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Oral and oropharyngeal cancer: time from first symptoms to treatment initiation and associated factors

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Abstract: The aim of this study was to evaluate the time elapsed from first symptoms to the treatment of oral and oropharyngeal cancer (OOC) and to identify variables associated with treatment delay. This is an observational study with retrospective and prospective data collection. Patients with a diagnosis of OOC seen at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital were included and followed up to treatment initiation. Participants answered a questionnaire for the collection of socioeconomic, demographic, cultural, and clinical information, as well as information about the time elapsed from first symptoms to the first appointment with a head and neck surgeon. Time to treatment was classified into four intervals: 1- first symptoms to first medical appointment; 2- first medical appointment to specialized medical care; 3- specialized medical care to preparation for treatment; and 4- preparation for treatment to treatment initiation. Bivariate statistics were computed. Out of 100 participants, nine died before treatment. Mean time to treatment was 217 days. Highest mean time was observed for interval 2 (94 days), followed by interval 1 (63 days), interval 4 (39 days), and interval 3 (21 days). At interval 1, a longer time was associated with severe alcohol consumption, severe smoking, and family history of cancer. At interval 2, the delay was associated with appointment with a general practitioner, clinical diagnosis of disease other than cancer, and antibiotic prescription. At interval 4, delay in treatment was associated with surgical treatment. Patients with OOC experience delays from symptom onset to treatment initiation. The longest interval was associated with professional delay, followed by patient delay in help-seeking.

Keywords: Mouth Neoplasms; Oropharyngeal Neoplasms; Time-to-Treatment; Diagnosis, Oral.

Introduction

Oral and oropharyngeal cancer (OOC) is a public health problem, accounting for approximately 160,000 deaths worldwide in 2020.[1] OOC is the sixth most common malignancy worldwide, and regions such as Latin America (Brazil, Uruguay, Puerto Rico, and Cuba), Asia (Sri Lanka, Pakistan, and Taiwan), and the Pacific Islands (Papua New Guinea and Melanesia) present the highest incidence rates.[2-4] Despite advances in

therapeutic modalities, the 5-year survival rate has not improved considerably, mostly due to late diagnosis.[5] Accordingly, early diagnosis and treatment significantly increase the survival rates and quality of life of patients.[5,6]

Comprehending the factors that affect OOC treatment delay is of paramount importance to prevent late diagnosis, but there is still no consensus on a time point beyond which a cancer diagnosis should be considered delayed. In this regard, different models have been proposed to standardize the evaluation of time intervals for cancer treatment.[5-9] The Aarhus statement[9] is a refined and updated version of the Andersen model[8] and standardizes the time intervals within a conceptual framework, suggesting four time intervals: appraisal, help-seeking, diagnosis, and pretreatment. This model considers events, processes, intervals, and contributing factors from the first symptoms to treatment initiation.[9]

Previous studies have reported a long interval from first symptoms to referral for diagnosis, and this has represented a risk factor for advanced staging and mortality from OOC.[10,11] In this sense, patient delay in seeking care has been reported as the main contributing factor for the overall delay in the diagnosis and treatment of OOC.[5,12-18] On the other hand, studies about the factors associated with patient, professional, and treatment delays are scarce, especially in the Brazilian population,[19,20] and they usually evaluate head and neck cancers all together.[11,21-23]

The aim of this study was to evaluate the time elapsed from the first symptoms to the beginning of treatment of OOC patients seen at a Brazilian public hospital, describing four intervals within this timeline, and to identify the variables associated with treatment delay. The rationale was to identify the intervals that contribute the most to the delay of OOC treatment and the determinants of this delay so that educational and training actions can be designed accordingly, thus favoring timely treatment, longer survival, and better quality of life of patients.

Methodology

The study was approved by the Research Ethics Committee of the "Hospital São João de Deus" (statement number: 40/2010; protocol no. 126). To confirm their voluntary participation, individuals signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki, assuring the anonymity of the participants.

