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The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma

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ABSTRACT

Objectives: To quantify the effect that time to initiation of treatment after diagnosis has on the outcomes of patients with head and neck squamous cell carcinoma (HNSCC).
Methods: This is a single institution retrospective analysis of 633 HNSCC patients treated from 2004 to 2017. Clinical information was abstracted from the medical records. Patients were divided into quartiles based on the time to treatment initiation (0–27 days, 28–41 days, 42–60 days, and > 60 days). Kaplan-Meier overall survival (OS) curves and multivariate cox proportional hazard ratios were determined for time to treatment quartiles.
Results: Differences in Kaplan-Meier estimates for OS based on treatment time quartiles were statistically significantly ($p = 0.02$), and multivariate Cox Proportional hazard ratios for OS revealed that patients in the 42–60 day treatment time group had better OS (hazard ratio = 0.55) compared to patients treated > days after diagnosis ($p < 0.01$).
Conclusions: For our study population, increased time to initiation of treatment did not impact overall survival. These results may help to alleviate patient anxiety while allowing time for useful interventions such as smoking cessation, nutritional counseling, and others that can affect clinical outcomes.

Introduction

The incidence of head and neck squamous cell carcinoma (HNSCC) continues to increase in the United States, with an estimated 65,410 new cases diagnosed in 2019 [1]. The number of new cases has increased by more than a thousand per year for the past several years [2,3]. HNSCC is managed with a combination of surgery, radiation, and chemotherapy depending on site and stage. Once a patient is diagnosed with HNSCC, staging is performed and a treatment plan is formed with input from physicians across multiple disciplines to choose the ideal therapeutic regimen. The complexity of this process can result in delays between initial diagnosis and initiation of therapy.

Further exacerbating this problem, radiotherapy planning and delivery has become more sophisticated over time [4], and its incorporation with other treatment modalities is a major contributor to increased time between diagnosis and treatment initiation of HNSCC [5]. Other factors associated with increased time to treatment initiation include advanced stage, treatment at academic medical centers, and transferring of care from another medical facility [5,6]. Moreover, HNSCC patients who are current smokers were recently reported to have significantly improved survival when given the opportunity to quit for at least 30 days prior to starting therapy [7].

Several studies suggest that increasing the time to definitive treatment may have a negative impact on disease recurrence and overall survival [8–11]. This may be due to the progression of disease during the interval between diagnosis and treatment with a decrease in effectiveness of any treatment to control disease [12–18]. However, several other studies have found no association between a delay in treatment initiation and outcomes [19–23]. In the context of such conflicting data, the purpose of this analysis was to determine the effect

Abbreviations: HNSCC, head and neck squamous cell carcinoma; OS, overall survival; KM, Kaplan-Meier; CCRT, concurrent chemoradiation therapy; RT, radiation therapy; HR, hazard ratio

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of length of time between diagnosis of HNSCC and the initiation of definitive treatment on overall survival of patients at a National Cancer Institute designated Comprehensive Cancer Center.

Methods

Patient selection

This study was approved by the Roswell Park Institutional Review Board. The study population consisted of patients diagnosed with squamous cell carcinoma of the oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx and treated with radiation therapy at Roswell Park between 2004 and 2017. Patients were excluded from the study if they had distant metastases at the time of diagnosis, underwent prior therapy for a previous head and neck cancer, or were not treated definitively. All patients were treated with radiation therapy alone or in combination with surgery and/or chemotherapy.

The date of diagnosis was defined as the date that a histopathologic determination of malignancy was first made. The date of treatment initiation was defined as the date that any treatment with curative intent (surgery, induction chemotherapy, definitive radiotherapy or chemo-radiotherapy) was started. Patients who were diagnosed pathologically on the date of surgery were assigned a time to treatment initiation of zero days.

Demographic and tumor characteristics, treatment information, and outcomes of the selected patient cohort were obtained from the medical record. Patients underwent radiation therapy and follow-up evaluation according to protocols previously described [24,25].

Statistical analysis

Patients were divided into quartiles based on the time to treatment initiation (0–27 days, 28–41 days, 42–60 days, and > 60 days). The effect of the length of time between diagnosis and initiation of treatment on overall survival (OS) was examined using multivariate cox proportional hazard regression models with the > 60 day quartile serving as the reference group. Models were adjusted for age, gender, and overall tumor stage. Kaplan-Meier (KM) survival curves were analyzed for differences in OS between treatment time groups. A p-value of < 0.05 was considered statistically significant. All analyses were conducted in SAS version 9.4.

