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Primary surgery for locoregional advanced oropharyngeal cancer: prognostic factors

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ABSTRACT

Background: Oropharyngeal squamous cell carcinoma (OPSCC) incidence is rising in developed countries. These malignancies usually present in advanced stages and are associated with poor outcome. This work aims to ascertain the clinical and histopathological prognostic factors of locoregional advanced OPSCC treated with primary surgery in a tertiary oncology centre.
Methods: Retrospective chart review of all patients with advanced OPSCC who underwent primary surgery from 2011 to 2016. Overall and disease-free survivals were estimated using Kaplan-Meier method. Clinical and histopathological prognostic factors were determined by univariate (Log Rank tests) and multivariate (Cox models) analyses.
Results: 89 patients (89.9% male) with a mean age of 57.6±10.0 years were included in the study. Five-year overall and disease-free survivals were 53.9% and 57.7%, respectively. Pathologic N stage (HR=2.65 95% IC 1.32-5.32, p<0.01), distant metastasis (HR= 3.26 95% IC 1.24-8.62, p=0.01) and postoperative radiotherapy (HR=0.02 95% IC 0.01-0.12, p<0.01) were significantly correlated with overall survival. Pathologic N stage (HR=2.41, 95% IC 1.04-5.63, p=0.04) perineural infiltration (2.45, 95% IC 1.01-5.95 p=0.04), distant metastasis (HR=5.24, 95% IC 2.31-11.89, p<0.01) and postoperative radiotherapy (HR=0.02 95% IC 0.00-0.18, p<0.01), were significantly correlated with locoregional disease-free survival.
Conclusions: Knowledge of survival prognostic factors is crucial for selection of the appropriate treatment of oropharyngeal cancer. Pathological nodal stage, postoperative radiotherapy and the occurrence of distant metastasis were the main prognostic factors for overall and disease-free survivals in the present series. These findings may help to provide proper stratification in future randomized trials.

Keywords: Oropharynx, Prognosis, Squamous cell carcinoma, Surgery, Survival

INTRODUCTION

Epidemiology and demographics of head and neck squamous cell carcinoma (HNSCC) have been changing in the last decades.[1] Following the progressive decline, since the early 1980s, of smoking habits, a known important risk factor for the majority of HNSCC, a decrease in the incidence of carcinoma of the larynx, hypopharynx and oral cavity was observed.[2] Oropharyngeal squamous cell carcinoma (OPSCC) has not, however, followed this trend and its frequency is rising in the developed countries.[1,2] This increasing incidence has been linked to previous human papilloma virus (HPV) infection, especially of the HPV-16 and HPV-18 subtypes, which is now accountable for more than 70% of OPSCC in Europe and USA.[1,2] Conversely, and given the fact that HPV+OPSCC affects younger patients, usually without smoking habits and has better

response to treatments, distinct staging criteria were defined in the 8th edition of American Joint Committee on Cancer Staging Manual.[3]

Regardless of these differences, patients with OPSCC usually present with advanced disease, namely with lymph node involvement in 15 to 75% of cases and are associated with poor outcome.[4-6] Ascertainment of risk factors that may influence therapeutic approach is a major concern. Several studies have been enrolled on this topic leading to the 8th edition of the National Comprehensive Cancer Network (NCCN) Guidelines that defined distinct treatment approaches to OPSCC according to the HPV status. Nevertheless, several risk factors (or adverse features) are common to both groups, namely extranodal extension, positive margins, pathological T3-4 stage, nodal disease in levels IV or V, perineural infiltration and lymphovascular invasion.[4]

The aim of the present study is to define clinical and histopathological prognostic factors for locally advanced oropharyngeal tumours, treated with primary surgery in a tertiary oncology centre.

METHODS

A retrospective study, reviewing the medical files of all patients with locally advanced OPSCC who underwent primary surgical resection with curative intent from January 2011 to December 2016 at Instituto Portugues de Oncologia Francisco Gentil- Porto was undertaken. Collected data were registered in a database program, including: number of institutional affiliation, age, gender, cigarettes and alcohol consumption, tumour location, clinical tumour (cT) and nodal (cN) stages, pathological tumour (pT) and nodal (pN) stages, type of surgery, margin status, limphovascular and perineural infiltration, extranodal extension, depth of tumour invasion and type of treatment. Patient with missing data in health record or who were lost to follow up were excluded from the present study.