This is an observational study with both retrospective and prospective data collection. The convenience sample was selected between July 2017 and June 2019 and included 100 consecutive patients with a diagnosis of OOC who attended their first appointment at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital ("Hospital São João de Deus", Divinópolis, Brazil). Patients with lip lesions were excluded. During the first appointment, participants answered a questionnaire on clinical, demographic, personal, cultural, social, and economic characteristics, as well as on the time elapsed from the first symptoms to the first appointment at the head and neck surgery outpatient clinic. Patients were then followed up to the beginning of cancer treatment.

Time to cancer treatment was analyzed based on the Aarhus Statement[9] and classified into four intervals (Figure): interval 1: time from the first symptoms to first medical appointment; interval 2: time from first medical appointment to first appointment at the Head and Neck Surgery outpatient clinic; interval 3: time from first appointment at the Head and Neck Surgery outpatient clinic to preparation for treatment (tests and exams prior to surgery or chemoradiation); and interval 4: time elapsed from preparation for treatment to treatment initiation. Information about intervals 1 and 2 was collected retrospectively from the patients during the first appointment at the Head and Neck Surgery outpatient clinic, whereas information about intervals 3 and 4 was prospectively registered by the head and neck surgery medical team.

The associated factors evaluated at interval 1 were sex, age at first medical appointment, marital status, place of residence, distance from home to the primary healthcare center, availability of dental care at primary healthcare center, access to private healthcare, alcohol consumption, smoking, time to schedule the first medical appointment, family