Results

Patient demographics

Descriptive characteristics of the 633 patients in the study population are given in Table 1. The mean age of the cohort was 61.3 years (standard deviation = 10.38). Early stage primaries (T_1–T_2) were diagnosed in 283 patients (44.7%), whereas 301 patients (47.5%) had advanced stage primaries (T_3–T_4). The majority of the patients had squamous cell carcinoma of the oropharynx (43.1%), larynx (28.6%), or oral cavity (14.8%). Concurrent chemoradiation (CCRT) was the most commonly used treatment modality, with 57.8% of the patients receiving CCRT. Radiation therapy (RT) was used alone in 10.4% of the cohort. The HPV status was unknown for a large portion of the study population, as HPV testing was not routinely performed in the early years of the study. Where reported (n = 356), 58.7% were HPV+ and 41.3% were HPV−. Over half (53.6%) of the patients in the study were former smokers, 26.1% were current smokers during treatment, and 20.4% of patients were never smokers.

Effects of time to treatment

The Kaplan-Meier survival analysis of the study population showed a statistical difference in survival between the four treatment time groups (p = 0.02) (Fig. 1). There was no statistically significant difference in overall survival for patients in the first two treatment time groups as compared to those who were treated beyond 60 days after diagnosis, but there was a significant increase in survival for patients

Table 1
Descriptive characteristics of patients with squamous cell carcinoma of the head and neck (n = 633).

Characteristic	Value (mean (std), Frequency (%))
Age at diagnosis (years)	61.32 (10.38)
Mean Follow up time (months)	36.21 (29.54)
Gender	
Male	509 (80.51%)
Female	124 (19.59%)
Race[a]	
White	547
African American	57
American Indian or Alaskan native	4
Asian	5
Unknown	21
Tobacco Status	
Never	129 (20.38%)
Former	339 (53.55%)
Current	165 (26.07%)
T stage (1–4)	
T1	93
T2	190
T3	185
T4	116
Other[b]	49
N-Stage	
N0	184
N1	79
N2	317
N3	53
HPV status	
Negative	147 (23.22%)
Positive	209 (33.02%)
Unknown	277 (43.76%)
Disease Subsite[a]	
Lip	5
Oral Cavity	90
Nasopharynx	19
Oropharynx	273
Hypopharynx	42
Supraglottis	112
Glottis	70
Subglottis	3
Maxillary Sinus	2
Nasal Cavity and Ethmoid Sinus	6
Parotid Gland	8
Submandibular Gland	1
Treatment Type	
RT only	66 (10.43%)
CCRT	366 (57.82%)
Surgery and CCRT	105 (16.59%)
Surgery and RT	34 (5.37%)
CCRT and neck dissection	10 (1.58%)
ICT and CCRT	52 (8.21%)
Current Status	
Alive	402 (63.51%)
Dead	231 (36.49%)
Time to treatment initiation	
0–27 days	164 (25.91%)
28–41 days	158 (24.96%)
42–60 days	163 (25.75%)
Greater than 60 days	148 (23.38%)

[a] Adds to 643 due to multi-racial patient and patient having cancer with multiple subsites.
[b] Other refers to unknown primary tumors, Tis, and Tx.

