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## Research article

# Thyroid-optimized and thyroid-sparing radiotherapy in oral cavity and oropharyngeal carcinoma: A dosimetric study



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## ABSTRACT

**Background:** Radiation-induced hypothyroidism is a common toxicity of head and neck radiation. Our re-planning study aimed to reduce thyroid dose while maintaining target coverage with IMRT.

**Methods:** We retrospectively identified patients with oral-cavity (n = 5) and oropharyngeal cancer (n = 5). Treatment plans were re-optimized with 45 Gy thyroid mean dose constraint, then we cropped the thyroid out of PTVs and further reduced thyroid dose. Target coverage was delivering 100% dose to  $\geq 93\%$  of PTV and 95% of dose to  $> 99\%$  of PTV.

**Results:** Originally, average mean dose to thyroid was 5580 cGy. In model I, this dropped to 4325 cGy (p < 0.0001). In model II, average mean dose was reduced to 3154 cGy (p < 0.0001). For PTV low and PTV int, all had acceptable target coverage.

**Conclusion:** In patients with oral-cavity and oropharyngeal cancers, mean dose could be significantly reduced using a thyroid-optimized or thyroid-sparing IMRT technique with adequate coverage.

## Introduction

In the United States, head and neck cancers make up about 3% of all cancers with an incidence of 53,000 new cases and 10,800 deaths per year [1]. The treatment options for these cancers include surgery, radiation therapy, chemotherapy, or a combination of the above. For advanced head and neck squamous cell carcinoma (HNSCC), radiotherapy is often employed in either definitive or adjuvant settings [2]. Historically, modalities of radiation delivery lacked high selectivity, making it difficult to avoid healthy tissues and non-target organs within the head and neck region. Thus, a myriad of side effects are associated with radiation to the head and neck, including endocrine abnormalities from irradiation of the thyroid gland.

The thyroid is a butterfly-shaped endocrine gland in the neck that produces the hormones triiodothyronine (T3) and thyroxine (T4). The thyroid gland is regulated by the hypothalamic-pituitary-thyroid axis, in

which thyrotropin releasing hormone (TRH) from the hypothalamus and thyroid stimulating hormone (TSH) from the pituitary promote T3 and T4 synthesis [3]. Regulatory mechanisms are in place so that high T3 and T4 levels negatively feedback on this axis to reduce TRH and TSH production [4]. T3 and T4 hormones play a crucial role in regulating temperature, metabolism, cholesterol levels, and growth of the human body. Thus, any thyroid disease or imbalance of thyroid hormone production can lead to detrimental effects in multiple organ systems.

The side effects of radiation to the thyroid are well documented, and can include hypothyroidism, Grave's disease, thyroiditis, euthyroid Graves' ophthalmopathy, benign adenomas, multinodular goiters, and thyroid cancers [5,6]. By far, the most common radiation-induced toxicity is hypothyroidism, which manifests in 40–50% of patients who undergo radiotherapy in the neck region [7]. While the majority of patients develop subclinical hypothyroidism, overt hypothyroidism occurs in approximately 2.6–10.7% of those affected [8]. These observed

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rates can be further delineated into those that experience hypothyroidism transiently or permanently after radiation therapy [9]. Studies have also shown that radiation-induced hypothyroidism follows a dose-dependent pattern, since patients receiving higher mean radiation doses are more affected [10]. This risk appears to be even higher in patients who also undergo chemotherapy, but this association is still being investigated [9].

Hypothyroidism occurs when the thyroid gland is underactive and produces insufficient levels of T3 or T4. Primary hypothyroidism describes when the thyroid gland itself fails to produce adequate amounts of hormone, whereas secondary hypothyroidism is when thyroid function is normal but there is inadequate TSH from the pituitary or TRH from the hypothalamus [11]. In addition, hypothyroidism can be categorized as clinically overt (high TSH with low free T4) or subclinical (high TSH with normal free T4) [12]. Approximately half of the incidents of hypothyroidism occur within 5 years of follow up, with a peak incidence at 1–2 years after radiation [13]. The mechanism of acute thyroid dysfunction is thought to be due to radiation induced damage to thyroid parenchymal cells, whereas late injury is due to vascular ischemia of the small thyroid vessels and atherosclerosis of the carotid artery [10].

