The Impact of Smoking, Alcohol Use, Recurrent Disease, and Age on the Development of Neck Fibrosis in Head and Neck Cancer (HNC) Patients Following Radiation Therapy

Keywords: head and neck cancer1, fibrosis2, radiotherapy3, risk factors4, tobacco use5.

**Objectives**

This study investigates the incidence of neck fibrosis in head and neck cancer (HNC) patients following radiotherapy with respect to patient age, treatment characteristics, history of alcohol and tobacco use, and disease recurrence.

**Design**

A retrospective review of all patients being treated for HNC at a rural tertiary care center between 2013 and 2017 was performed.

**Participants**

90 patients being treated for HNC, aged 19 to 99 years.

**Main outcome measures**

Incidence and Grade of head and neck fibrosis. Correlation with treatment/patient characteristics was performed using Chi-squared and Mann-Whitney U tests for univariate analysis and multiple logistic regression for multivariate analysis.

**Results**

Factors associated with an increased incidence of fibrosis included smoking during radiotherapy (*p* < 0.001), alcohol use (*p* = 0.026), recurrent disease (*p* = 0.042), and age less than 60 (*p* < 0.001) on univariate analysis. Factors associated with increased grade of fibrosis in HNC patients included recurrent HNC (*p* = 0.033), alcohol use (*p* = 0.013), patient age younger than 60 years (*p* = 0.018), smoking during radiotherapy (*p* < 0.001), and non-Caucasian race (*p =* 0.012).

**Conclusions**

Identification and intervention directed at patients who possess risk factors associated with fibrosis prior to treatment has the potential to improve the long-term quality of life for HNC patients.

**Key Points**

* There is a paucity of information regarding the demographic factors associated with the development of neck fibrosis in head and neck cancer (HNC) patients following radiotherapy.
* A retrospective review of all patients being treated for HNC at a tertiary care center between 2013 and 2017 was performed. Univariate and multivariate analyses were used to identify differences in incidence and grade of fibrosis, respectively, between populations.
* Factors associated with an increased incidence of fibrosis included smoking during radiotherapy (*p* < 0.001), alcohol use (*p* = 0.026), recurrent disease (*p* = 0.042), and age less than 60 (*p* < 0.001) on univariate analysis.
* Factors associated with increased grade of fibrosis in HNC patients included recurrent HNC (*p* = 0.033), alcohol use (*p* = 0.013), patient age younger than 60 years (*p* = 0.018), smoking during radiotherapy (*p* < 0.001), and non-Caucasian race (*p =* 0.012).
* The findings reported in this paper seem to indicate that ongoing tobacco and alcohol use during treatment both appear to separately contribute to the development of fibrosis in the observed population following head and neck radiotherapy.

# Objectives

# Head and neck cancers (HNC) carry a significant disease burden, accounting for 3% of all cancers in the United States. More than 53,000 Americans are diagnosed with HNC each year, with approximately 10,800 deaths1. Although the overall incidence of HNC is decreasing in the US2, the incidence of human papilloma virus (HPV)-associated cancers, especially of the oropharynx, is increasing2,3. HPV-positive HNC is also more prevalent in younger adults in their 40’s and 50’s4. As medical advances continue to improve treatment of HNC, the population of HNC patients continues to increase. Thus, quality of life in HNC patients becomes a topic of increasing importance.

The side effects of chemotherapy, radiotherapy, and/or surgery can significantly affect the quality of life of HNC survivors5. Radiation fibrosis is commonly described as a late complication of HNC treatment modalities that may not manifest clinically for several months or years after treatment. Fibrosis impacts quality of life due to associated pain, sensory loss, myopathy, dysphagia, trismus, and limitation in range of motion, impacting patients’ ability to perform self-care, speak, eat, etc.6,7. Current potential treatments used for fibrosis secondary to radiation therapy include pentoxifylline, vitamin E, and Low-Level Light Therapy (LLLT); devices designed to aid with jaw strength rehabilitation following the development of trismus also exist8.

