American Journal of Otolaryngology and Head and Neck Surgery

Research Article
Published: 04 Jan, 2021

# Time to Treatment Analysis of Head and Neck Cancer Patients Undergoing Proton Therapy

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## Abstract

**Aim:** To define treatment planning times for patients with head and neck cancers undergoing curative-intent proton therapy at a regional academic proton center.

**Methods:** We performed a retrospective institutional review board approved study of patients diagnosed with head and neck cancers treated with curative-intent proton therapy at a single center from 2015 to 2020. Time from CT simulation to initiation of treatment was recorded for each disease site and compared using a one-way ANOVA.

**Results:** We identified 177 patients that met our inclusion criteria of which 53 (30%) had oropharynx, 44 (25%) paranasal sinus, 27 (15%) salivary gland, 22 (12%) oral cavity, 20 (11%) nasopharynx, and 11 (6%) cutaneous squamous cell cancers. Median time from simulation to treatment initiation was 21 days with locally advanced cutaneous squamous cell carcinoma exhibiting the longest time at 27 days ($p<0.05$).

**Conclusion:** Proton therapy time from simulation to treatment was similar across most disease sites. The diffuse pattern of perineural disease spread common to locally advanced cutaneous squamous cell carcinomas suggests the need to optimized work flow to ensure timely treatment initiation.

**Keywords: Proton therapy; Head and neck cancer; Dosimetry; Treatment planning time**

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**Received Date**: *11 Nov 2020*
**Accepted Date:** *08 Dec 2020*
**Published Date:** *04 Jan 2021*

***Citation:***
*Arons D, Alexander GS, Kouralakis AI, Zakary MJ, Molitoris JK, Miller RC. Time to Treatment Analysis of Head and Neck Cancer Patients Undergoing Proton Therapy. Am J Otolaryngol Head Neck Surg. 2021; 4(1): 1116.*



## Introduction

In 2018 there were 890,000 new head and neck cancer cases worldwide, making it the seventh most common cancer [1,2]. Early-stage Head and Neck Squamous Cell Carcinoma (HNSCC) is treated with surgery or radiotherapy alone, while locally advanced cases are often treated with a combination of surgery, radiation, chemotherapy, and/or chemoradiation [3]. As a large percentage of these patients are curable, significant effort has been put forward to reduce treatment related morbidity. Developments in Intensity-Modulated Radiotherapy (IMRT) have had tremendous success in sparing normal tissue during treatment. Given the high rate of cure, many are seeking to decrease acute and long term toxicities which may have large impact on quality of life with improved treatment modalities [4,5]. Proton Therapy (PT) is an emerging radiation modality that has become increasingly accessible and widespread in recent years [6]. Given the unique physical properties of particle therapy, PT can reduce normal tissue dosage, which could reduce acute and long term toxicities when compared to IMRT. This hypothesis is currently the subject of an ongoing randomized, prospective Phase III clinical trial NCT01893307 [7].

However, with the emergence of PT, concerns have arisen regarding not only cost-effectiveness of the treatment but also the potential for treatment delays in initiation of radiotherapy delivery times given the complexity of proton delivery as well as the paucity of radiation centers [4,8]. As delayed treatment times are associated with inferior oncologic outcomes, timely delivery of curative treatment is of paramount importance. A variety of factors may influence the initiation of PT including complexity of patient's disease, referral patterns, and complexity of treatment planning. To help identify patients who have higher complexity of treatment planning, we sought to examine our institutional experience and identify disease subsites that may warrant expedited care paths. Further we discuss other factors that can possibly result in increased time to treatment initiation and suggest strategies to mitigate these challenges.

## Methods

A retrospective cohort study was completed of patients diagnosed with a head and neck cancer that were treated at a single proton center from 2015 to 2020. Patients were included for analysis if they were treated with PT to a disease site in the head and neck with curative intent. Treatment initiation was defined as number of days from the date of CT simulation to delivery of the first fraction of radiotherapy. Patients who had a treatment initiation time of greater than 90 days were excluded from analysis. Additionally, we excluded patients who received mixed photon-proton plans or patients who transferred their care to us partially through external beam treatment from at an outside institution. Data was extracted from available electronic medical records. Primary cancer sites included the paranasal sinus, oropharynx, nasopharynx, oral cavity; salivary gland and cutaneous squamous cell carcinoma. Median time from CT simulation and treatment initiation were reported and compared using a one-way ANOVA.

## Results

Overall, 177 patients were included for analysis. Median time from CT simulation to treatment initiation was 21 days (range 2 to 75 days). Patients with locally advanced cutaneous squamous cell carcinoma had the highest median time for treatment initiation with a median treatment initiation time of 27 days. Patients treated for oropharynx cancer exhibited the narrowest range of treatment initiation time of 2 to 40 days, while patients with related in the oral cavity region experienced the largest range of 7 to 70 days (Figure 1).

