

## Radiation Induced Hypothyroidism and its Relationship with Gender and Smoking History in Head and Neck Cancer Patients

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### Abstract

**Introduction:** Patients with head and neck cancers are often treated with external beam radiation therapy. Unfortunately this therapy is not without its unintended consequences. One of these side effects include the development of radiation induced hypothyroidism. Our study is designed to pay special attention to variables like gender and smoking history and analyze their relationship with the development of hypothyroidism.

**Methods:** Tumor Registry Database at the University of Florida, College of Medicine in Jacksonville was utilized for our retrospective study to gather information on patients who had previously received external beam radiations for head and neck cancers. Patients' charts were reviewed over a period of thirteen years from January 1st 2000 to November 30th 2013. General characteristics were examined including age, gender, race/ethnicity, and smoking history. Hypothyroidism was defined as TSH value greater than 5.0 along with appropriate decrease in free serum thyroxine (T4) levels after exposure to external beam radiation. Results were then analyzed using the Univariate statistical analysis which was done using the SAS software. Alpha level of significance was set to 0.05 and associations were expressed in terms of Odds ratio (OR) with 95% confidence intervals (CI).

**Results:** We found a total of 1116 patients in our database who have received external beam radiations for head and neck cancers. Out of these 72 (6.45%) patient developed hypothyroidism. Out of 263 African American patients 20 (7.6%) had hypothyroidism, whereas 49 (6%) out of 819 white people had this outcome. As for gender 32 out of 341 females (9.4%) and 40 out of 775 males had hypothyroidism. Thirty five out of 544 (6.4%) with no family history and 19 (2.4%) out of 205 (9.3%) with positive family history for cancer had the outcome too. Finally 43(6.5%) out of 664 smokers and 17(8.3%) out of 206 non-smokers were found to develop hypothyroid as well. Both groups were found to have homogenous average age at diagnosis.

When conducting the univariate analysis, the strongest predicting variable was gender as hypothyroid patients were 1.90 (95% CI 1.17 – 3.09) times more likely to be females, and these results were statistically significant with p-value of 0.008. More patients tended to be African Americans with OR 1.21 (CI 0.822 - 1.78), had positive family history of cancer, (negative family history had OR 0.67 (CI 0.38 – 1.21), and less likely to be smokers (OR 0.77 (0.43 – 1.38)). However, Race, family history of cancer and smoking history did not achieve any statistical significance as evident by the p-values.

**Conclusion:** In our patient population, females were more likely to develop radiation induced hypothyroidism.

**Keywords:** Neck cancers; External beam radiation; Gastrointestinal track

### Introduction

Thyroid gland is often irradiated as an unintended consequence of external beam radiation therapy for head and neck cancers (HNC) [1]. The cells of the thyroid gland have a very low proliferation rate and this renders them the beneficial effect of radiotherapy resistance compared to the highly proliferative cell in the gastrointestinal track and the mammary gland and [2]. However, the thyroid gland is by no means completely protected from the adverse effects of external beam radiation. Over the years several reports have established the advent of hypothyroidism after radiation therapy for the treatment of head and neck cancers and the role of certain variables like age and gender is an area under intense investigation [3]. The current study aims to

specifically analyze the relationship of variables such as gender and smoking history with the development of hypothyroidism from external beam radiation for the treatment of head and neck cancers.

### Method

Tumor Registry Database at the University of Florida, College of Medicine in Jacksonville was utilized for our retrospective study to gather information on patients who had previously received external beam radiations for head and neck cancers. Patients chartes were reviewed over a period of thirteen years from January 1st 2000 to November 30<sup>th</sup> 2013. General characteristics were examined including age, gender, race/ethnicity, and smoking history. Hypothyroidism was defined as TSH value greater than 5.0 along with appropriate decrease in free serum thyroxine (T4) levels after exposure to external beam radiation. Results were then analyzed using the Univariate statistical

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## Results

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## Discussion

External beam radiation is an integral part of the treatment for head and neck cancers. In early stage tumors, the treatment may involve external beam radiation (XRT) alone, however, in more advanced stages the HNCs are treated with XRT along with surgery and or chemotherapy [4]. The incidence of clinical hypothyroidism is described in the literature is between 5-10% [5,6]. Clinical

hypothyroidism is defined as the increase in TSH (thyroid stimulating hormones) above 5.0 and a decrease in free thyroxine levels (Free T4) in the serum. Results obtained from our patient population are in agreement with these findings. In the current study 6.45% of our patient population developed clinical hypothyroidism. As expected, the incidence of hypothyroidism is much higher in the patients receiving radiation therapy in addition to surgical interventions involving the thyroid gland [1-6]. Our lower incidence of clinical hypothyroidism is in agreement with the published data deduced from patients treated with XRT alone.