All patients enrolled in the study had surgery with curative intent. Patients were staged according to the 7th edition of American Joint Committee on Cancer Staging Manual. The option for post-operative radiotherapy (RT) was decided at the Multidisciplinary Head and Neck Tumour Board, based on histological findings in the surgical specimen, including pT stage ≥3 or any pT-stage with surgical margins <5 mm, perineural and/or vascular infiltration. Regarding neck disease, all pN ≥2 or lymph nodes presenting extranodal extension were also selected for adjuvant therapy. All tumours resected with positive margins that were not candidates for revision surgery were considered locally advanced tumours, under the rationale that these patients have worse prognosis and, therefore should benefit of postoperative treatments, according to the NCCN guidelines.[7] Adjuvant intensity-modulated RT was given at 2 Gy per fraction, with a total radiation dose ranging from 60-70 Gy. Patients were treated five days per week, once time per day, except on public holidays. In patients with good performance status, RT was associated with cisplatin or carboplatin-based chemotherapy, unless contra-indicated.

Assessments

Routine follow-up consisted of visits every 1-2 months in the first year, 2-3 months in the second year, 4-6 months from the third to fifth year and annually beyond. CT scan or MRI were not routinely requested, unless there was clinical suspicion of tumour recurrence. For study purposes, local and regional recurrences were grouped as locoregional recurrences. Survival was defined as the period of time from the end of treatment to a serious event or to the last follow-up. The cut-off point for statistical analysis was June 2018, encompassing a minimum follow up of 18 months.

Statistical analysis

Data analyses were performed with SPSS software version 23.0 (SPSS INC. 2011, Chicago, Illinois, USA). Differences in proportions between groups were tested with Fisher's exact test and Chi-square test. Actuarial overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan-Meier method and statistical significance was determined by Log-Rank test. Multivariate analysis to define independent prognostic factors for OS and DFS was performed by Cox regression. All statistical tests were 2-sided, and significance was defined as $p<0.05$.

RESULTS

Patient characteristics

Eighty-nine out of the 94 patients with locally advanced OPSCC treated with primary surgery during the analyzed period were considered, as 5 were excluded due to missing data. Eighty patients (89.9%) were males. Mean age at presentation was 57.6 ± 10.0 years (range, 39 to 78 years). Tumours were grouped according to their location: palatine tonsil was identified in 46 (51.6%), tongue base in 25 (28.1%), soft palate in 11 (12.4%); in the remaining 7 (7.9%) it was not possible to ascertain the primary location. Patients' demographics are shown in (Table 1).

Treatment characteristics

All patients underwent resection of the primary tumour associated with cervical neck dissection (Table 1). The extent of neck dissection was guided by the clinical situation. Functional neck dissection and modified radical neck dissection was performed in 74 (83.1%) and 15 (16.9%) patients, respectively. Pediculated myocutaneous flap reconstruction was performed in 20 (22.5%) patients. Histopathological resection results are shown in (Table 2). Seventy (78.7%) patients were staged as pT3-T4 and

74 (83.1%) had pathological positive nodal disease (pN+).

Table 1: Patients demographic and treatment details (n=89).

Parameter	N (%)
Gender	
Male	80 (89.9)
Female	9 (10.1)
Mean age (years)	57.6±10.0
Smoking habits	76 (85.4)
Pathological tumour stage	
T2	19 (21.3)
T3	43 (48.3)
T4	27 (30.3)
Pathological nodal stage	
N0	15 (16.9)
N1	20 (22.5)
N2	31(34.8)
N3	23 (25.8)
Tumour site	
Tonsil	46 (51.6)
Tongue base	25 (28.1)
Soft palate	11(12.4)
Other	7 (7.9)
Type of resection	
Partial pharyngectomy (transoral approach)	38 (42.7)
Basiglossectomy	4 (4.5)
Basiglossectomy with supraglottic	4 (4.5)
laryngectomy	28 (31.5)
Glossopelvectomy	
Glossopelvectomy with mandibulectomy	9 (10.1)
COMMANDO	6 (6.8)
Type of neck dissection	
Unilateral	33 (37.1)
Bilateral	56 (62.9)
Flap reconstruction	20 (22.5)
Adjuvant treatments	
Chemoradiotherapy	58 (65.2)
RT	63 (70.8)

COMMANDO: Combined mandibulectomy and neck dissection operation.

Postsurgical average length of hospital stay was 16.8±12.4 days. Prolonged hospital stay was due to pneumonia (33.8%), wound dehiscence (4.1%), fistula (5.4%), postoperative stroke (2.2%) and local infection (25.6%). All patients fulfilled the selection criteria for adjuvant therapy, but only 63 (70.8%) completed the latter, distributed as follows: 5 patients received exclusive RT and 58 received concomitant platinum-based chemotherapy. Reasons for not completing adjuvant therapy included death (n=5), patient refusal (n=1) and clinical contraindications (n=20).

