PHILIPPINE JOURNAL OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY VOL. 39 NO. 2 JULY – DECEMBER 2024

Association of Treatment Delays with Survival for Patients with Head and Neck Cancer Undergoing Surgery and Radiotherapy at the Philippine General Hospital

Nicole D. Sacayan-Quitay, MD[1]
Sean Patrick C. De Guzman, MD[2]
Johanna Patricia A. Cañal, MD, MHA, MSc[2,3]
Cesar Vincent L. Villafuerte, III, MD[1,2,4]

[1]*Department of Otolaryngology - Head and Neck Surgery*
Philippine General Hospital
University of the Philippines Manila
[2]*Division of Radiation Oncology,*
Department of Radiology, Philippine General Hospital
University of the Philippines Manila
[3]*Department of Radiology*
College of Medicine – Philippine General Hospital
University of the Philippines Manila
[4]*Philippine National Ear Institute*
National Institutes of Health
University of the Philippines Manila

ABSTRACT

Objective: To identify in what phases in the treatment of head and neck cancer do delays happen at a tertiary hospital and to determine the association between the length of treatment delays and the oncologic outcomes (disease-free survival and overall survival) for patients with head and neck cancer.

Methods:

Design: Retrospective Cohort Study

Setting: Tertiary National University Hospital

Participants: Sixty-eight (68) patients who had surgery and adjuvant radiotherapy for invasive head and neck cancer at the Philippine General Hospital during the 5-year period of January 2014 to December 2019 were included in the initial consideration. Only 15 had survival data and were thus eligible for inclusion in this study.

Results: The median treatment package time for head and neck cancers in our institution was 27.6 weeks or 193 days. The treatment package time statistically correlated with both overall survival, $F(1,13)=12.952$, $p<0.005$, $R^2=0.499$, and disease-free survival, $F(1\text{-}13)=12.823$, $p<0.005$, $R^2= 0.497$. However, the independent effects of other predictors such as time interval between first consult to histopathologic diagnosis, diagnosis to surgery, and surgery to post-operative radiotherapy, showed no statistically significant association with overall survival and disease-free survival.

Conclusion: All study patients experienced treatment delays from diagnosis to surgery, and surgery to adjuvant radiation therapy, and in their total treatment package time. The positive correlation among treatment package time, and disease-free and overall survival in this study must be further investigated in order to elucidate the true effect of delays across time intervals in the treatment of head and neck cancer in the Philippine General Hospital. Every effort should be made towards timely management of these patients.

Keywords: *head and neck neoplasms; radiotherapy, adjuvant; survival rate; treatment outcome; time-to-treatment; surgery; disease-free survival; delayed diagnosis; retrospective studies; postoperative care*

Correspondence: Dr. Cesar Vincent L. Villafuerte III
Department of Otolaryngology – Head and Neck Surgery
University of the Philippines Manila
Ward 10, Philippine General Hospital, Taft Ave.,
Ermita, Manila 1000
Philippines
Phone: (632) 8554 8467
Fax: (632) 8524 4455
Email: clvillafuerte@up.edu.ph

The authors declared that this represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere, in full or in part, in print or electronic media; that the manuscript has been read and approved by all the authors, that the requirements for authorship have been met by each author, and that the authors believe that the manuscript represents honest work.

Disclosures: The authors signed disclosures that there are no financial or other (including personal) relationships, intellectual passion, political or religious beliefs, and institutional affiliations that might lead to a conflict of interest.