Treatment factors such as history of previous neck dissection, concurrent chemotherapy, corticosteroid administration, and dosage of radiation have been identified as risk factors for fibrosis development9. However, variation in radiosensitivity is observed even amongst patients undergoing the same treatment regimen. There is limited data on the demographic risk factors associated with the specific development of fibrosis in HNC patients following radiotherapy. Identification of at-risk patients prior to or early on in the treatment process can help providers address potential side-effects prior to symptomatic manifestation and help patients prepare for functional changes. Furthermore, helping patients address modifiable risk factors associated with fibrosis can decrease the incidence and severity of fibrosis.

This study was performed at a tertiary care hospital with a relatively large minority and underserved patient population. The authors sought to evaluate the demographic and treatment factors as well as cancer grade associated with a greater incidence and grade of neck fibrosis in HNC patients following radiotherapy.

# Design

Retrospective data were collected from the patients’ electronic medical records. Demographic data were collected regarding potential risk factors for fibrosis including race, socioeconomic status (as defined by insurance coverage), use of tobacco, consumption of alcohol, age, and treatment of recurrent disease. Other data collected included AJCC 7th edition tumor stage, radiotherapy modalities used, overall survival, and incidence/severity of radiation related toxicities. The common terminology criteria for adverse events (CTCAE) version 4.0 was used to grade the severity of radiation-related toxicities10. The STROBE methodology was utilized in this study.

# Settings

At a tertiary care hospital serving a largely rural region, patients with a diagnosis of cancer of the head and neck from the years 2013 through 2017 were identified. Exclusion criteria included age under 18 years old at time of initiation of treatment, patients being treated without curative intent, death before completion of radiotherapy, and non-primary head and neck cancers. Patients lost to follow-up and those with insufficient follow-up in the 6-month post-treatment period were also excluded from the final data analysis.

# Participants

A total of 141 HNC patients were identified. A primary neoplasm found outside of the head and neck excluded 16 patients. There were 24 patients lost to follow up, and 6 patients died during treatment. A noncurative intent of the treatment excluded 5 patients, and 2 patients were less than 18 years old. A total of 90 patients (**Table 1**) were included in the final study cohort, including 62 males and 28 females with a median age of 62. African Americans made up 49% of the study population, while Caucasians comprised 49%.

# Main outcome measures

MedCalc V12.6 statistical software (Ostend, Belgium) was used for data analysis. Chi-squared and Mann-Whitney U tests were used to identify differences in incidence and grade of fibrosis, respectively, between populations. Logistic regression analysis was used to further evaluate the impact of these factors on the development of fibrosis. Logistic variables assessed include smoking versus non-smoking history, patient positive for alcohol use versus negative for alcohol use, tumor Stage less than 4 versus Stage greater than or equal to 4, tumor recurrence versus no recurrence, patient age less than 60 years versus greater than 60 years, patient race being Caucasian versus non-Caucasian, and patient being on Medicaid or uninsured versus having other insurance; continuous variables (e.g. age) were converted into binary values via grouping. P values < 0.05 were the threshold used to determine significance.

# Results

## Incidence of Fibrosis

Factors associated with increased incidence of fibrosis are shown in **Table 2**. On univariate analysis, active smoking at the time of radiation oncology consultation was associated with an increased incidence of fibrosis (*p* < 0.001). This was affirmed by multivariate analysis, which showed a logistic regression *p*-value of less than 0.001. Active alcohol use during treatment was associated with an increased incidence of fibrosis on univariate analysis (*p* = 0.026) but was not found to be significantly associated on multivariate analysis. Treatment of recurrent disease was found to be significantly associated on univariate analysis (*p* = 0.042) but was not retained on multiple logistic regression. Patient age less than 60 years was significantly associated with incidence of fibrosis on univariate analysis (*p* < 0.001) but was not retained on multiple logistic regression.