With conventional RT techniques, the thyroid was often included in the treatment fields. With recent advancements in radiation delivery methods like Intensity Modulated Radiation Therapy (IMRT), it was now feasible to minimize radiation dose to healthy tissues, including thyroid avoidance. Based off prior longitudinal studies, the threshold parameter of 45 Gy was found to be predictive of the development of hypothyroidism [7].

In this study, we reassessed original thyroid-non-optimized treatment plans (TNO-IMRT) of patients who had already been treated for head and neck cancers and re-optimized those plans using thyroid-optimized (TO-IMRT) and thyroid-sparing (TS-IMRT) techniques. With the re-planning, we aimed to achieve a thyroid mean dose constraint of 45 Gy (TO-IMRT) and dose as low as possible (TS-IMRT) while maintaining acceptable and adequate target coverage in patients felt to have a very low risk of lower-neck tumor recurrence.

## Materials and methods

We retrospectively identified 10 previously treated patients with N0-N2a oral cavity (5 patients) and oropharyngeal cancer (5 patients) with no gross disease in proximity of the thyroid gland, including no grossly involved level 3 and 4 neck nodes (Table 1). Only 1 of 10 had the thyroid contoured initially and none of the treated plans were optimized for thyroid avoidance.

First, the thyroid was contoured on the original planning CT scan. IMRT was used for the whole field, with bilateral neck coverage for all oropharyngeal cases and PTV margins set to 3 mm. We hypothesized that with the absence of gross tumor presence near the thyroid gland, significant sparing of the gland should be possible with adequate treatment planning optimization. Each plan utilized 6 MV photons with 3 volumetrically modulated partial arcs. Arcs spanned from gantry 200

degrees to 160 degrees (staggered clockwise and counterclockwise) to promote sparing of the posterior neck, while collimation was independently chosen based on lymph node involvement. Using the collimator rotation and jaw settings, the three arcs were dividing into an upper field (collimator 80–90 degrees), a lower field (collimator 80–90 degrees), and a neutral field (0–5 degrees). For the upper and lower fields, X jaws were offset superiorly and inferiorly, forcing a manual carriage shift as to not exceed MLC travel limitation of 15 cm beyond collimator jaw. Upper and lower fields maintained at least a minimum of 3 cm overlap at the isocenter plane with Y width covering supraclavicular volumes. Positioning of the X jaw direction promoted MLC travel from superior and inferior to spare centrally located organs at risk (OAR) such as the spinal cord, larynx, esophagus, and thyroid.

For the first model of the study, we retrospectively delineated thyroid on our contrast-enhanced planning CT. To establish our baseline, we recorded our thyroid metrics on the original clinically used plans. This was our control, dose to thyroid without intervention. These original treatment plans were re-optimized using a mean thyroid dose constraint of 45 Gy, with treatment goals of 95% coverage to PTV High, Intermediate, Low levels, while sparing all other associated OAR with the same objectives as the original plan. During planning, the thyroid structure was cropped from existing PTV structures (to the PTV edge). For this structure, optimization goals were less than 40 Gy. This priority would be increased until the running coverage of PTV's dropped below our defined threshold. At that point, optimization was completed, and thyroid doses were recorded.

The second model involved cropping PTVs to exclude thyroid contours to reduce mean thyroid dose as low as possible while maintaining adequate target volume coverage. The goal was to assess how much thyroid could be spared if the surrounding target volume was deemed to be low-risk and could be cropped from the thyroid. In this case, we created PTV Evaluation structures for PTV intermediate and low that were cropped directly to the edge of the thyroid. During optimization, existing objectives for all OAR were used with the exception that PTV\_Eval was used as a surrogate for coverage at 95% rather than original PTV structures. True thyroid structures were pushed with a mean below 30 Gy, or until PTV\_Eval coverage dropped below our threshold of 95%.

Target volume coverage and thyroid mean doses were evaluated with a goal of delivering 100% of the prescription dose to  $\geq 93\%$  of the PTV and 95% of the dose to  $> 99\%$  of the PTV. 80% of patients had 3 PTV volumes – PTV High (Range – 6000–7000 cGy); Intermediate (Range – 6000–6300 cGy); and Low (Range – 5400–5600 cGy). All the plans were rendered in the Varian Eclipse (v13.6) for Varian TrueBeam linear accelerators (Varian Medical Systems, Palo Alto, CA).