Philipp J Otolaryngol Head Neck Surg 2024; 39 (2): 7-11

Timely care of head and neck cancer (HNC) has been associated with increased overall survival.[1] Early-stage cancers have a favorable prognosis with high cure rates while oncologic outcomes remain poor for HNC especially for locally advanced disease. Diagnosis-to-treatment intervals are particularly important for patients with head and neck cancer because these relatively fast-growing tumors affect anatomically and functionally complex areas which in turn affect important functions such as breathing, swallowing, and speaking.[2] Delays in management may further lead to prolonged length of hospital stay. Moreover, the economic burden of treating complex cases affects public health systems not to mention the families of the patients.[3]

Numerous studies have shown that increasing the time to initiate treatment increases the tumor burden and worsens the prognosis.[4] Specifically, a delay in diagnosis-to-treatment time of more than 60 days, and a treatment package time of 87 days or more confer poorer oncologic outcomes.[1,2,5] In a previous unpublished study on patients with nasopharyngeal cancer undergoing radiation therapy at the Philippine General Hospital in 2011, delays in diagnosis and management were caused by delayed consult, lack of funds, misdiagnosis, delayed biopsies, time for dental clearance and delayed radiation therapy planning. These delays can be noted to be both patient-related and health care-related factors.[6]

As oncologic outcomes of HNC patients remain poor despite aggressive therapy, strategies to improve timeliness of care delivery to HNC patients may have a significant impact on survival. There is a lack of local studies that determine disease-to-treatment time among head and neck malignancies and its implication on survival. A search of HERDIN Plus, the ASEAN Citation Index (ACI) and the *Philipp J Otolaryngol Head Neck Surg* for local studies using the search terms "head and neck cancer", "survival" and "treatment delay" only yielded three articles.[5,7,8] As health care institutions differ across regions and countries, identification of phases in the treatment of patients where delays happen and the impact these have on patient survival will allow the institutions to make appropriate measures to address them. This study seeks to identify in what phases in the treatment of head and neck cancer do delays happen at the Philippine General Hospital, and determine the association between the length of treatment delays and the oncologic outcomes (disease-free survival and overall survival) for patients with head and neck cancer.

METHODS

Following University of the Philippines Manila Research Ethics Board approval (UPMREB 2020-132-01), total enumeration of patients with diagnosed locally advanced and neck cancer under the Department of Otolaryngology – Head and Neck Surgery (ORL-HNS) of the Philippine General Hospital from January 2014 to December 2019 was done. Using a frequency of 45% delayed patients with treatment package time greater than 87 days, an adjusted hazard ratio of 2.2 and a 95% level of confidence, the minimum sample size was determined to be 51.[1] Patient censuses from both the Department of ORL-HNS and Division of Radiation Oncology of the Department of Radiology were searched for all treated patients with non-metastatic, non-recurrent, non-thyroid, primary invasive cancer of the head and neck region. All patients were required to have undergone both definitive surgery and postoperative radiotherapy.

Excluded were patients less than 18 years old, those with missing data or who were admitted for tumor recurrence. Patients with prior chemotherapy or radiotherapy, with no pathologic diagnosis, and with unknown survival data were also excluded.

After identifying potential participants from the censuses, their medical records were retrieved to identify age, sex, address, primary site of cancer, date of pathological diagnosis, date of surgery and date of radiotherapy, as well as TNM Stage based on the American Joint Committee on Cancer Staging in 2010 (7th edition)[9] and 2017 (8th edition)[10] during the time of diagnosis and pathologic staging post-surgery for each patient. Phone numbers and email addresses were noted to facilitate interviews. All patient information was kept confidential. Study participants were coded by number and were not identified in the study files.

Each participant, or a legally acceptable representative (e.g., for those with issues or problems with reading or writing, who were unable to speak or otherwise physically incapable, or deceased), was invited for a 15 to 20 minutes standardized interview by the principal investigator or a research assistant trained to conduct the interview. Informed consent was obtained. The interview included asking the participants or informants if they felt delays in their treatment, as well as open-ended questions identifying reasons for delays divided into specific points in time: from the time of their first symptom to their first consult, consult to diagnosis, diagnosis to treatment initiation, surgery to initiation of postoperative radiotherapy (S-PORT) and time from surgery through completion of postoperative radiotherapy (treatment package time or TPT). Time intervals between first consult to histopathologic diagnosis, diagnosis to surgery, and surgery to adjuvant radiotherapy were likewise noted.