## Discussion

While PT is an attractive technique to potentially reduce short- and long-term side effects, treatment time initiation is an important consideration and treatment planning should be optimized to prevent treatment delays. A national cancer database report demonstrated that patients who underwent PT were more likely to have treatment delays compared to those that received IMRT. The median radiation initiation from time of diagnosis was 59 days for patients undergoing proton radiation when compared to a median of 45 days in patients undergoing photon-based radiotherapy [9]. However, these results are limited by its retrospective nature and differences in patient population between those PT and IMRT cohorts. In our single institution retrospective review, we described time from CT simulation to initiation of treatment planning times for patients undergoing treatment with PT with curative intent based on disease subsite. We identified patients with locally advanced cutaneous squamous cell carcinomas having the longest median time from CT simulation to initiation of first fraction of treatment. This likely represents the common presentation of perineural invasion a with disease approximately important structures such as the optic nerves, optic chiasm, and brainstem making planning and clinical decision making difficult. To ensure timely initiation of therapy delivery, these patients should have optimized care paths to prevent treatment delays to prevent the possibility of untoward clinical outcomes. Given proper prioritization of institutional resources such as dosimetrists, medical physicists, and attending physicians it is feasible to generate plans in a timely fashion as noted by many treatment plans being delivered within 3 weeks from CT simulation.

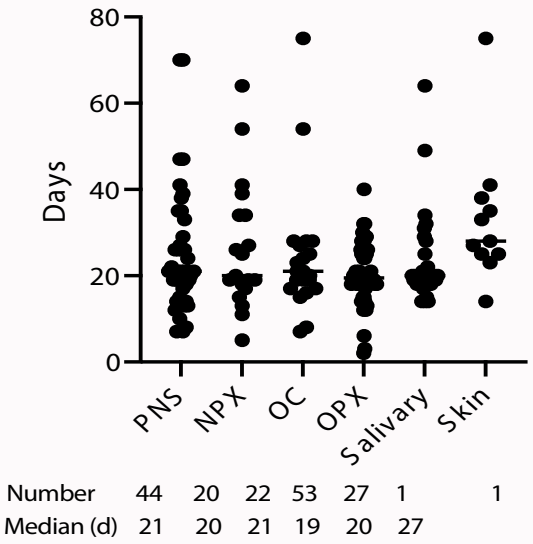


**Figure 1:** Graphical representation of CT simulation to proton therapy initiation time in days for patients with Paranasal Sinus (PNS), Nasopharynx (NPX), Oral Cavity (OC), Oropharynx (OPX), salivary, and skin cancer, $p<0.05$.

Several steps in the PT planning process can result in delays. Image registration and fusion of MRI and/or PET/CT generally occurs on the same day of CT simulation. Target delineation and contouring of normal organs at risk requires input from the physician. Most institutions allow several days for contouring, but more stringent care path goals could be considered for head and neck patients. Given the complexity of contouring decision and clinic work flow demands, this may not always be feasible. Another solution to increase speed of the planning process would be to optimize dosimetry expertise, automated contouring of normal structures, and standardized approaches in terms of beam arrangement and weighting for each head and neck subsite. Yet another consideration is the length of time required to perform Patient Specific QA (PSQA). The PSQA process is typically more time-intensive for PT compared to photon therapy. Phantom-based measurements are the standard of practice for PSQA for both IMRT/VMAT photon therapy as well as proton therapy [9,10]. Such measurements are typically more laborious for proton therapy due to the generally-accepted practice of measuring multiple depths per field, as well as the relative scarcity of proton beam time [10]. While some proton therapy centers have begun moving away from phantom-based measurements towards log file analysis and secondary calculation verification for PSQA [11], this is not yet a common practice.

Of note, PT planning times are only a single factor which is incorporated into treatment initiation and the time of CT simulation to treatment initiation may be increased by other factors such as hospitalization for acute medical illness, coordination with chemotherapy, or other patient related factors. While our analysis examined only CT simulation to treatment planning time, total package time is also an important consideration so CT simulation should be obtained as soon as feasible and ideally on the day of consultation with the radiation oncologist. Despite this recommendation, several important logistic considerations exist which may prevent this from being a viable option in every case such as machine availability, pending insurance approval, or patient indecision regarding choice of definitive treatment modality.

Furthermore, many patients with head and neck cancer require dental evaluation and will often need to have dental extractions prior to initiation of radiotherapy. Adequate time to allow for post-

extraction healing is necessary to prevent serious complications such as osteoradionecrosis [12]. Ideally, to minimize treatment delays institutions should initiate dental evaluation as soon as possible so that they have all required dental extractions and adequate post-extraction healing to initiate radiotherapy in a timely manner. This is of particular importance as post-extraction edema may more significantly affect dose distribution with PT compared to photon therapy.

Additionally, referral patterns and institutional patterns have been reported to play a role in treatment delays with definitive treatment initiation appearing to vary significantly when compared across different institutions in similar geographic areas [13,14]. These analyses have also noted that treatment delays appear to be more common in patients with more advanced disease who require multi-disciplinary input as they often will require combined modality treatment which necessitates consultation with several physicians who may have limited availability for appointment. If possible, these visits should ideally be coordinated on a single visit day in multi-disciplinary clinics and patients should be discussed in a multi-disciplinary tumor board in a timely manner to swiftly decide the most optimal path of patient management.

A final note of consideration, while our median start time from date of CT simulation was 21 days, this may not necessarily reflect only the treatment planning time but also other logistic considerations. For example, many physicians prefer to start radiotherapy patients in the beginning of the week rather than start the first fraction on a Thursday or Friday. Occasionally, even though the RT plan may be ready for delivery, the start of treatment is delayed to coincide with the start of concurrent systemic therapy.

## Conclusion

Proton therapy may offer dosimetric advantages over photon-based treatment modalities, but treatment planning may be more resource intensive and require work flow optimization. To ensure prompt initiation of definitive PT, prompt coordination between all multi-disciplinary teams should occur to allow initiation of CT simulation as soon as possible to minimize further delay in treatment. Locally advanced cutaneous squamous cell carcinomas require particular consideration as treatment planning may take longer.

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