## Results

In the original thyroid non-optimized (TNO-IMRT) treatment plans (Initial - Fig. 1a), the average mean dose to the thyroid was  $5580 \pm 313$  cGy (range 4922–5966 cGy). None of the patients had PTV high volumes at or near the level of the thyroid gland in the lower neck. The average

**Table 1**  
Patient characteristics.

	Site	Sex	Age	P16	T-stage	N-stage	RT Dose	#Fx	Chemo	Elapsed Days
1	Oropharynx	M	51	+	1	2a	6600	30	None	39
2	Oropharynx	M	56	+	2	2a	7000	35	Carboplatin	48
3	Oropharynx	M	60	+	2	1	7000	35	Cetuximab	57
4	Oropharynx	F	81	+	2	2c	7000	35	Cisplatin	50
5	Oropharynx	M	57	+	3	1	7000	35	Cisplatin	48
6	Oral Cavity	F	33	UNK	2	1	6600	33	None	44
7	Oral Cavity	F	31	–	2	0	6000	30	None	45
8	Oral Cavity	M	58	–	1	1	5000	25	None	32
9	Oral Cavity	M	35	UNK	1	1	6600	33	Cisplatin	65
10	Oral Cavity	M	65	+	1	1	6400	32	Cetuximab	41

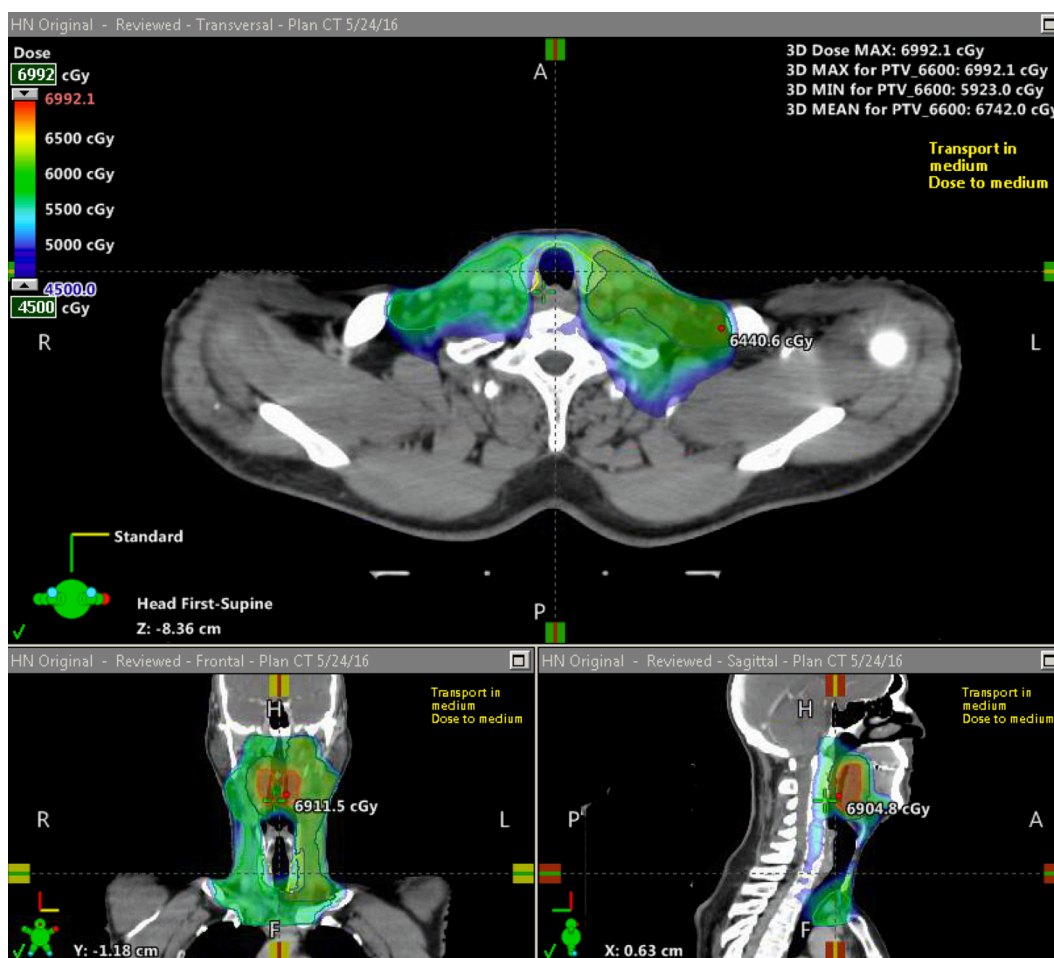


Fig. 1a. Initial - Thyroid non-optimized plan (TNO-IMRT).