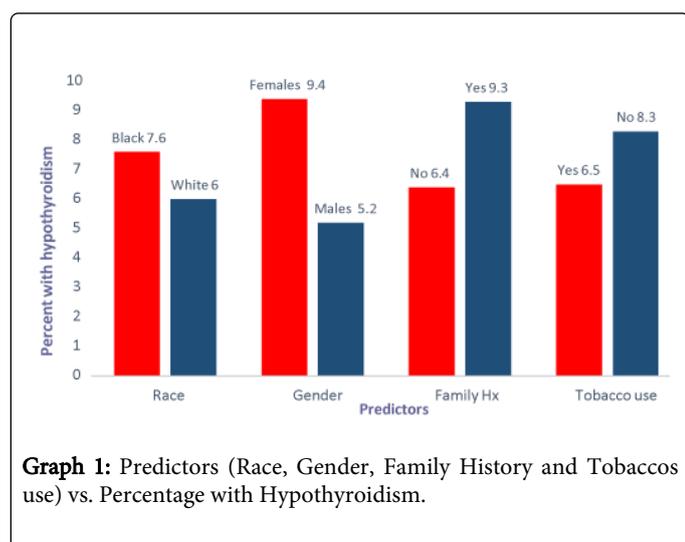
Both the exact dose of XRT and the mechanism behind the destruction of thyroid gland are not well understood. There is conflicting evidence on the exact amount of XRT needed to affect the thyroid gland with a wide range from 3000 to 8000 rads [7,8]. On the other hand, several mechanisms of injury to the thyroid have been proposed over the years ranging from vascular or immunologically mediated damage to prevention of cell division to the direct follicular destruction of the thyroid gland [4]. The most widely accepted mechanism involves the micro-and macrovascular damage to the thyroid gland itself along with the area around it which then leads to the ischemia and fibrosis leading to the destruction of thyroid gland's synthetic ability [9].

Certain risk factor factors have been consistently reported throughout the literature. These include the location of the tumor, the extent/intensity of the XRT and the treatment modality or modalities like chemotherapy or surgery used in conjunction with the radiation therapy [9]. Variables like age and gender have been studied previously but the research is very limited. Several authors including Mercado et al., Tell et al., and Aich et al., have shown no correlation between gender and iatrogenic hypothyroidism secondary to XRT [4,10,11]. This makes our current study very unique in that we looked at gender at our institution and the advent of hypothyroidism over a thirteen year period. A detailed version of our results is mentioned in Table 1 below. A bar graph is also shown below a better visual depiction (Graph 1).

Predictors	Hypothyroid		Total	% positive	OR (CI)	P value
	Yes	No				
<b>Race</b>					1.29(0.74-2.22)	0.349
<b>Black</b>	20	243	263	7.6	1.21(0.82-1.78)	
<b>White</b>	49	770	819	6	0.934(0.801-0.9)	
<b>Gender</b>					1.90(1.17-3.09)	0.008*
<b>Female</b>	32	309	341	9.4	1.50(1.14-1.98)	
<b>Male</b>	40	735	775	5.2	0.79 (0.64-0.97)	
<b>Patient status</b>					1.76(1.09-2.86)	0.02*
<b>Alive</b>	42	462	504	8.3	1.32(1.07-1.62)	
<b>Dead</b>	30	582	612	4.9	0.75(0.57-0.99)	
<b>Family History</b>					0.67(0.38-1.21)	0.181
<b>No</b>	35	509	544	6.4	0.89(0.72-1.08)	
<b>Yes</b>	19	186	205	9.3	1.32(0.89-1.93)	

<b>Tobacco History</b>					0.77(0.43–1.38)	0.38
<b>Current/previous</b>	43	621	664	6.5		
<b>Never used</b>	17	189	206	8.3		
<b>Mean Age at Diagnosis (SD)</b>	60.93 (10.66)	59.59(12.19)				0.363

**Table 1:** Descriptive and univariate statistics for possible predictors of hypothyroidism in cancer after external beam radiation.



**Graph 1:** Predictors (Race, Gender, Family History and Tobacco use) vs. Percentage with Hypothyroidism.

Interestingly we found that the female gender was positively associated with the development of iatrogenic hypothyroidism with an odds ratio of 1.90 and a 95% confidence interval between 1.17–3.09. Using a univariate analysis we were also able to show that the difference between the genders was statistically significant with a p-value of 0.008. Gender predilection for iatrogenic hypothyroidism can have significant implications on public awareness programs and on future guidelines for more stringent followup of the TSH and Free T4 in the female gender.

Another area of controversy is the effect of cigarette smoking on thyroid dysfunction. Published research on the influence of cigarette smoking on thyroid malfunction has shown both hypothyroidism and hyperthyroidism. Yet in other studies smoking has shown to have no effect on thyroid function [12-18]. Impact of smoking thus remains an area of intense investigation and is a variable that was studied in the current study as well. We found that smoking was negatively associated with Iatrogenic hypothyroidism with an odds ratio of 0.77 and a CI 0.43 – 1.38. While on the surface there appears to be a protective effect of cigarette smoking, this finding did not bode statistical significance with a p-value of 0.38.

Our study reports some very significant findings, however it also emphasizes the need to carry out future investigations based on data pooled from multiple cancer centers and possible future meta-analysis of predictors of post-radiotherapy hypothyroidism. This can help provide more information about possible other risk factors and more in-depth analysis of the aforementioned ones. Interesting other variables to examine can be gender differences in family history of hypothyroidism, presence of thyroid and non-thyroid autoimmune

diseases as well as the effect of preceding, concomitant, and subsequent chemotherapy in patients based on gender.

### Conclusion

In our patient population, the development of hypothyroidism after external beam radiation for the treatment of head and neck cancers was more common among the female population. There is also some evidence that smoking may have a protective effect on the development of hypothyroidism, however this association could not reach statistical significance. More patients tended to be African Americans, with positive family history of cancer, and less likely to be smokers. However, these variables did not achieve any statistical significance emphasizing the need for future research involving collaboration between multiple centers on a much bigger scale. Bigger sample size will allow more accurate estimation of the possible protective effect and its magnitude. It will also enable us to better estimate possible statistical significance. These findings can have future public policy implications for guidelines pertaining to more stringent screening of radiation induced hypothyroidism in the subgroups at the highest risk.

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