Data were tabulated using Microsoft® Excel 2019 MSO version 2407 (Microsoft Corp. Redmond, WA, USA) and thereafter summarized. Disease-free survival and overall survival were recorded. Disease-free survival was defined as the length of time from the end of primary treatment to the time the patient survives without any signs or symptoms of cancer. Overall survival was defined as length of time from the start of treatment for the cancer to patient's death from any cause. Mean and median time intervals were calculated for each period. The independent effects of predicted time intervals to overall survival and disease-free survival were determined. To determine the impact of TPT

on overall survival and disease-free survival, a linear regression model was used using IBM® SPSS Statistics Software Version 28.0.1.1(14) (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 101 patients who had surgery for invasive cancer of the head and neck region were initially considered. Thirty-three (33) patients who underwent surgery for palliative intent or for recurrence, as well as those who had prior chemoradiotherapy were excluded. Further excluded were 20 patients who failed to start or complete their radiotherapy treatment, and 33 with incomplete records (23 with incomplete/missing chart data, 10 with outdated contact information), leaving a total of 15 patients with available data for analysis.

Ages ranged from 44 to 85 years old (mean age of 60.9 years old), with 53.3% of the patients being more than 60 years old and 73.3% male. The most common primary site was the oral cavity (46.7%), followed by the larynx (26.7%), the skin and maxilla at 13.3% each. Eleven (11) patients had squamous cell carcinoma, two had adenoid cystic carcinoma, one had salivary duct carcinoma and one had basal cell carcinoma. Of the 15 patients included in the study, two were at Stage II, 4 were at Stage III and 8 were at Stage IVA.

Table 1 summarizes the mean and median time intervals across specific periods investigated in the study. All participants had S-PORT times greater than 6 weeks, regardless of subsite and stage. The treatment package time ranged from 15.4 to 40.3 weeks (107 to 282 days), with a median of 27.6 weeks or 193 days. Out of the 15 patients included in the study, four (26.7%) experienced significant delay in the initiation of treatment or more than 60 days from diagnosis to treatment.

Most participants (73%) claimed that they subjectively did not feel that there were delays in their treatment. Two patients cited financial limitations (e.g., acquiring imaging or facilitating dental clearance) in proceeding with treatment. Two patients cited weakness and post-operative wound healing as factors that delayed post-operative radiotherapy. A portion of the study was done during the time the COVID pandemic. One patient who had surgery at the end of 2019 cited difficulties in scheduling radiation therapy upon the start of the pandemic in early 2020.

At time of follow-up, 9 out of 15 participants had no evidence of disease, with median disease-free survival of 127.9 weeks. The other 6 participants had already passed away at the time of data collection. Three had oral cavity SCCA; the other three had glottic SCCA, cutaneous SCCA, and salivary duct carcinoma of the parotid gland. Four of these patients were already Stage IVA at the time of diagnosis. Three of these reportedly developed recurrent disease prior to demise.

The treatment package time for this cohort of patients statistically correlated with overall survival, $F(1,13)=12.952$, $p<0.005$, $R^2=0.499$ with a regression equation of y = 5.7492x - 18.089. *(Table 2 and Figure 1)* Treatment package time likewise correlated with disease-free survival, $F(1-13)=12.823$, $p<0.005$, $R^2= 0.497$ with a regression equation of y = 5.7958x - 31.191. (*Table 3* and *Figure 2*) However, the independent effects of other predictors such as time interval between first consult to histopathologic diagnosis, diagnosis to surgery, and S-PORT, showed no statistically significant association with overall survival and disease-free survival.