On univariate analysis, overall Stage at diagnosis and insurance type were not associated with the development of fibrosis (*p* = 0.19 and 0.21, respectively, see **Table 2**). No statistical significance was found for patients to develop greater than or equal to Stage 4 fibrosis vs for patients to develop less than Stage 4 fibrosis. The impact of race on fibrosis approached significance for non-Caucasian patients developing fibrosis vs Caucasian patients on univariate analysis (*p* = 0.06) but did not meet the authors’ cutoff for significance.

## Severity of Fibrosis

Factors associated with increased grade of fibrosis in HNC patients treated with radiotherapy (**Figure 1**) included patients being treated for recurrent HNC (*p* = 0.033), consumption of alcohol during treatment (*p* = 0.013), patient age younger than 60 (*p* = 0.018), smoking during treatment (*p* = <0.001) and non-Caucasian race (*p* = 0.012). A higher grade of fibrosis in uninsured patients or patients with Medicaid approached significance (*p* = 0.054).

1. **Conclusions**

Radiotherapy plays a vital role in the multimodal treatment of patients with HNC: approximately 80% of patients receive radiation at least once during their disease course11. Fibrosis following radiotherapy is a well-described phenomenon, although the pathogenesis behind this late reaction has not been fully elucidated. One of the proposed mechanisms is that radiation-induced maladaptive inflammation leads to a misguided wound healing response; this response is characterized by increased collagen deposition, poor vascularization, and scarring12. Because of this potential association, it stands to reason that factors related to increased or ongoing inflammation during and immediately after treatment may increase the likelihood and/or severity of patients developing fibrosis.

The findings reported in this paper seem to indicate that ongoing tobacco and alcohol use during treatment both appear to separately contribute to the development of fibrosis in the observed population following head and neck radiotherapy. Tobacco smoke has been found to be an irritant, which can cause an increase in the severity and duration of inflammation, and additionally may delay the healing process, which may be related to tobacco smoke toxicity13. This is particularly problematic, considering that research has shown that nearly half of smokers found to have oral or oropharyngeal cancer will continue to smoke after their diagnosis14. However, tobacco cessation programs during HNC treatment have proven effective in reducing smoking and could be a useful resource for many patients15. Emphasis on cessation during and after radiotherapy could be associated with an increased quality-of-life. Further studies regarding the impact of smoking cessation during head and neck cancer treatment are needed.

Patients younger than 60 years of age at the time of diagnosis appear to have a higher risk for developing neck fibrosis. This finding is in contrast to previous studies in breast cancer patients which found that increased age was significantly associated with the development of radiation-induced fibrosis16,17. Although the authors are unsure of the etiology of this response, it is hypothesized that more vigorous inflammatory responses in the robust immune systems of younger patients during radiation treatment may lead to more extensive post-radiation remodelling. The potential correlation of age and fibrotic response provides an interesting direction of future research in patient populations with different demographics and forms of cancer.

On univariate analysis, ethnicity and insurance impact the Grade but not the incidence of neck fibrosis. Although not robust independent risk factors, they may still aid in identifying an at-risk population. It has been shown in some studies that black patients are more likely than Caucasian patients to be diagnosed at a young age with HNC, in addition to rural patients being less likely to be diagnosed with HNC at a young age18. Further research is needed to confirm the trends seen in this study across a larger population.

A limitation of this study is that it is retrospective in nature and the study population was limited to 90 patients. Furthermore, there was a variation of treatment modalities in this patient population, though radiotherapy was the common denominator in all subjects. Further research is needed to confirm these trends across a large population and to determine the possible mechanisms by which age, tobacco, and alcohol use may be associated with fibrosis.

In summary, the data reported in this paper revealed several patient-related factors that are associated with the development of fibrosis in HNC patients following radiotherapy. Although chemotherapy, radiation, and surgery all remain the cornerstones of treatment of HNC, recent developments in the field such as immunomodulators and radiation dose de-escalation have allowed for improved post-treatment quality of life while still maintaining high therapeutic efficacy19,20. These new approaches along with pre-treatment identification of those at risk for radiation-related toxicities such as fibrosis could help reduce the incidence and severity of these toxicities. Ultimately, addressing the identified risk factors for fibrosis in HNC patients has the potential to improve patients’ quality of life.