percent PTV receiving the prescription dose was 97.3% and 95.6% for the low-risk volume (PTV low) and intermediate-risk volume (PTV int), respectively. For the PTV low and PTV int, 95% of the volume received an average of 101.3% and 100.2% of the prescribed dose.

In thyroid-optimized plan (TO-IMRT) (Model I - Fig. 1b), the average mean dose to the thyroid was significantly reduced to  $4325 \pm 194$  cGy (range 4037–4573 cGy,  $p < 0.0001$ ). The prescription dose was delivered to 94% and 93.9% of the PTV low and PTV int respectively. Ninety-five percent of the PTV low and PTV int received an average of 99.3% and 99.6% of the prescribed dose.

In the thyroid-sparing plan (TS-IMRT) (Model II - Fig. 1c), the average mean dose to the thyroid was  $3154 \pm 218$  cGy (range 2874–3537 cGy,  $p < 0.0001$ ). In this model, 96% and 94% of the PTV low and PTV int received 100% of the prescribed dose and for both volumes, 95% received 100% of the prescribed dose.

Dosimetric data for all 3 plans are summarized in Table 2. Dose volume histograms showing acceptable PTVs coverage with both TO-IMRT and TS-IMRT in comparison to initial thyroid non-optimized plans are shown in Figs. 2a and 2b.

Thyroid sparing was achieved with very minimal, insignificant changes in doses to the surrounding OAR's. The average mean doses (cGy) for the original, model I and model II plans respectively were: larynx – 3624/3690/3698 cGy; and esophagus – 3367/3500/3467 cGy. The average maximum doses (cGy) for the original, model I and model II plans respectively were: brachial plexus – 6379/6420/6416 cGy; and spinal Cord – 3941/4039/4056 cGy.

## Discussion

In radiation planning studies for head and neck cancers, it is difficult to avoid the thyroid due to its midline location and proximity to the carotid sheath containing the carotid artery, internal jugular vein, and lymph nodes that are common sites of tumor involvement. Fortunately, with the development of advanced radiation modalities like IMRT, critical structures could be better spared. Many initial studies on IMRT and thyroid avoidance focused on setting dosimetric parameters in order to protect the thyroid, since complications follow a dose-dependent pattern. In a retrospective study by Cella et al. that looked at patients with Hodgkin's lymphoma treated with sequential chemotherapy and 3D-CRT, the threshold V30 of 62.5% was determined to be an independent predictor for developing hypothyroidism [14]. However, the focus on Hodgkin lymphoma meant these parameters were less applicable to head and neck cancer patients. A prospective cohort study by Boomsa et. al used the NTCP model to estimate the risk of hypothyroidism in the first two years after radiation therapy, and estimated that a dose of V45 or more to the whole thyroid gland was highly associated with complications within 5 years [15]. In a longitudinal, prospective study by Zhai et al., a thyroid mean dose of 45 Gy was predictive for developing primary hypothyroidism in head and neck cancer patients [7].

In this study, we retrospectively identified 10 patients previously treated for head and neck cancers with IMRT without accounting for the thyroid. We took the original dosimetric plans and re-optimized them with a thyroid dose constraint of 45 Gy mean (TO-IMRT, model I), and cropped out parts of the thyroid from PTV's to further reduce mean radiation dose (TS-IMRT, model II) while maintaining acceptable target