Table 1. Summary of treatment intervals (weeks)

Time Interval	Range (weeks)	Median (weeks)
Consult to Diagnosis	0 - 13	2.6
Diagnosis to Surgery	0.6 – 23.4	7.3
Surgery to Radiotherapy (S-PORT)	8.7 – 29.7	18.3
Treatment Package Time	15.4 – 40.3	27.4

Table 2. Regression analysis of treatment package time as a predictor of over-all survival

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.706[a]	.499	.461	59.3698

a. Predictors: (Constant), TreatmentPackageTime

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	45652.578	1	45652.578	12.952	.003[b]
	Residual	45822.115	13	3524.778		
	Total	91474.693	14			

a. Dependent Variable: Overall Survival
b. Predictors: (Constant), Treatment Package Time

Table 3. Regression analysis of treatment package time as a predictor of disease-free survival

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.705[a]	.499	.458	60.1498

a. Predictors: (Constant), TreatmentPackageTime

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	46394.763	1	46394.763	12.823	.003[b]
	Residual	47033.935	13	3617.995		
	Total	93428.697	14			

a. Dependent Variable: DiseasefreeSurvival
b. Predictors: (Constant), TreatmentPackageTime

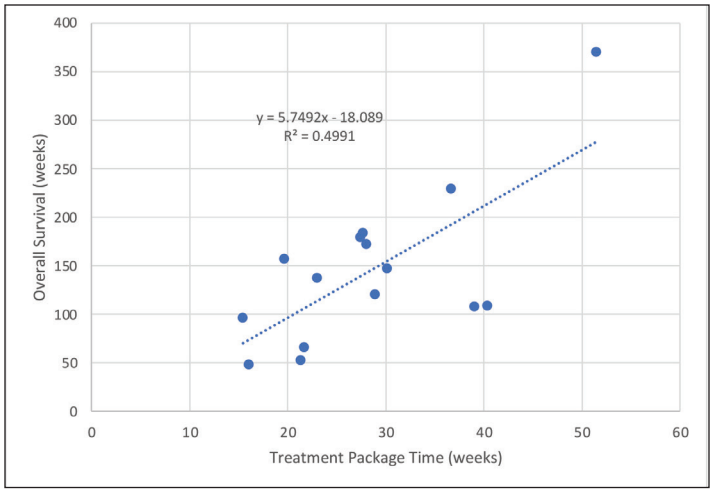

Figure 1. Association of overall survival to treatment package time

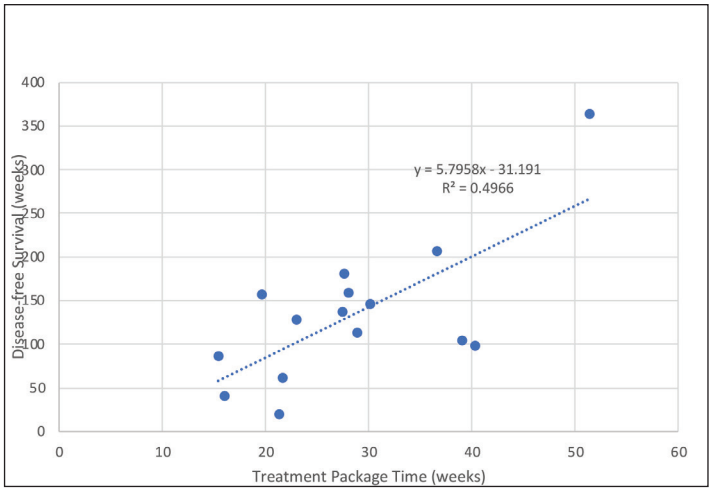

Figure 2. Association of disease-free survival to treatment package time

DISCUSSION

Our study found that the median treatment package time at our institution from 2014-2019 was 27.6 weeks or 193 days. Substantial contributors to the prolonged treatment package time were the length of time from diagnosis to surgery, and surgery to adjuvant radiation therapy. Our study further found that there was no statistically significant association between independent predictors such as time interval between first consult to histopathologic diagnosis, diagnosis to surgery, and that of surgery to adjuvant radiation therapy. According to our study, only the treatment package time statistically correlated with both overall survival and disease-free survival.

Patients attributed treatment delays to financial constraints and time for post-operative wound healing. Despite the data, most did not perceive a delay in their treatment. This finding differs from those of a previous local study in which 86% of patients felt that they experienced delays in their treatment for nasopharyngeal cancer.[6] This may be problematic because patients were probably satisfied with a longer treatment time despite the risks of poorer oncologic outcomes, mainly because of financial constraints.