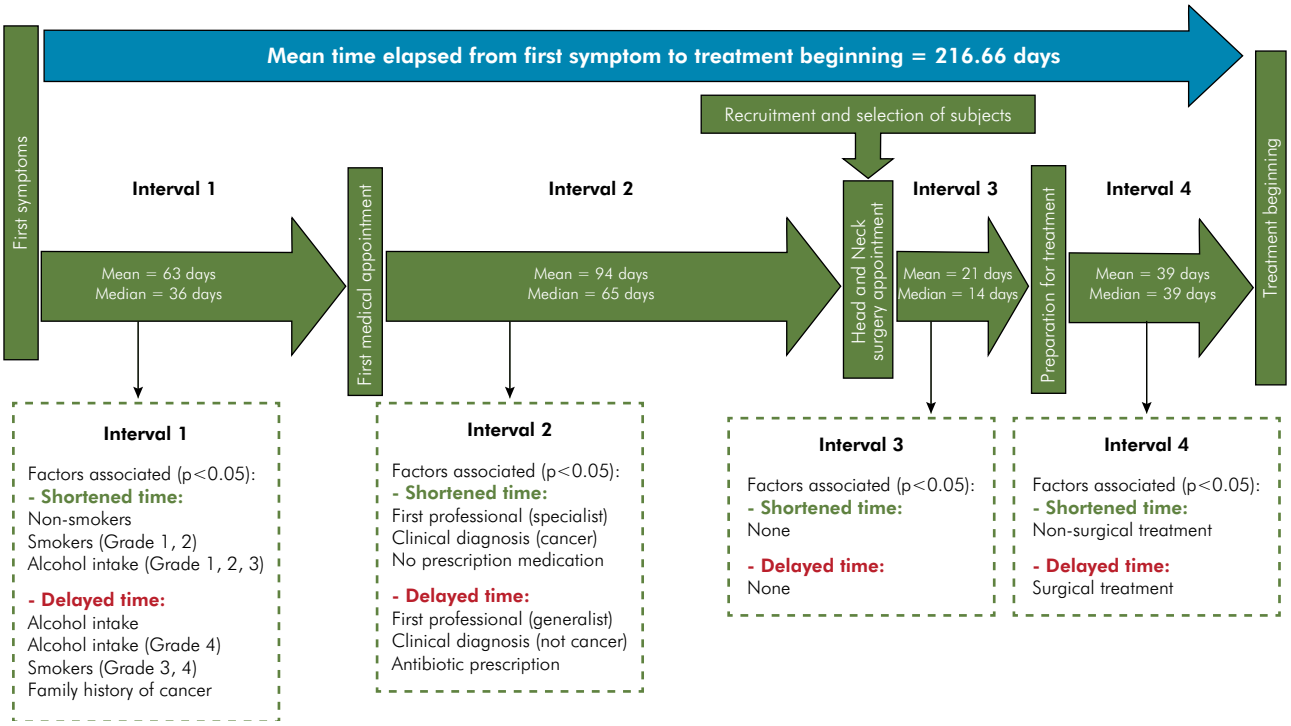

Figure 1. Timeline and associated factors, based on Aarhus Statement.[9] Time from first symptoms to treatment initiation of patients with oral and oropharyngeal cancer at a Brazilian public hospital, considering the four intervals. Factors associated with shortened or delayed time are shown. The green arrows are proportionally sized.

history of any type of cancer, family history of head and neck cancer, and clinical stage of the disease (TNM). For interval 2, the factors evaluated were qualification of the first healthcare professional who attended to the patient, clinical diagnosis, appointment at the private healthcare center, drug prescription, antibiotic prescription, and clinical staging. For interval 3, family income, access to private healthcare, treatment preparation in the private healthcare system, and clinical staging were analyzed. Finally, at interval 4, two variables were evaluated: treatment modality and clinical staging. All variables were dichotomized for statistical analysis considering the median time of each time interval as a reference (see the Results section).

Alcohol consumption was graded considering daily intake, as follows: grade 1: one bottle of beer (600 mL), one glass of wine (150 mL), or one dose of distilled spirits (50 mL); grade 2: two bottles of beer, two glasses of wine, or two doses of distilled spirits; grade 3: three bottles of beer, three glasses of wine, or three doses of distilled spirits; and grade 4: four bottles of beer, four glasses of wine, or four doses of distilled spirits. Smoking habit was also graded considering daily usage: grade 1: 10 conventional cigarettes or one roll-your-own cigarette; grade 2: 20 conventional cigarettes or two roll-your-own cigarettes; grade 3: 30 conventional cigarettes or three roll-your-own cigarettes; and grade 4: 40 conventional cigarettes or four roll-your-own cigarettes.

Statistical analysis was performed using the SPSS® software, version 19.0. Pearson's chi-square and Fisher's exact tests were performed to assess the association between time intervals and clinical, demographic, personal, cultural, social, and economic characteristics. p-values < 0.05 were considered significant.

Results

One hundred patients were included (78 males and 22 females), and the age range was 38 to 91

Table 1. Factors associated with time from the first symptoms to first medical appointment (time interval 1) of patients with oral and oropharyngeal cancer seen at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital.

Variable	Time from first symptoms to first appointment - n (%)		p-value*
	≤ 30 days	> 30 days	
Sex			0.281
Male	35 (46.1)	41 (53.9)	
Female	13 (59.1)	9 (40.9)	
Age at first medical appointment			0.542
≤ 55 years	22 (45.8)	26 (54.2)	
> 55 years	26 (52.0)	24 (48.0)	
Marital status			0.670
Not married	21 (46.7)	24 (53.3)	
Married	27 (50.9)	26 (49.1)	
Place of residence			0.415
Urban	43 (50.6)	42 (49.4)	
Rural	5 (38.5)	8 (61.5)	
Distance from home to primary healthcare center			0.673
≤ 3 blocks	21 (46.7)	24 (53.3)	
> 3 blocks	27 (50.9)	26 (49.1)	
Availability of dental care at primary healthcare center			0.101
No	21 (60.0)	14 (40.0)	
Yes	26 (42.6)	35 (57.4)	
Access to private healthcare			0.302
No	41 (47.1)	46 (52.9)	
Yes	7 (63.6)	4 (36.4)	
Alcohol consumption			0.005**
Yes	41 (45.1)	50 (54.9)	
No	7 (100)	0 (0.00)	
Alcohol consumption intensity			0.007**
Grades 1, 2, 3	17 (68.0)	8 (32.0)	
Grade 4	24 (36.4)	42 (63.6)	
Smoking			0.015**
Yes	40 (44.9)	49 (55.1)	
No	8 (88.9)	1 (11.1)	
Smoking intensity			0.001**
Grades 1, 2	25 (65.8)	13 (34.2)	
Grades 3, 4	15 (29.4)	36 (70.6)	
Time to schedule the first medical appointment			0.483
≤ 7 days	34 (50.7)	33 (49.3)	
> 7 days	12 (42.9)	16 (57.1)	