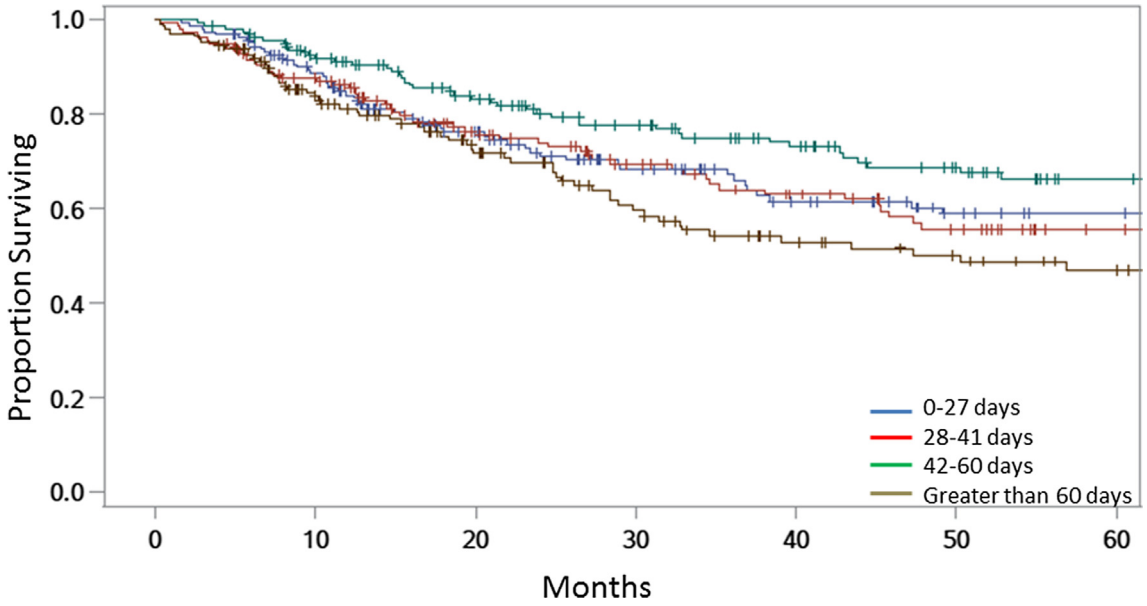

Fig. 1. Kaplan Meier overall survival of squamous cell carcinoma of the head and neck from stratified by treatment initiation time; 0–27 days, 28–41 days, 42–60 days, and greater than 60 days. Patients with 42–60 days before treatment initiation exhibited the best overall survival (n = 633, p = 0.02).

Table 2
Cox proportional hazard ratio models for overall survival in patients with squamous cell carcinoma of the head and neck (n = 633).

Group	Age – Adjusted Model		Multivariate Model*	
	HR (95% CI)	P-value	HR (95% CI)	p-value
> 60 days (ref)	1.00		1.00	
42–60 days	0.499 (0.344, 0.725)	< 0.01	0.548 (0.367, 0.819)	< 0.01
28–41 days	0.730 (0.51, 1.045)	0.086	0.790 (0.543, 1.148)	0.22
0–27 days	0.729 (0.511, 1.039)	0.08	0.756 (0.525, 1.087)	0.13

* Multivariate model adjusted for age, T stage, and smoking status.

treated between 42 and 60 days ($p < 0.01$) in both the age-adjusted model (hazard ration (HR) = 0.50) and the multivariate model (HR = 0.55) (Table 2).

When the survival analysis was stratified by primary tumor site, the difference in OS between treatment time groups was not significant between groups for laryngeal, oropharyngeal, or oral cavity tumors. There were too few nasopharyngeal and hypopharyngeal patients for meaningful analysis.

When the cohort was stratified by T stage, patients with low stage primaries (T_1–T_2) had a combined OS that was better than patients with locally advanced primaries (T_3–T_4) (Figs. 2 and 3). Differences in OS between treatment time groups, however, were only statistically significant for patients with T_3–T_4 primaries (p = 0.02) (Fig. 3). Delaying treatment initiation did not have a significant effect on OS for patients treated with CCRT with or without surgery. Similarly, there was no significant difference in the OS between treatment time groups according to tumor HPV status. There were too few patients treated with either ICT + CCRT or RT alone for meaningful analysis.

Discussion

Our analysis shows that HNSCC patients treated between 42 and 60 days after diagnosis had significantly better OS than patients treated before or after this period of time. When stratified by tumor site, treatment type, tumor T stage, and HPV status, no significant difference in survival between treatment time groups was shown for most of the subset analyses. The only significant differences were found among those with stage T_3 or T_4 tumors.

Improved OS at 42–60 days after diagnosis is similar to findings reported by van Harten et al., which found that patients who were treated within 30 days of diagnosis had significantly worse survival than the patients treated after 30 days [20]. With respect to larger delays in treatment initiation, Fortin et al. found that a delay in RT initiation greater than 40 days resulted in worse OS [9]. Their definition of time to treatment, however, was from the first consult with a radiation oncologist to treatment initiation. In this context, after considering the additional time between diagnosis and consultation, our finding of a worse outcome after 60 days may be more equivalent than indicated by the numerical discrepancy. In our study, the patients treated within 42 days after diagnosis may have been rushed to treatment because they had, on average, more rapidly progressing or symptomatic tumors that would explain their poorer OS than the patients treated between 42 and 60 days after diagnosis. Patients with more aggressive tumors may experience more symptoms, leading to more rapid treatment and therefore patients with an inherently decreased survival may be overrepresented in the first quartile. This phenomenon has been observed in both head and neck cancers [27] and other malignancies [26,27].

