathies (46.3% vs. 26.9%, p=0.022), in initials stages

of the disease (65.5% vs. 26.6%, p<0.001) and non-smokers (63.6% vs. 30.4%, p=0.041) were more likely to have been submitted to surgery.

The distribution of initial treatment types and their response are displayed in Table 2. Overall, 46 (34.8%) were treated with surgery and 86 (65.2%) were submitted to non-surgical treatment as first option. Persistent disease after initial treatment was found in 46.2% of the patients, mainly on non-surgical group. Most of the relapses were at the primary site and two-thirds of those (63.8%) were submitted to salvage treatment.

After a mean (SD) follow-up time of 24.2 (21.6) months, 49 (37.1%) patients were alive and 83 (62.9%) had died.

Overall, the survival rate was significantly higher among patients submitted to surgery (p=0.001). However, after stratifying by clinical stage, there were important differences between the two treatment groups. Surgical treatment was associated with higher survival probability only among pa-

TAB 1

DISTRIBUTION OF SOCIAL, BEHAVIOURAL AND CLINICAL CHARACTERISTICS OF THE PATIENTS BY TREATMENT GROUPS				
	n	Treatment		*p*
		Surgical *n* (%)	Non surgical *n* (%)	
Age				
Mean (SD)	132	56.2 (12.7)	54.7 (9.9)	0.449
Sex				
Male	132	40 (32.5)	83 (67.5)	0.065
Female		6 (66.7)	3 (33.3)	
Smoking status				
Non-smoker	123	7 (63.6)	4 (36.4)	0.041
Smoker/Ex-smoker		34 (30.4)	78 (69.6)	
Drinking status				
< 40 g/day	118	9 (56.3)	7 (43.7)	0.078
≥ 40 g/day		26 (29.2)	63 (70.8)	
Ex-drinkers		3 (23.1)	10 (76.9)	
Time since 1st symptom				
< 3 months	132	24 (32.4)	50 (67.6)	0.511
≥ 3 months		22 (37.9)	36 (62.1)	
Adenopathies				
Yes	132	25 (46.3)	29 (53.7)	0.022
No		21 (26.9)	57 (73.1)	
Clinical TNM stage				
I-II	132	19 (65.5)	10 (34.5)	<0.001
III-IV		27 (26.6)	76 (73.8)	

TAB 2

	Type of treatment	n (%)	Persistence after 3 months n (%)
Non Surgical	Radiotheraphy	18 (12.0)	7 (11.5)
	Quimiotherapy	29 (19.3)	28 (45.9)
	Quimioradiotherapy	29 (19.3)	13 (21.3)
	Concomitant Quimioradiotherapy	10 (6.7)	4 (6.6)
Surgical	Local surgery	19 (12.7)	1 (1.6)
	Locoregional surgery	27 (18.0)	8 (13.2)
	Paliative care	18 (12.0)	---

TYPE OF TREATMENT AND 3 MONTHS PERSISTENCE DISTRIBUTION OF THE PATIENTS

TAB 3

CRUDE AND AGE-ADJUSTED HAZARD RATIO ESTIMATED BY COX REGRESSION ANALYSIS

		Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Clinical stage I-II	Treatment		
	Surgical	1[b]	1[b]
	Non surgical	3.26 (1.06-9.99)	3.31 (1.07-10.2)
Clinical stage III-IV	Treatment		
	Surgical	1[b]	1[b]
	Non surgical	1.58 (0.86-2.90)	1.58 (0.86-2.91)

[a] Hazard ratio adjusted for age.
[b] Reference class.

tients at early stages (p=0.028) (Figure 1-A). For those at later stages, we found no significant differences between the survival rates of the two treatment groups (p=0.125) (Figure 1-B).

