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Research Article
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Impact of Delay in Treatment Initiation in Overall Survival in Head and Neck Cancer

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Abstract

Introduction: The purpose of our study was to identify the impact the delay from diagnosis to treatment interval has on Overall Survival (OS) in head and neck cancer patients.

Materials and Methods: We performed a retrospective study of head and neck cancer patients diagnosed in the "Hospital de Clinicas" in Montevideo, Uruguay, between 2005-2015. Recursive partitioning analysis was used to find the prognostic cut off of Diagnosis to Treatment Interval (DTI) that affects survival.

Results: We identified a prognostic cut off time that differentiates OS in 40.5 days. Median OS was 36.16 months for patients with DTI ≤ 40.5 days, and 23.14 months for DTI >40.5 days (p=0.006). In localized disease median OS was 116.3 months for DTI ≤ 40.5 days *vs*. 55 months for DTI >40.5 days. In advanced is ease they were 27.6 *vs*. 21.1 months respectively (p=0.009). In laryngeal cancer median OS was 70.58 months for ≤ 40.5 days *vs*. 27.75 months for DTI >40.5 days. The difference was more pronounced in patient treated with radiotherapy (35.7 *vs*. 21.1 months) than in treated with surgery (34.2 *vs*. 49.9 months) (p=0.041). Multivariable analysis found that sex, DTI, site and tumor stage impact on the survival.

Conclusion: A DTI greater than 40.5 days is associated with worse OS in patients with head and neck tumors, independently of the treatment received, the stage and the anatomic site of the primary tumor.

Keywords: Treatment delay; Head and neck cancer; Diagnostic to treatment interval, Uruguay

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Introduction

Head and neck squamous cell carcinoma accounts worldwide for more than 650,000 cases and 330,000 deaths annually. We can describe an important variation in the observed distribution of head and neck cancer in different areas of the world, related to different risk factors [1]. The most relevant prognostic factor in these patients is the stage according to American Joint Committee on Cancer (AJCC) [2]. Most patients often present with variable conditions (comorbidity, performance status) which contributes to advanced stage disease at presentation [1]. Oncologic outcomes for these patients remain poor, despite advances in target agents and immunotherapy [3-7].

Improving cancer care delivery, it's critical to improving clinical outcomes and remains a challenge. The ideal Diagnosis to first Treatment Interval (DTI) has been an issue of debate. It has not been tested in a randomized fashion, and although many studies have shown improved outcomes with shorter times, the issue remains controversial [8,9]. The purpose of this study is identifying a threshold for DTI based on the overall survival a cohort of patients with head and neck cancer. Secondly, we analyzed the association of DTI with overall survival.

Material and Methods

We conducted a retrospective, observational cohort study with patients with squamous cell carcinoma of head and neck diagnosed in the Hospital de Clinicas, in Montevideo, Uruguay, between 2005-2015. The study protocol was approved by the institutional review board of the center. Patient variables included were age, sex, race, smoking status, alcoholism, consumption of mate (hot infusion prepared with Ilex paraguariensis). All patients had ECOG PS 0-2. Disease covariates

included American Joint Committee in Cancer (AJCC) stage in 7th edition, anatomic location and treatment received. We defined DTI as the number of days between histopathological diagnosis and first treatment. Recursive partitioning analysis (rpartofR®) was used to find the prognostic cutoff of DTI that affects survival. Patient who did not receive any treatment were excluded.

Descriptive statistics were used to summarize variables. The survival was estimated with Kaplan Meier methods. Median survival times and their 95% Confidence Interval (CI) were presented. Differences in overall survival were tested with log-rank test, in relation to tumor stage, anatomic site, gender, as well as the delay in the initiation of treatment. Cox proportional hazard regression model was used to study the interaction of variables. All analyses were performed in SPSS® version 25. For all analyses a p value less than or equal to 0.05 was considered to be statistically significant.

Results

Population characteristics

A total of 480 patients with head and neck cancer were included (mean age 62.6 years (22-89), 81.9% male).

The most common primary tumor site was larynx 38.9% followed by oropharynx in 29.1% and oral cavity 17.4%. Most patients presented advances disease at diagnosis, 53.4% in stage IV and 25.2% in stage III. Patients' characteristics were summarized in Table 1.