Table 2: Histopathological data of resection specimens (n=89).

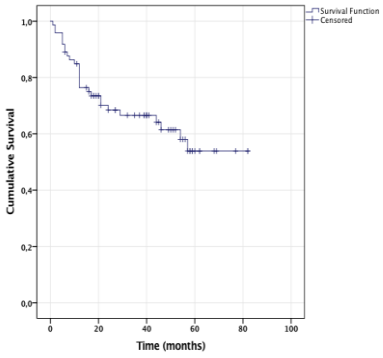
Margin status	N (%)
Negative	41 (46.1)
Positive	48 (53.9)
Perineural infiltration	54 (60.7)
Lymphovascular infiltration	35 (39.3)
Extranodal extension	42 (47.2)
Depth of invasion	
<5 mm	16 (18.0)
>5 mm	73 (82.0)

Survival and prognostic factors

The median follow up period was 37 months (25-75% IQR 14-54). There were 25 registered locoregional failures, occurring after a median interval of 11.0 months (25-75% IQR 6-21). Additionally, metastatic disease was reported in 15 patients.

Overall survival

Three and 5-year OS was 66.6% and 53.9%, respectively (Figure 1). On univariate analysis, cN stage (p=0.04), pN stage (p=0.02), and distant metastasis (p<0.01) had statistically significant negative impact on OS (Figure 2). Both postoperative RT (p<0.01) and chemoradiotherapy (p<0.01) were correlated with better OS. None of the other examined clinical variables were associated with the outcome measures (Table 3).



Time (months)	0	12	24	36	48	60	80
N events	0	11	21	23	25	26	27
Survival	1.00	0.85	0.68	0.67	0.64	0.54	0.54

Figure 1: Overall survival Kaplan Meyer curve for 89 patients operated for locally advanced OPSCC.

The prognostic role of pN stage (HR=2.65 95% IC 1.32-5.32, p<0.01) distant metastasis (HR=3.26 95% IC 1.24-8.62, p=0.01) and postoperative RT (HR=0.02 95% IC 0.01-0.12, p<0.01) was confirmed on Cox multivariate analysis.

Table 3: Univariate analysis of factors associated with overall and DFS.

Variable	Overall survival		DFS	
	Hazard ratios (95% IC)	P value	Hazard ratios (95% IC)	P value
Gender				
Female	0.04 (0.00-21.1)	0.31	0.29 (0.04-2.13)	0.22
Male	1		1	
Age	1.00 (0.97-1.04)	0.99	1.00 (0.96-1.04)	0.95
Smoking habits				
No	1		1	
Yes	2.59 (0.61-10.95)	0.20	1.57 (0.47-5.26)	0.47
Alcohol abuse				
No	1		1	
Yes	1.76 (0.66-4.68)	0.26	1.60 (0.60-4.29)	0.35
Primary site				
Tonsil	1		1	
Base of tongue	1.06 (0.42-2.63)	0.90	0.93 (0.35-2.44)	0.88
Soft palate/uvula	1.88 (0.67-5.29)	0.23	1.93 (0.69-5.42)	0.21
Oropharynx	1.62 (0.37-7.22)	0.53	0.68 (0.09-5.25)	0.72
Clinical T stage				
2	1		1	
3	1.29 (0.56-3.00)	0.45	1.13 (0.32-4.00)	0.84
4	1.53 (0.54 -4.34)	0.43	1.53 (0.33 -5.88)	0.65
Clinical N stage				
N0- N1	1		1	
N2-N3	1.53 (1.02-2.30)	0.04	1.60 (1.01-2.60)	0.04
Pathologic T stage				
2	1		1	
3	2.18 (0.95-4.99)	0.07	1.58 (0,68-3.65)	0.29
4	1.70 (0.46-6.30)	0.42	1.72 (0.47-6.25)	0.51
Pathologic N stage				
N0-N1	1		1	
N2-N3	2.69 (1.14-6.38)	0.02	2.54 (1.06-6.10)	0.04
Flap reconstruction				
No	1		1	
Yes	1.61 (0.70-3.68)	0.26	1.46 (0.61-5.50)	0.40
RT				
No	1		1	
Yes	0.03 (0.01-0.08)	<0.01	0.04 (0.01-0.13)	<0.01
Margins				
Negative	1		1	
Positive	1.04 (0.50-2.23	0.91	1.01 (0.46-2.21)	0.99
Lymphovascular invasion				
No	1		1	
Yes	1.30 (0.60-2.81)	0.51	1.54 (0.69-3.40)	0.29
Perineural invasion				
No	1		1	
Yes	1.94 (0.86-4.39)	0.11	2.54 (1.05-6.15)	0.04
Extranodal extension				
No	1		1	
Yes	1.29 (0.61-2.76)	0.51	1.60 (0.72-3.51)	0.25
Depth of invasion, categorical				
≤5 mm	1		1	
>5 mm	1.19 (0.39-3.69)	0.77	1.41 (0.41-4.88)	0.59
Depth of invasion, continuous	1.08 (0,72-1,60)	0.72	1.21 (0,82-1,78)	0.34
Distant metastasis				
No	1		1	
Yes	3.45 (1.56-7.65)	<0.01	5.74 (2.58-12.78)	<0.01
Length of hospital stay, days	1.02 (1.00-1.06)	0.07	1.02 (1.00-1.06)	0.14