Continue

Continuation			
Family history of cancer			0.043**
No	29 (59.2)	20 (40.8)	
Yes	19 (38.8)	30 (61.2)	
Family history of head and neck cancer			0.076
No	45 (52.3)	41 (47.7)	
Yes	3 (25.0)	9 (75.0)	
Clinical stage (TNM)			0.307
I, II	16 (57.1)	12 (42.9)	
III, IV	32 (45.7)	38 (54.3)	

Missing data were not considered for statistical comparisons. *Chi-square and Fisher's exact tests. **statistically significant.

years. Fifty-five patients had oral cancer and 45 had oropharyngeal cancer. Most patients (n= 72) were diagnosed at clinical stages III and IV, whereas the remaining patients (n= 28) were diagnosed at stages I and II. The mean time from the first symptoms to treatment initiation was 217 days. Figure shows the mean and median time for each interval and the factors associated with shortened and delayed time. Tables 1, 2, 3, and 4 show the results for all factors analyzed at time intervals 1, 2, 3, and 4, respectively.

The mean time to schedule an appointment with a head and neck surgeon was shorter (61 days) when the first medical appointment was performed by a specialist (of any area) rather than by a general practitioner (124 days). Moreover, the nine patients who died before treatment showed longer time for intervals 1 and 2 (mean of 83 and 137 days, respectively) when compared to those who started treatment (mean of 61 and 90 days, respectively). Finally, patients with oral cancer had a slightly shorter time from symptom onset to treatment initiation (mean of 202 days) compared with those with oropharyngeal tumors (227 days).

Discussion

The delay from the onset of OOC symptoms to diagnosis and treatment is known to be associated with advanced-stage disease and lower survival rates.[11,13,24,25] The mean time from the first symptoms to the treatment initiation of OOC found in this study is consistent with the findings of previous studies from developing countries, such as Brazil (217.3 days, n = 180),[19] India (210 days, n = 201),[26] and Thailand (166.1 days, n = 154).[27] On the other hand, research from developed countries reported a lower average time, as observed in a Spanish population (107.18 days, n = 183).[28]

Brazil has a well-established public health system – the Unified Health System ("Sistema Único de Saúde" – SUS) –, which is organized based on the principles of universal and equitable access to healthcare.[29] In 2012, a Brazilian federal law[30]established that for patients with a main clinical suspicion of malignant neoplasia, confirmatory exams must be performed within 30 days after medical request and treatment must be started within 60 days after conclusive and histopathologically proven cancer diagnosis.[31] The results of the current study seem to be in accordance with the deadlines established by the law; however, it is noticeable that the patient journey before cancer treatment initiation has not evolved since 2007,[19] evidencing the need to prevent OOC late diagnosis and delayed treatment.

Importantly (and alarmingly), the longest interval was that of professional delay, as previously reported.[32-34] Factors such as first appointment with a general practitioner, who made a clinical diagnosis of a disease other than cancer and prescribed antibiotics, clearly delayed the final diagnosis. Likewise, Esmaelbeigi et al.[32] also reported that patients who were treated with drugs such as analgesics had a higher risk of professional delay

Table 2. Factors associated with time from the first medical appointment to head and neck surgery appointment (time interval 2) of patients with oral and oropharyngeal cancer seen at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital.