The crude and age-adjusted hazard ratios of death and their respective 95% confidence intervals obtained by Cox regression model are shown in Table 3. At the early stages, the risk of death, after adjustment for age, was higher in the non surgical group (HR= 3.31; 95% CI 1.07-10.2).
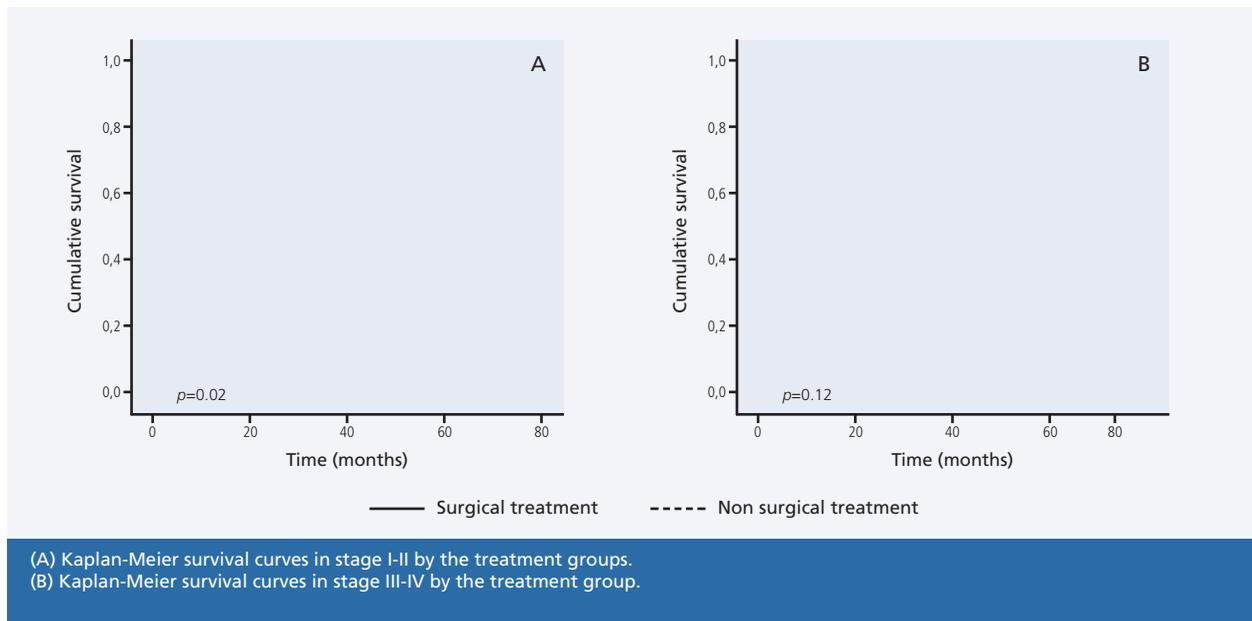
DISCUSSION

As in all similar studies, tobacco and alcohol abuse have an outstanding prevalence, reflecting their fundamental role in this cancer ethiopathogenesis [2]. We found a greater amount of patients in the 5th decade of life, a decade earlier than published before [2], probably related to higher addictive habits. In the U.S., the incidence diminished in the last 20 years, probably due to a reduction in alcohol consumption and smoking. Nevertheless, there is a growing minority of

patients whom develop this disease without alcohol or tobacco exposure [7].

One explanation lays on the role of Human Papilloma Virus (HPV) in the carcinogenesis of tonsil SCC. Klussmann et al. [8] established a 58% prevalence of HPV in the tonsil SCC specimens, a percentage much higher than other locations in the aero-digestive mucosa. Several studies, including a meta-analysis, support this fact and establish a better prognosis for these cases, and even suggest different physiopathology and subtype of carcinoma [9,10].

Our time gap between the first symptom and diagnosis is similar to other previously published [11], and neither have we found it to be influential on survival after stage-adjustment.

Our staging was usually done including direct observation and Computerized Tomography (CT). In our study cervical ganglia invasion was treated preferentially by surgery, although some studies claim that in limited neck disease radical radiotherapy has proven equal efficacy [12]. Also, it has been published that as many as 27% of the image negative ganglia are histologicaly positive, so the exact efficacy and cost-benefit of complementary techniques as sentinel ganglion and Positron Emission Tomography (PET) in the staging or follow-up of these patients must be cleared out [13,14].

FIG 1

(A) Kaplan-Meier survival curves in stage I-II by the treatment groups.
(B) Kaplan-Meier survival curves in stage III-IV by the treatment group.

This study reinforces the staging as main prognostic factor. Unfortunately, as in others institutions, we also dealt with many advanced-stage cases (78%), due mainly to wide loco-regional dissemination and not to the rare distant metastasis found. According to AJCC data in 2001, only 8% of new cases are diagnosed in stage I, 20% in stage II, 34% in stage III and 38% in stage IV [15]. This late diagnosis is explained by the often asymptomatic disease in its early stages, the rapid progression of disease, the common symptoms underestimated by the physicians or a less health-aware population such as this. We also found a significant percentage of synchronous e metachronous tumours (8.4% total), which would probably increase if the follow-up study time was longer. Sundaram [16] claims up to 20% of other aero-digestive carcinomas in these patients during a life time, reminding the concept of "condemned mucosa" due to accumulation of genetic mutations.

As expected by the late diagnosis and the aggressive behaviour, and in agreement with published data, we had a low overall survival at two years follow-up, with a significant rate of persistent and recurrent disease, no matter the treatment chosen at the beginning.

The data reveals that the patients at initial stages (I-II) were mainly treated surgically and with better results. These better results obtained with surgical treatment in our study must be cautiously read under the light of a lower staging and the frequent adjuvant use of radiotherapy. There is no gold-standard treatment is these cases. Lee *et al* [12] reported an 87% 3-years-survival for radiotherapy compared to 70% for surgery alone. The newer techniques as intensity modulated radiotherapy or brachytherapy seem to have equal efficacy with less morbidity [17].

In advanced stages (III-IV), our study reveals very similar survival rates in both surgical and non-surgical initials options. In these cases, the non-surgical option was the most frequent, with expected higher rates of disease persistence. Therefore, many times surgery was needed afterwards for primary salvage or neck treatment. This last fact together with the common use of adjuvant therapy in surgical cases, and the wide variety of treatments adapted to each case introduce many uncontrolled variables than restricts more conclusive results. Also the previously published data doesn't allow conclusions on the best treatment regimen for advance-staged cases. The concomitant radioquimiotherapy protocols have a raising popularity in tonsil SSC treatment. A meta-analysis concludes an 8-10% increase in 5-years survival rate compared to conventional treatments on advance-stage disease [18]. This increase tends to fade when disseminated neck disease (N2 or N3) is the criteria for up--staging.