In our cohort of patients, the treatment package time was positively correlated to disease-free survival and overall survival, contrary to data from other studies which proved the association between prolonged treatment package time and poorer oncologic outcomes. The median treatment package time in our study was much longer than published data of other institutions that reported increased risk of death if treatment package time was more than 9.7 to 13 weeks.[11,13,14] Our median time interval from diagnosis to surgery was already 7.3 weeks. Our data also showed that the median time interval between surgery and adjuvant radiotherapy ranged from 8.7 to 29.7 weeks, with a median time of 18.3 weeks. This goes beyond the National Comprehensive Cancer Network Guidelines for Head and Neck Cancer (version 4.2024) recommendation which states that adjuvant radiotherapy should commence within six weeks from surgery.[15]

This unexpected positive correlation between treatment package time and disease-free and overall survival may be due to several possible reasons. First, exclusion of patients who were unable to undergo surgery or initiate radiation therapy may have favored selection of patients with better prognosis by: 1) excluding patients who progressed to an unresectable or metastatic disease due to treatment delays between diagnosis to surgery, and 2) excluding those who may have presented with early recurrence and/or progressed to metastatic disease post-surgery before they could initiate radiation therapy. The patients who had controlled disease despite treatment delays may have less aggressive disease tumor biology, leading to selection of patients with more durable local control and subsequent disease-free and overall survival. Another factor that may have contributed to this finding was the inclusion of patients with other pathologic tumor types such as adenoid cystic carcinoma and basal cell carcinoma since these tumor types do have a more favorable prognosis and slower rates of progression compared to squamous cell carcinoma. The inclusion of other tumor histologies may have confounded the study findings.

Aside from these potential confounders, there were a number of limitations in this study. First, the study was not able to reach the minimum computed sample size. The study was conducted during the time of the SARS-COV2 pandemic, which limited communications and movement of people. Several potential subjects could not be contacted, hampering accrual of patients for follow-up and interview. Accrual of a larger sample size is recommended for future studies which aside from being more reflective the true population, may also allow for

multi-variate (such as Cox regression) analysis of factors contributing to the relationship of treatment delays and survival.

In the included 5-year retrospective scope of 2014-2019, health records in our institution were largely handwritten; and the documentation system was not yet standardized. The data from the chart review was therefore prone to incomplete clinical information leading to exclusion of a significant number of potential participants. Improvement of head and neck cancer databases and follow-up documentation is recommended to aid in the study of long-term disease-associated complications and survival analysis. In addition, the use of third-party national databases (e.g., the Philippine Statistics Authority) is recommended to obtain verified mortality data. Since the study period, there have been significant improvements in the patient information systems in our hospital. A future repeat study may be warranted to evaluate improvements (or lack thereof) since the initiation of digitized databases.

Retrospective studies also have unavoidable selection and recall bias. Further prospective studies with intention-to-treat analysis are recommended. Lastly, several patient factors may also be associated with overall and disease-free survival that have not been identified in this analysis. Several potential confounding variables, such as lifestyle practices, financial capacity, and tumor histology may also affect the time to diagnosis and treatment but have not been included in the analysis of this study.

Several developments have been noted in the institution since the time of the study: 1) migration to an electronic medical information system, improving patient follow-up and documentation, and facilitating early referrals among oncologic services; and 2) acquisition of additional linear accelerators to improve access and shorten or remove delays in initiating radiation therapy.

In conclusion, patients with advanced head and neck cancer from our study experienced treatment delays from diagnosis to initiation of surgery, and surgery to adjuvant radiation therapy. Future investigation and analysis of the factors affecting these treatment intervals may further elucidate the effect of treatment package time on survival. Implemented and planned improvements in our hospital and the national health care system can hopefully lead to better patient outcomes.

ACKNOWLEDGEMENTS

We would like to thank Ms. Mary Jane Yapo for providing administrative assistance. This work was supported by the UP-PGH Expanded Hospital Research Office (EHRO).