The majority of studies assessing treatment initiation times and outcomes analyzed patient populations treated solely with RT [9,19,21–23,28]. Two other studies analyzed cohorts treated with a combination of surgery, radiotherapy, and chemoradiotherapy [8,20]. Of these studies, only the study by Murphy et al. [8] stratified the analysis of time to treatment initiation and overall survival by treatment modality and concluded that treatment initiated beyond 60 days after diagnosis was associated with an increased risk of mortality [8]. Additionally, survival of patients treated with CCRT was largely unaffected by delays in treatment initiation out to 90 days after diagnosis. [8] These results are in concordance with our study; delaying treatment initiation did not have a significant effect on OS for patients treated with CCRT.

A retrospective study of 61 patients with HNSCC treated with radiation therapy demonstrated a 38% increase in tumor volume occurred in the weeks between staging and treatment planning scans, with 16% of patients progressing in T or N stage [16]. When

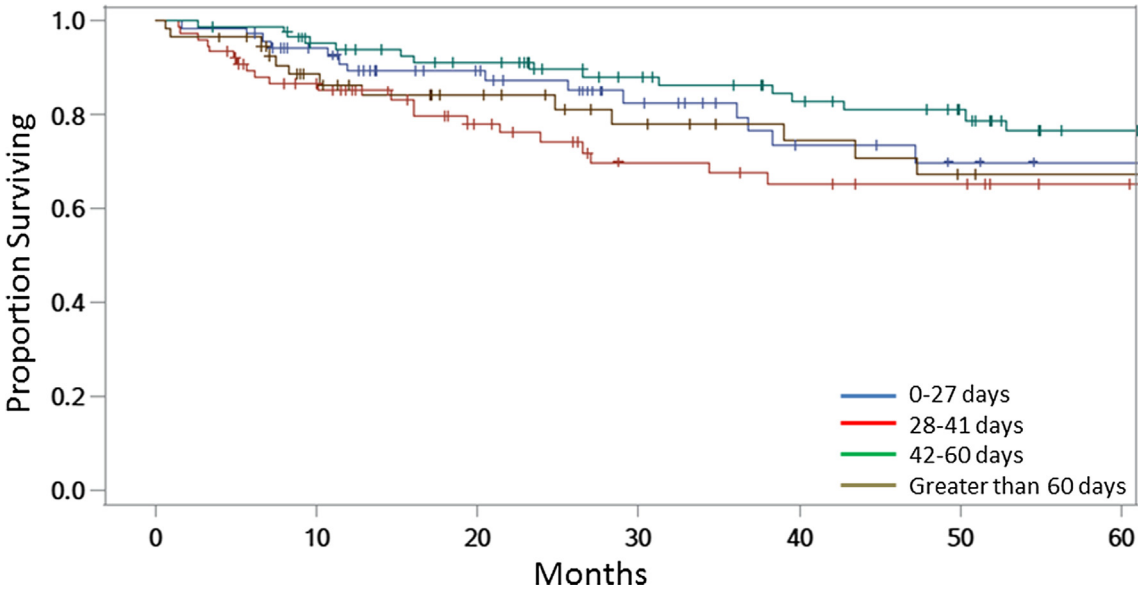

Fig. 2. Kaplan Meier overall survival of stage T1 and T2 squamous cell carcinoma of the head and neck stratified by treatment initiation time; 0–27 days, 28–41 days, 42–60 days, and greater than 60 days (n = 283, p = 0.25).

considering any effect that a delay in treatment initiation may have on OS, the literature suggests that patients with lower T stage tumors may be more sensitive to this delay as their tumors have more potential to progress in a shorter time period [8,9,12,16]. Results from this study do not support this. There was only a significant difference in OS among those with locally advanced primaries (T_3–T_4) and not for patients with low stage primaries (T_1–T_2). Perhaps this reflects the efficacy of CCRT in our population to deal with any tumor growth except in the most advanced tumors with long treatment delays.