Variables	Time from first medical appointment to head and neck surgery appointment - n (%)		p- value*
	≤ 60 days	> 60 days	
First professional (generalist *versus* specialist physician)			0.007**
General practitioner (physician)	16 (37.2)	27 (62.8)	
Specialist (physician)	19 (70.4)	8 (29.6)	
First professional (physician *versus* dentist)			0.189
General practitioner (physician)	16 (37.2)	27 (62.8)	
Dentist	8 (57.1)	6 (42.9)	
Clinical diagnosis			0.024**
Cancer	23 (62.2)	14 (37.8)	
Not cancer	24 (38.7)	38 (61.3)	
Appointment at private healthcare center			0.541
No	20 (51.3)	19 (48.7)	
Yes	27 (45.0)	33 (55.0)	
Drug prescription			< 0.001**
No	30 (68.2)	14 (31.8)	
Yes	17 (30.9)	38 (69.1)	
Antibiotic prescription			0.035**
Yes	7 (41.2)	10 (58.8)	
No	29 (70.7)	12 (29.3)	
Clinical stage (TNM)			0.226
I, II	16 (57.1)	12 (42.9)	
III, IV	31 (43.7)	40 (56.3)	

Missing data were not considered for statistical comparisons. *Chi-square and Fisher's exact tests. **statistically significant.

than did those patients undergoing appropriate procedures such as biopsy at the first appointment. Actually, several studies have revealed that clinical misdiagnosis is associated with greater professional delay.[32-35]

In addition, we found no difference between first appointment with a dentist and with a general practitioner. Accordingly, previous studies have reported a lack of commitment of dentists and general practitioners to oral cancer diagnosis.[19,32] Finally, professional delay occurred irrespective of patients having attended their medical appointment at the private healthcare center, suggesting that the challenges to overcome cancer treatment delay are not circumscribed to the public healthcare centers, as previously evidenced.[13] Taken together, these findings reinforce the need for constant training and for educational campaigns about OOC for generalist professionals (physicians, dentists, and nurses),[32,35] as well as routine screening for OOC.[33] Within the Brazilian Unified Health System, these professionals see many patients periodically for clinical control of diverse diseases; therefore they could be important players in the early detection of OOC cancer.

As previously reported,[10,25-27,36] another large interval was the patient delay in seeking healthcare, which can be motivated by the belief that the lesions are unproblematic and will get better by themselves.[10,27] Panzarella et al. found that "personal experience of cancer," "knowledge of cancer," "unawareness", and "denial" were the most meaningful factors associated with patient delay in seeking care.[36] Moreover, other variables such as level of education and occupation[27]

Table 3. Factors associated with time from the appointment with head and neck surgeon to preparation for treatment (time interval 3) of patients with oral and oropharyngeal cancer seen at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital.

Variables	Time from appointment with head and neck surgeon to preparation for treatment - n (%)		p-value*
	≤ 14 days	> 14 days	
Family income			0.333
< 1 minimum wage	12 (57.1)	9 (42.9)	
1 to 3 minimum wage	13 (43.3)	17 (56.7)	
> 3 minimum wage	2 (66.7)	1 (33.3)	
Access to private healthcare			0.669
No	25 (52.1)	23 (47.9)	
Yes	2 (33.3)	4 (66.7)	
Treatment preparation at private healthcare center			0.413
No	11 (44.0)	14 (56.0)	
Yes	16 (55.2)	13 (44.8)	
Clinical stage			0.564
I, II	8 (44.4)	10 (55.6)	
III, IV	19 (52.8)	17 (47.2)	

Missing data were not considered for statistical comparisons. * Chi-square and Fisher's exact tests. **statistically significant.