377 patients received any treatment. The median follow-up was 6.9 years (3.84-13.84). The rest were excluded. The median OS of this cohort was of 29.16 months (CI 95% 23.08-35.04) (Figure 1). The 3-year OS rate was 44.5% and the 5-year OS rate was 35% for all patients. OS for larynx cancer was superior to other anatomic sites: 49.84 months (23.2-76.7) vs. 25.34 months (CI 95% 19.8-30.9) (Figure 2). The 5-year OS rate was 46.5% vs. 26.2% respectively. For localized disease (stage I-II) the median overall survival was 84.1 months (18.4-138) vs. 24,1 (2.8- 87.3) months for advance disease (p<0.0001, Figure 3), with 5-year OS rate of 57.7% vs. 28.9% respectively. The first treatment was radiotherapy ± chemotherapy in 42.2%, and surgery in 57.8%. The median DTI for any treatment was of 32.0 days (rang 0-189). In the case of RT was 61.0 days (1-185) and for surgery was 22.2 days (0-189).

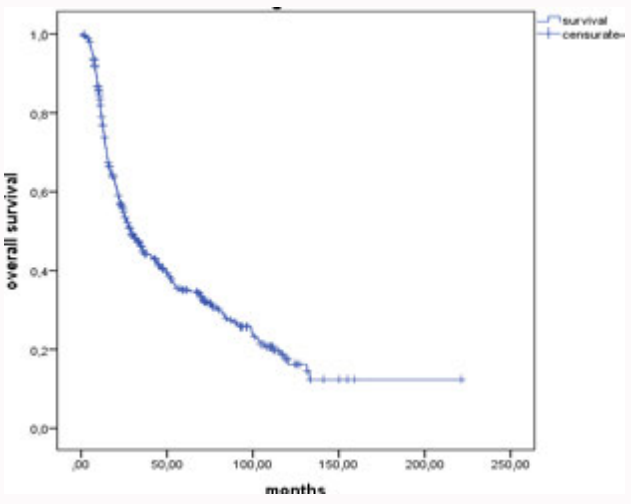

Figure 1: Overall survival.

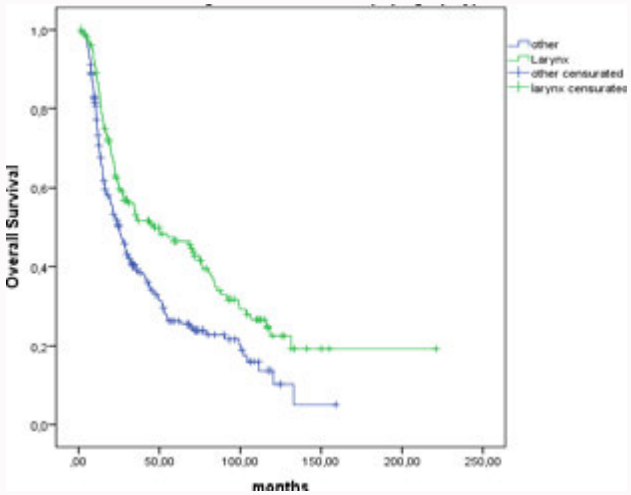

Figure 2: Overall survival (topography).

Table 1: Characteristics of patients.

		n	%
		488	100
Sex			
- Female		87	18.1
- Male		393	81.9
Smoke			
- Yes		402	83.8
- No		74	15.4
- sd		4	
Alcoholism			
- Yes		326	67.9
- No		150	31.3
- sd		4	
Consume of mate			
- Yes		407	84.8
- No		68	14.2
- sd		5	
Stage			
-	1	49	2.8
-	2	48	10.6
-	3	114	25.2
-	4	243	53.4

Association of DTI with overall survival

With recursive partitioning analysis, we identified a prognostic cut off to differentiate overall survival in 40.5 days. Median overall survival was 36.16 months for patients with 40.5 days or less, whereas for the DTI group of over 40.5 days was 23.14 months (p=0.006), with a difference between both groups of 13 months (Figure 4). The 5-year OS rate was 41.5% vs. 21.0% respectively.

Based on our threshold of 40.5 days, 241 of our patients (50.2%) experienced treatment delay. 127 patients (26.6%) started treatment 60 days after diagnosis.

Similar results were found independently of tumor stage and

Table 2: Multivariable analysis found that gender, DTI, anatomic site and tumor stage impact on survival.