# Data Sharing and Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**TABLES/FIGURES**

|  |  |
| --- | --- |
| **Characteristics** | **# of Patients (%)** |
| **Median Age** | 62 years (range: 19-99 years) |
| **Gender** | |
| Male  Female | 62 (69%)  28 (31%) |
| **Race** | |
| African American  Caucasian  Hispanic  Other | 44 (49%)  44 (49%)  1 (1%)  1 (1%) |
| **Insurance Coverage** | |
| Private  Medicare + supplemental  Medicare only  Medicaid  Uninsured | 14 (16%)  17 (19%)  29 (32%)  29 (32%)  1 (1%) |
| **Primary Site of Tumor** | |
| Larynx/hypopharynx  Oropharynx  HPV positive  HPV negative  HPV unknown  Oral cavity  Nasopharynx  Salivary gland  Thyroid  Other | 32 (36%)  27 (30%)  9 (10%)  5 (6%)  13 (14%)  6 (7%)  12 (13%)  6 (7%)  1 (1%)  6 (7%) |
| **HPV Status (overall cohort)** | |
| HPV positive  HPV negative  HPV unknown | 15 (17%)  16 (18%)  59 (65%) |
| **Overall Stage** | |
| I  II  III  IVA  IVB  IVC | 8 (9%)  12 (13%)  16 (18%)  45 (50%)  8 (9%)  1 (1%) |
| **Histology** | |
| Squamous  Other | 77 (86%)  13 (14%) |
| **Treatment of Recurrent Cancer** | |
| No  Yes | 79 (82%)  11 (12%) |
| **Prior head and neck radiation** | |
| No  Yes | 84 (93%)  6 (7%) |
| **Treatment modality** | |
| Radiation alone  Chemotherapy and radiation  Surgery and radiation  Surgery, chemotherapy, radiation | 7 (8%)  38 (42%)  10 (11%)  35 (39%) |
| Table 1. Patient demographics, tumor characteristics, and treatment characteristics of the study population (N=90). | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Demographic** | **Fibrosis** | **No Fibrosis** | **Univariate *p*-value** | **Logistic Multivariate**  ***p*-value** |
| Smoker  Nonsmoker | 8  3 | 15  64 | **<0.001\*** | **<0.001\*** |
| Drinker  Non-drinker | 6  5 | 15  64 | **0.026\*** | NR |
| Stage < 4  Stage ≥ 4 | 35  44 | 2  9 | 0.19 | NR |
| Tumor recurrence  No tumor recurrence | 7  4 | 22  57 | **0.042\*** | NR |
| Age < 60  Age > 60 | 11  0 | 50  29 | **<0.001\*** | NR |
| Caucasian  Non-Caucasian | 2  9 | 42  37 | 0.06 | NR |
| Medicaid/uninsured  Other insurance | 6  5 | 24  55 | 0.21 | NR |
| Table 2. Demographics contributed to incidence of fibrosis. P-values are reported as derived from univariate analysis (chi-squared) and logistic multivariate analysis. (N=90) \* = significant. NR = not retained. | | | | |

n=4

n=1

Figure 1. Factors associated with increased grade of fibrosis in HNC patients treated with radiotherapy. **A** - Patients being treated for recurrent HNC experience higher grade of fibrosis(***p* = 0.033\***). **B** - Consumption of alcohol during treatment is associated with higher grade of fibrosis (***p* = 0.013\***). **C** - HNC patients younger than 60 experience higher grade of fibrosis (***p* = 0.018\***). **D** -Smoking during treatment is associated with increased grade of fibrosis (*p* = **<0.001\***). **E** - Non-Caucasian race is associated with increased grade of fibrosis (***p =* 0.012\***). **F** - Grade of fibrosis in uninsured patients or patients with Medicaid approaches significance (*p* = 0.054). **\* = significant**

n=1