DFS

Three- and five-year DFS was 66.5% and 57.7%, respectively (Figure 3). On univariate analysis, cN stage (p=0.04), pN stage (p=0.04), perineural infiltration (p=0.04) and distant metastasis (p<0.01) had statistically significant negative impact on DFS (Figure 2). Postoperative RT was correlated with better DFS (p<0.01). None of the other studied variables were associated with the outcome measures (Table 3).

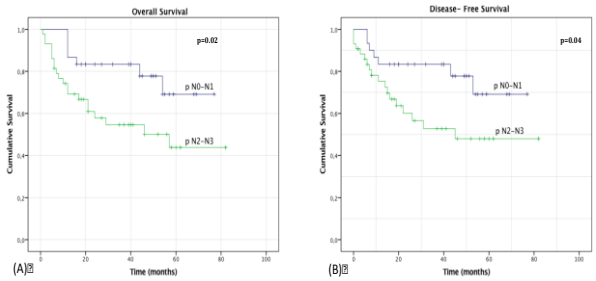
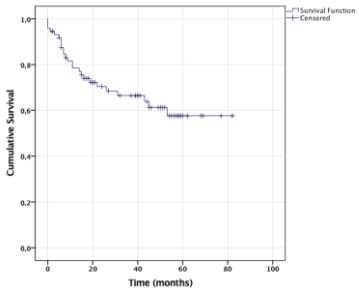


Figure 2: (A) Overall survival; (B): Disease free survival according to pN stage.



Time (months)	0	12	24	36	48	60	80
N events	0	15	20	22	24	25	25
Survival	1.00	0.79	0.70	0.66	0.61	0.58	0.58

Figure 3: Disease free survival Kaplan-Meyer curve for 89 patients operated for locally advanced OPSCC.

On Cox multivariate analysis, pN stage (HR=2.41, 95% IC 1.04-5.63, p=0.04) perineural infiltration (2.45, 95% IC 1.01-5.95 p=0.04) and distant metastasis (HR=5.24, 95% IC 2.31-11.89, p<0.01) were independent predictors of worse prognosis, in contrast to postoperative RT (HR=0.02 95% IC 0.00-0.18, p<0.01), which was a positive prognostic factor.

DISCUSSION

The present study was based on a patient series with locally advanced OPSCC treated with primary surgery. The median follow-up was 37 months, which was suitable for analysis of survival and prognostic factors, given the fact that tumour recurrences occurred after a median interval of 11 months. Regarding long-term outcome measures, patients presented 5-year OS of 53.9%, similar to the literature, in which it ranges from 33 to 77% 7-8 and 5-year DFS of 57.7%, comparable to previous reports.[7-8]

As previously mentioned, NCCN guidelines4 for OPSCC defined several risk factors, namely extranodal extension, nodal disease in levels IV or V, positive surgical margins, pT3-4 stage, perineural infiltration and lymphovascular invasion. Besides evaluating these traditional recognized risk factors, other clinical and histopathological features were analysed in the current study, aiming to identify other prognostic factors that might help in risk stratification and selection of appropriate treatment.

Analysis of socio-demographic profile of patients showed that the majority of them were in the sixth or seventh decade of life with a male-to-female ratio of 8:1, in agreement with previous reports.[9,10] While some authors have not found a significant association between age or gender with survival, 9 others sustain that patients with advanced age present with worse outcome.[10] In the present series, age or gender were not prognostic factors for survival or locoregional control. Smoking habits have a known pejorative effect on mortality and disease recurrence.[11,12] Their relevance, however, was not possible to ascertain in the present study and a reasonable explanation may be that most of the patients (85.4%) were current or past smokers.