It is well known that the location of the primary tumor in HNSCC can have an effect on OS [29]. Less understood, however, is the interaction of primary tumor location and time to treatment initiation on OS. In this study, the difference in OS between treatment time groups was not significant between groups for laryngeal, oropharyngeal, or oral cavity tumors. There were too few nasopharyngeal or hypopharyngeal patients for meaningful analysis. Similarly, difference in OS between treatment time groups was not significant when stratified by HPV status.

Overall for HNSCC patients, treatment should always be carried out in a timely manner and without unnecessary delays. However, an increased interval between diagnosis and treatment initiation is not a reason to omit newer technologies, such as intensity-modulated radiation therapy that requires more time for sophisticated treatment planning but spares more normal tissues than older RT techniques.

While their oncologists are carefully planning a patient's treatment the patient themselves may experience anxiety about the wait time. Prior to treatment they have already experienced waiting periods between symptom onset and first contact with primary care physicians, between investigation of symptoms and referrals to oncologists, and finally between pathologic diagnosis and treatment initiation [30]. Much of this concern may be attributed to the patient's perceived risk of waiting to initiate treatment and cancer progression [30]. Studies

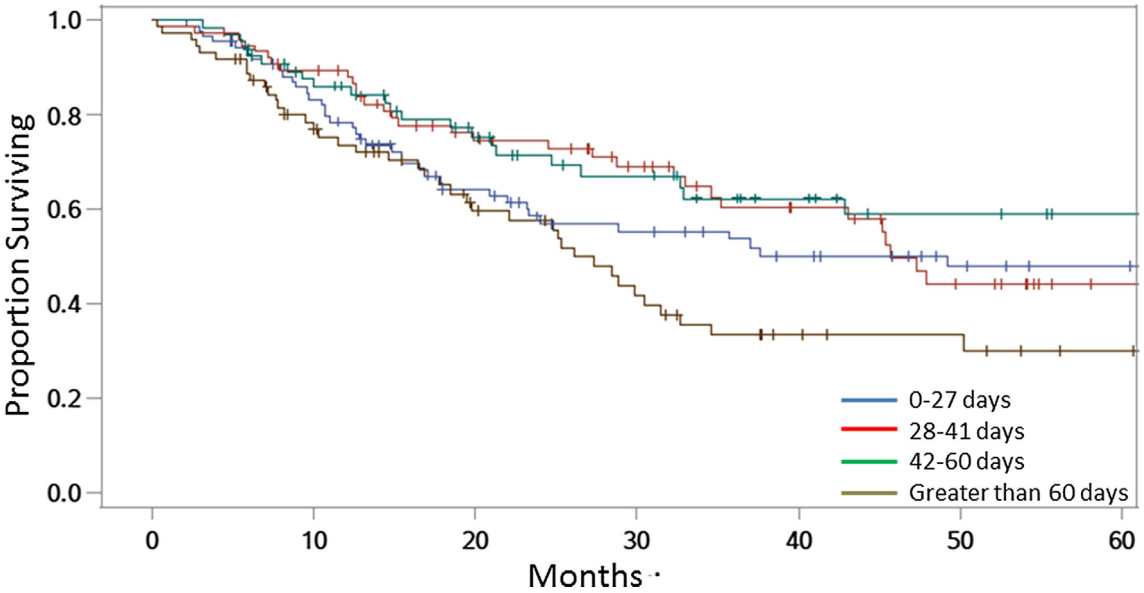

Fig. 3. Kaplan Meier overall survival of stage T3 and T4 squamous cell carcinoma of the head and neck stratified by treatment initiation time; 0–27 days, 28–41 days, 42–60 days, and greater than 60 days (n = 301, p = 0.02).

looking at populations of prostate and breast cancer patients demonstrate that patient's experience significant concern in the initial period waiting to initiate treatment [31,32]. These studies all cite the need for improved patient-physician communication regarding how wait times may impact a patient's prognosis. Studies like ours may be used in that conversation to alleviate patient's anxiety. In addition to improved patient-physician conversations this lag time before treatment could be used to initiate useful interventions such as smoking cessation and nutrition counseling potentially impacting clinical outcomes [7,33].

Conclusions

The outcomes of patients treated with radiation therapy were not affected by delays in treatment initiation. For some patients, wait time to treatment initiation (i.e. 42–60 days) might not negatively impact treatment outcome; this data may alleviate patient anxiety. This additional time should be used to ensure optimal treatment planning, promote smoking cessation, as well as improve nutritional status and other factors that can affect clinical outcomes.

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Declaration of Competing Interest

None declared.

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