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CONCLUSION

In our Institution, initial stage tumours will mostly continue to be treated initially by surgery (with or without adjuvant radiotherapy) based on the relatively good results obtained. There is a changing pattern in the treatment of advanced cases, which were usually submitted to aggressive surgery and adjuvant therapy. The similar survival results obtained with conservative treatment, especially with the introduction of concomitant protocols, together with alleged better quality-of-life scores, has been shifting our institution practise towards this direction, although many times followed

by surgical treatment when needed. The decision remains dependent on other factors as patient's will, age and health status.

The prognosis of this disease is still unsatisfactory and has not showed significant improvement in the last years, despite the treatment advances. Research to optimise tonsil SCC staging must continue in order to improve patient treatment selection. Alcohol abuse, smoking prevention and education measures are still needed among the Portuguese population to reduce incidence and to promote early detection of the disease. Other etiologic agents such as HPV must be studied, not only for prevention measures but also as a possible target for future therapies.

BIBLIOGRAFIA

1. Greene FL: Head neck oncology. In: AJCC Cancer Staging Manual, 6th ed. Springer; 2002.

2. Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ: Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control* 11:489-95 (2000).

3. Rothman K, Keller A: The effect of joint exposure to alcohol and tobacco on the risk of cancer of the mouth and pharynx. *J Chronic Dis* 25:711-716 (1972).

4. Genden EM, Ferlito Alfio, Scully C, Shaha A, Higgin K, Rinaldo A: Current management of tonsillar cancer. *Oral Oncology* 39:337-342 (2003).

5. Poulsen M, Porceddu SV, Kingsley PA, *et al*: Locally Advanced Tonsillar Squamous Cell Carcinoma: Treatment Approach Revisited. *The laryngoscope* 117:45-50 (2007).

6. Bento MJ: Registo Oncológico 2005. Instituto Português de Oncologia de Francisco Gentil – Centro Regional de Oncologia do Porto, EPE. (2005) Available at http://www.ipoporto.min-saude.pt/Downloads_HSA/IPOP/Estat%C3%ADstica/IPO_final_2005.pdf.

7. Licitra L, Chiara R, Bossi P, Locati LD: Advances in the changing patterns of aetiology of head and neck cancers. *Curr opin Otolaryngol Head Neck Surg* 14:95-99 (2006).

8. Klussmann JP, Weissenborn SJ, Wieland U, Dries V, Kolligs J, Jungehuelsing M, *et al*: Prevalence, distribution, and viral load of human papillomavirus 16 DNA in tonsillar carcinomas. *Cancer* 92:2875-84 (2001)

9. Kreimer AR, Clifford GM, Boyle P, Franceschi S: Human Papillomavirus Types in Head and Neck Squamous Cell Carcinoma World wide: A Sistematic Review. *Cancer Epidemiol Biomarkers Prev* 14(2):467-75 (2005).

10. Puscas l: The role of human papilloma virus infection in the etiology of oropharyngeal carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 13:212-16 (2005).

11. Ho T, Zahuraz M, Kock WM: Prognostic Significance of Presentation-to-Diagnosis Interval in Patients with Oropharyngeal Carcinoma. *Arch Otolaryngol Head Neck Surg* 130:45-51 (2004).

12. Lee WR, Mendelhall WM, Parsons JT, Million RR, Cassini NJ, Stringer SP: Carcinoma of the tonsillar region: a multivariate analysis of 243 patients treated with radical radiotherapy. *Head Neck* 15:283-8 (1993).

13. Ross G, *et al*: The use of Sentinel Node Biopsy to Upstage the clinically N0 Neck in Head and Neck Cancer. *Arch Otolaryngol Head Neck Surg* 128:1287-1291 (2002).

14. Goerres GW *et al*: Positron Emission Tomography in the Early Follow-up of Advanced Head and Neck Cancer. *Arch Otolaryngol Head Neck Surg* 130:105-109 (2004).

15. Groome PA, Schultze KM, Mackillop WJ, Grice B, Goh C, Cummings BJ, *et al*: A comparison of published head and neck stage groupings in carcinomas of the tonsillar region. *Cancer* 92:1484-94 (2001).

16. Sundaram K, Schwartz J, Har-El G, Lucente F: Carcinoma of the Oropharynx: Factors affecting outcome. *The Laryngoscope* 115:1536-1542 (2005).

17. Levendag P, Nudam W, Noever I, *et al*: Brachytherapy *versus* surgery in Carcinoma of tonsillar fossa and/or soft palate: late adverse sequelae and performance status: can we be more selective and obtain better tissue sparing? Int *J Radiation Oncology Biol Phys* 59(3):713-724 (2004).

18. Brownman GP, Hodson GI, Mackenzie RJ, Bestic N, Zuraw L: Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer. A systematic review of the published literature with subgroup analysis. *Head Neck* 23:579-89 (2001).