Table 4. Factors associated with time from preparation for treatment and treatment initiation (time interval 4) of patients with oral and oropharyngeal cancer seen at the Head and Neck Surgery outpatient clinic of a Brazilian public hospital.

Variable	Time from preparation for treatment to treatment initiation - n%		p-value
	≤ 30 days	> 30 days	
Treatment modality			0.001*
Surgical	11 (22.0)	39 (78.0)	
Non-surgical	23 (56.1)	18 (43.9)	
Clinical stage (TNM)			0.606
I, II	9 (33.3)	18 (66.7)	
III, IV	25 (39.1)	39 (60.9)	

Missing data were not considered for statistical comparisons. [a] Chi-square and Fisher's exact tests. * statistically significant.

and the distance from the patient's home to the healthcare center[26] have been previously related to time to seek healthcare for suspected cancer. Conversely, no association was observed between some sociodemographic variables and patient delay in the current sample, highlighting that patients will postpone seeking healthcare irrespective of their sex, age, marital status, place of residence, distance from their home to the healthcare center, access to the private care system, availability of dental care at healthcare centers, time to schedule a medical appointment, or family history of head and neck cancer. Other studies have also found no association between some of these sociodemographic variables and patient delay in seeking care.[27,36] This lack of association may be partially explained by the universal coverage of the Brazilian Unified Health System,[29] which provides healthcare to a population with a broad and diverse sociodemographic profile.

Heavy smokers, drinkers, and people with family history of cancer were the ones who took longer to seek healthcare in the current study, indicating probable fear of having cancer and low self-care with health. Conversely, previous studies

have shown that non-smokers had a longer delay in cancer diagnosis than did smokers, and no association with alcohol consumption,[37-39] maybe because the suspicion of oral cancer is lower in this population. Taking these controversies into consideration, educational campaigns targeted at the population should stimulate people to seek healthcare periodically, regardless of bad habits, thus favoring the early diagnosis of OOC.

The shortest intervals in this study – intervals 3 and 4 – comprise time to hospital treatment. The few studies that have analyzed time to hospital treatment of oral cancer patients usually reported shorter intervals, from 23.4 to 28 days.[3,23,40] None of the variables analyzed in the present study were associated with interval 3, revealing that the time from the appointment with a head and neck surgeon to preparation for treatment will be similar, regardless of family income and of whether the preparation for treatment was performed at a private healthcare center.

In the current study, surgical treatment was associated with delayed time at interval 4, and it has been shown that patients who underwent surgical treatment in early stages (I-II) were most affected (disadvantage in survival) by treatment delay.[23,40] Therefore, the health team should be committed to prompt treatment of early-stage OOC, preferably with a multidisciplinary approach at the first appointment to speed up treatment initiation and prevent cancer stage progression.[3] Finally, the clinical stage of the tumor was not associated with any time interval, reinforcing the continuous need for early-stage diagnosis of OOC.[19,34]

Some limitations of the present study should be acknowledged. First, the study was conducted before the COVID-19 pandemic outbreak; therefore, further studies will be able to provide a post-pandemic outlook on OCC time to treatment. Second, the study population was selected from a public hospital, thus there could be some selection bias. In this sense, generalization of results for non-hospital scenarios and for private institutions should not be made. Third, memory bias could compromise some of the information recalled by the patients. Fourth, each time interval was dichotomized and this might have hindered statistical comparisons.

Conclusion

In conclusion, OOC patients seen at a Brazilian public hospital had a long journey from symptom onset to treatment initiation. Professional delay comprised the longest interval and was associated with misdiagnosis, reinforcing the need for continuing education of health professionals. Patient delay in seeking healthcare was also important and was associated with bad social habits and family history of cancer. Once the patient could be seen by the head and neck surgeon, treatment had a reasonable time flow, irrespective of cancer stage and sociodemographic variables.

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