Univariate Analysis	HR (IC 95%)	Multivariate Analysis	HR (IC 95%)
Sex		**Sex**	
- Female	P=0.015	- Feminine	P=0.01
- Male	HR: 0.68 (0.5-0.93)	- Masculine	HR: 0.78 (0.61-0.98)
Alcoholism		**Alcoholism**	
- No	P=0.007	- No	P=0.25
- Yes	HR 0.84 (0.74-0.95)	- Yes	HR 1.18 (0.8-1.6)
Site		**Sitio**	
- Larynx	P=0.0001	- Larynx	P=0.0001
- No larynx	HR 1.68 (1.3-2.2)	- No larynx	HR 1.66 (1.3-2.1)
Stage		**Stage**	
- Stage I-II	P=0.025	- Stage I-II	P=0.001
- Stage III-IV	1.4 (1.04 y 1.9)	- Stage III-IV	1.72 (1.3y 2.4)
TTD		**TTD**	
- <40.5 days	P=0.019	- <40.5 days	P=0.044
- ≥ 40.5 days	1.29 (1.04-1.6)	- ≥ 40.5 days	1.32 (1.18-1.5)

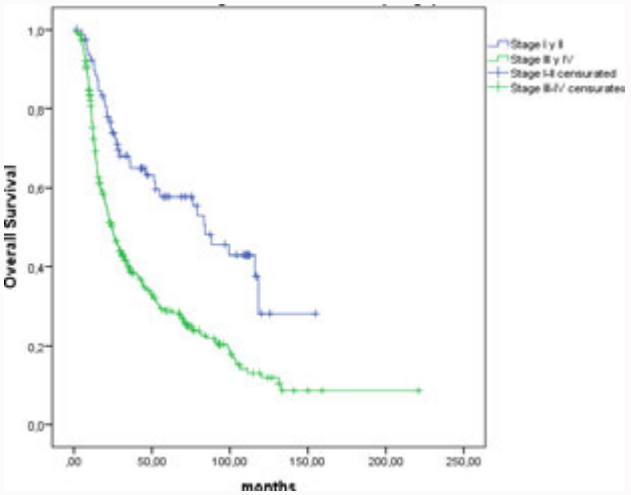

Figure 3: Overall survival (Stage).

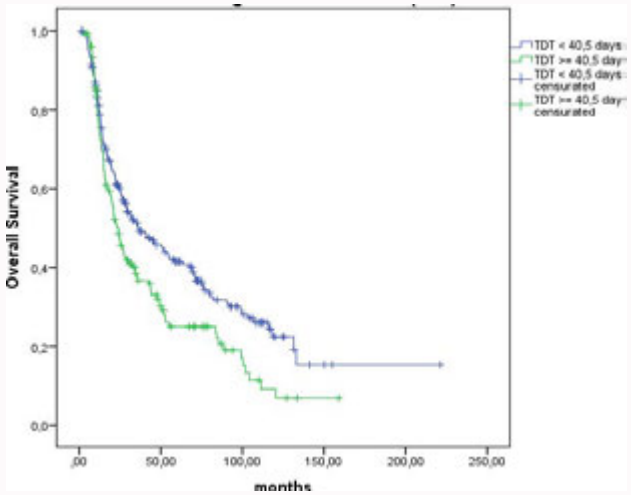

Figure 4: Overall survival (TDT).

anatomic site. In localized disease (stage I and II) median overall survival was 116.3 months for patients with 40.5 days or less, versus 55 months for the DTI group over 40.5 days. In advanced disease OS was 27.6 vs. 21.1 months respectively (p=0.009). In larynx cancer this difference was more pronounced. Median overall survival was 70.58 months for patients with 40.5 days or less, versus 27.75 months for the group over 40.5 days. For other anatomic sites the OS was 29.26 vs. 40.4 months (p=0.001). The difference was largest in patient treated with radiotherapy (35.7 vs. 21.1 months) compared to those treated with surgery (34.2 vs. 49.9 months) (p=0.041). Multivariable analysis (Table 2) found that gender, DTI, an atomic site and tumor stage impact on survival.

Discussion

We investigated the consequences of delay in the initiation of treatment in patients with head and neck cancer in the largest teaching hospital of Montevideo, Uruguay. This is the first study in Uruguay to analyze this factor and how it impacts on overall survival of patients with head and neck cancer. We found a higher prevalence of male patients, as reported in national and international. Literature [10], which is associated to higher alcohol and tobacco use in this population. The median age in our cohort was 62.69 years (range 22-89), similar to that reported [9,11-13]. The most frequent site was the larynx (38.9%), as was previously reported by our group [13-15], whereas in the literature the oropharynx is often reported as the most prevalent site for head and neck tumors. In Chile, Canada, and some European countries, there is a higher prevalence of oropharyngeal and oral cavity tumors [15]. The higher incidence of larynx tumors we observed is likely due to the high prevalence of tobacco use in our population [11] and the strong association between larynx cancer and smoking [16]. The incidence of oropharyngeal cancer in developed countries particularly in white men, has increased where there also has been a decrease in the incidence of other head and neck cancers among men. This is probably related to the association of the Human Papilloma Virus (HPV) as a causal factor in this subset of tumors alongside a decrease in tobacco and alcohol use [17].