REFERENCES

1. Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of treatment delays with survival for patients with head and neck cancer: A systematic review. 2019 Feb 1;145(2):166-177. *JAMA Otolaryngol Head Neck Surg*. DOI: 10.1001/jamaoto.2018.2716; PubMed PMID: 30383146; PubMed Central PMCID: PMC6494704.
2. Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. *J Clin Oncol*. 2016 Jan 10;34(2):169-78. DOI: 10.1200/JCO.2015.61.5906; PubMed PMID: 26628469; PubMed Central PMCID: PMC4858932.
3. Marfil-garza BA, Belaunzarán-Zamudio PF, Gulias-Herrero A, Zuñiga AC, Caro-Vega Y, Kershenobich-stalnikowitz D. et al. Risk factors associated with prolonged hospital length-of-stay: 18-year retrospective study of hospitalizations in a tertiary healthcare center in Mexico. *PLoS One*. 2018 Nov 8;13(11): e0207203. DOI: 10.1371/journal.pone.0207203; PubMed PMID: 30408118; PubMed Central PMCID: PMC6224124.
4. Lee JM, Turini M, Botteman MF, Stephens JM, Pashos CL. Economic burden of head and neck cancer. *Eur J Health Eco.* 2020: *5*(1):70-80. https://doi.org/10.1007/s10198-003-0204-3
5. Lapiña GF, Castaneda SS. Diagnostic-to-treatment interval and disease progression among head and neck cancer patients undergoing surgery. *Philipp J Otolaryngol Head Neck Surg*. 2017 Jan-Jul;32(1):33-36. DOI: https://doi.org/10.32412/pjohns.v32i1.175.
6. Cañal J, Capito R. Delays in the diagnosis and management of patients undergoing radiotherapy at the Philippine General Hospital: Real and preventable? Term paper presented as a final requirement for the course Master of Science in Medical Anthropology, University of the Philippines Manila 2011. Unpublished.
7. Hernandez AKM, Cabungcal ACA. Maxillary sinus squamous cell carcinoma in a tertiary hospital in the Philippines. *Philipp J Otolaryngol Head Neck Surg*. 2019 June: 34(1): 34-37. DOI:10.32412/pjohns.v34i1.155.
8. Gonzales ICA. Lethal midline granuloma in a 15-year-old girl: A diagnostic dilemma". *Philipp J Otolaryngol Head Neck Surg.* 2018 Nov: 33(2):37-40. DOI:10.32412/pjohns.v33i2.273.
9. American Joint Committee on Cancer. AJCC Cancer Staging Manual: Seventh Edition. Chicago: Springer. 2010.
10. American Joint Committee on Cancer. AJCC Cancer Staging Manual: Eight Edition. New York: Springer. 2017.
11. Guttmann DM, Kobie J, Grover S, Lin A, Lukens JN, Mitra N, et al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. *Head Neck*. 2018 Jun;40(6):1147-1155. DOI: 10.1002/hed.25091; PubMed PMID: 29394465.
12. Fortpied C, Vinches M. The statistical evaluation of treatment and outcomes in head and neck squamous cell carcinoma clinical trials. *Front Oncol.* 2019 Jul 12;9:634. DOI: 10.3389/fonc.2019.00634; PubMed PMID: 31355146; PubMed Central PMCID: PMC6640189.
13. Suzuki H, Terada H, Hanai N, Nishikawa D, Koide Y, Beppu S, et al. Treatment package time predicts cancer-specific survival and distant metastasis in laryngeal cancer. *Oncol Lett*. 2019 Jan;17(1):1384-1390. DOI:10.3892/ol.2018.9664; PubMed PMID: 30655910; PubMed Central PMCID: PMC6313000.
14. Tam M, Wu SP, Gerber NK, Lee A, Schreiber D, Givi B, et al. The impact of adjuvant chemoradiotherapy timing on survival of head and neck cancers. *Laryngoscope*. 2018 Oct;128(10):2326-2332. DOI:10.1002/lary.27152; PubMed PMID: 29481712.
15. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers [Internet]*. National Comprehensive Cancer Network c2017 – [cited 2019 August 19]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437.