The majority of patients enrolled were treated with adjuvant RT often combined with platinum-based chemotherapy. As expected, postoperative RT was found to correlate with better DFS and OS (p<0.001).[4] Conversely, multivariate analysis confirmed that postoperative RT was an independent positive prognostic factor for patients with advanced OPSCC treated with primary surgery.

Advanced pT stage (pT3-T4) is a known adverse feature in patients with OPSSC and, accordingly, in the present series, pT3 tumours presented better OS and DFS than pT4.[4,13] Nonetheless, pT stage was not identified as an independent prognostic factor of OS and DFS in the current study, which might be attributable to the heterogeneous distribution of pT stages among the studied population. Regarding nodal disease, advanced pathologic stage (pN2-3) was a major independent prognostic factor for DFS (p=0.04) and OS (p<0.01), as supported by the literature.[4-6] Conversely, in the present work, patients presenting pN2-3 necks, regardless of pT stage, had superior risk of recurrence and death. Although cN2-3 were correlated with poorer survival outcome, their role as independent prognostic factors were not confirmed on multivariate analysis, which indicates that performing neck dissection might be an important issue disentangling the prognostic influence of nodal disease in OPSSC patients.

The former results suggest that pN stage might have greater importance than local tumour stage (pT) in the

ultimate disease control, in agreement with previous reports.[14]

Post-operative histopathological assessment of tumour specimens revealed close or positive surgical margins in 48 (53.9%) patients, without significant impact on OS and DFS. A possible explanation for these findings might be that all patients with close or positive margins received adjuvant therapies, which may represent a confounding factor.[15,16] In addition, authors have considered the NCCN guidelines definition of positive margins, although the criteria to define a margin as adequate or inadequate and the role of margins on patients' outcome are still controversial issues in the literature.[4,15,16] Conversely, although positive margins have long been considered an important risk factor for recurrence, some studies have failed to find this association and recent researches by Molony et al, and Iyer et al, have even suggested that the adverse impact of positive margins on survival might be restricted to HPV negative OPSCC.[14-20] Interestingly, although tumoral histopathologic HPV status was not systematically evaluated as, by the time lapse of the surgical treatment (2011-2016), the role of HPV on prognosis had not yet been established, the demographic characteristics of the studied patients suggest that the majority of tumours were probably HPV- and, consequently, that impact of close and positive margins on OS and DFS on these tumours might be reduced.

Extranodal extension (ENE) was found in 42 (47.2%) patients with no significant impact on OS and DFS. Regarding OPSCC, some authors found a negative impact of ENE on clinical outcome, whereas others have shown no significant differences and the role of ENE in the HPV positive OPSCC is, inclusively, under research.[4,20,21] Nonetheless, NCCN guidelines recommend adjuvant treatments in the presence of ENE and, as previously stated for surgical margins, adjuvant therapies might be the reason for the absence of association between this finding and outcome.[4] Interestingly, the presented results suggest that pN stage might be more relevant than ENE in long-term survival of patients with advanced OPSCC.

Lymphatic and vascular invasion, as well as depth of tumour invasion did not show significant association with DFS or OS, in the present series, in contrast to previous reports.[4,14] Curiously, perineural infiltration (PNI), occurring in 54 (60.7%) patients, was found to be an independent negative prognostic factor (p= 0.04) for DFS, but not for OS. In the literature, PNI is a well-established indicator of poor prognosis in OPSCC, with association with aggressive tumour behaviour, disease regional recurrence and mortality.[22,23]

In the follow up, distant metastases were observed in 15 (16.8%) patients, and this was an independent prognostic factor for OS and DFS in this series (p>0.01). There are few studies regarding predictors of survival after distant recurrence of OPSCC, but according to them, in patients with single organ metastatic disease and good performance status, long-term disease control is achievable.[24,25]

Limitations of this present study includes despite the judicious selection of patients with advanced OPSCC aiming to provide a homogeneous population, this is a single-institution retrospective study with an inherent selection bias given the size of sample. Additionally, it is now well established that HPV related OPSCC present different epidemiological, clinical and histopathological characteristics with impact on survival and disease control and, conversely, the absence of control for HPV status is an important limitation of the present study. Future large prospective cohort studies that include clinical, treatment and histopathological characteristics, controlled for the presence of HPV status, might provide more information about prognostic factors in advanced OPSCC.

CONCLUSIONS

Five-year survival rate for locoregional advanced OPSCC treated with primary surgery was 53.9%. Pathological nodal stage and distant metastasis were the main prognostic factors for OS and DFS in the present series. Despite the advances in treatments, prognosis of OPSCC remains poor and knowledge of risks factors is crucial for selection of the more appropriate treatment and for proper stratification in future randomized trials.

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