More than 75% of patients were diagnosed with an advanced stage disease. Most of our patients come from deficient socioeconomic and

cultural contexts, which has been associated with late diagnosis and worse prognosis [18]. The median OS of patients receiving treatment was 29.16 months, with a 5-year OS rate of 35%. We also observed in our cohort a better survival for larynx cancer compared to the rest of the anatomic sites, being almost double (49.84 vs. 25.34 months). Survival of larynx cancer is associated to the site within the larynx where the tumor develops. In glottic tumors survival is greater, which is due to several causes (early diagnosis, lower lymph node dissemination) [19]. Our results are slightly below those reported in the literature. The world health organization reports a 5-year survival rate of 40% to 50% in locally advance disease [1,10]. Gatta et al. [20], in Eurocare-5 population-based study report five-year relative survival for localized cases ranged between 42% (hypopharynx) and 74% (larynx). In clinical trials (EORTC 22931 and RTOG9501) patients receiving adjuvant treatment concurrent with radiotherapy showed 5-year overall survival of 53% to 40% [21]. The large number of patients diagnosed at advanced stages and the use of OS instead of disease specific survival or relative survival could explain our comparatively lower results.

We found that controlling other factors, a DTI exceeding 40.5 days was associated to a decrease in overall survival. A DTI within 40.5 days resulted in an improved survival of 13 months (median overall survival 36.16 vs. 23.14 months), with a HR of 1.32 (CI 95% 1.18-1.5; p=0.044). In view of this result, efforts should be made to start treatment as quickly as possible. We found that the surgery had a median time from diagnosis of 22.2 days (0-189) and in the case of RT was 61.0 days (1-185). In both treatment modalities the prognosis value of time of delay was statically significant. Fifty percent of our patients experiment treatment delay based on our calculated threshold of 40.5 days. Murphy et al. [3], describe the results of patients who received curative therapy in the National Cancer Data Base (NCDB) of United State. They found that a DTI of 61 to 90 days vs. less than 30 days (Hazard Ratio [HR], 1.13; 95% CI 1.08 to 1.19) independently increased mortality risk. If we used the same threshold of 60 days, 26.6% of our population received late treatment. This may reflect the more vulnerable characteristics of our patient population. In the report of Liao et al. [7], who take an underserved urban population, 20.8% of patients experiment treatment delay, closer to our results. They found a difference of 18 to 24 months with a threshold of 60 days.

Some studies did not show an impact in OS with a delay of the DTI. Richardson et al. [22], only studied patients with larynx and oropharynx cancers and they believed that the patients had other good prognostic factors. Caudell et al. [22], only included advanced patients (stage III-IV) treated with radiotherapy and state that this may have been the reason they found no difference. We performed subgroup analysis in patients' stage III-IV (compared with I-II) and in larynx cancer vs. other primary sites. We found that the difference was more pronounced in early stages. In localized disease (stage I and II) median overall survival was survival was double in those with DTI beyond 40.5 days. In larynx cancer the difference was more marked also (more than 40 months). In multivariate analysis, DTI was an independent predictor of overall survival disregarding tumor stage, and tumor primary location.

A recently systematic review published [23], with the aims to provide the effects of DTI on oncological and functional outcomes, included a total of 51 studies with important variation in methodology and incomplete adjustment for confounding factors. All studies were retrospective, with multiplicity of biases. Disregarding the level of evidence, they concluded that treatment delay affects oncology outcomes. We did not analyze the reasons behind of the delay in the initiation of treatment, this being very important factor because understanding them would allow us to design strategies to deliver timely treatment to those patients who are being delayed, improving their survival. There are some limitations to our study. It is a single center study and the sample size is relatively small. It is a retrospective study, so it depends on the accuracy of the clinical file registry, thus we believe results need to be validated prospectively.

Conclusion

A diagnosis to treatment interval greater than 40.5 days impacts negatively on the overall survival of head and neck cancer patients, independently of the treatment received, disease stage and an atomic site. Future studies must focus on the causes of such delay in order to improve our therapeutic outcomes.

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