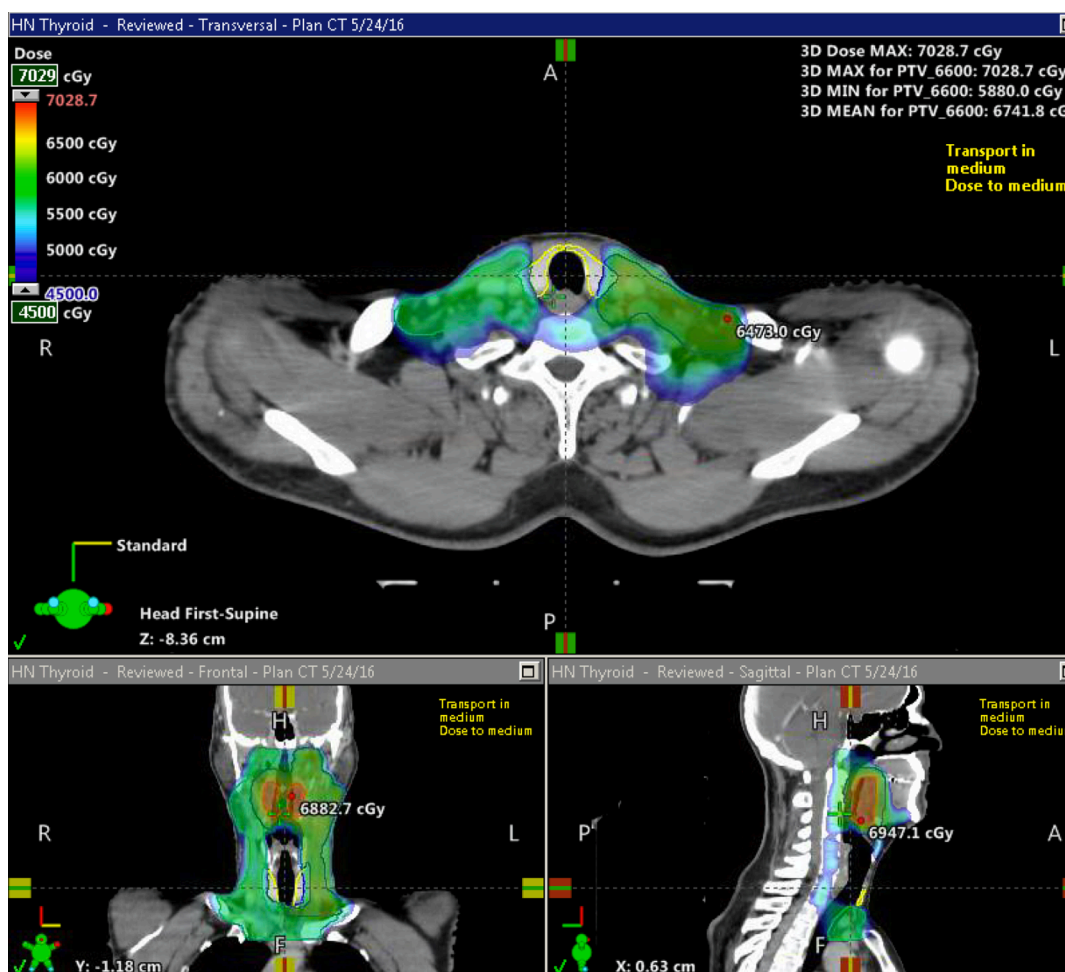


Fig. 1b. Model I - Thyroid optimized plan (TO-IMRT).

volume coverage. Since the monitor units (MU) were similar across the original and modeled plans, we are confident that the optimized plans would have no issues with plan robustness or quality assurance (QA). In addition, dosage to surrounding OAR's were relatively unchanged from the original plan (larynx, esophagus, brachial plexus and spinal cord), further supporting the feasibility of thyroid sparing and optimization with IMRT.

Radiation-induced hypothyroidism is a common toxicity after radiation therapy to the neck. Of all patients with radiation induced hypothyroidism, approximately 30% will be clinically overt (elevated TSH and low T4), and 70% will have subclinical hypothyroidism (elevated TSH with normal T4) [10]. Clinical symptoms of hypothyroidism can include lethargy, weakness, depression, coarse hair, weight gain, cold intolerance, hypercholesterolemia and accelerated atherosclerosis [16]. Severe hypothyroidism can additionally present with pleural effusion, pericardial effusion, hemodynamic instability, and coma [17]. Untreated or inadequately treated hypothyroidism can cause infertility, cardiac complications, and neurological and musculoskeletal symptoms [18].

The risk of thyroid complications from irradiation is highly dependent on the dosage of radiation delivered. In a retrospective study of over 1,500 patients with Hodgkin's Lymphoma who received 15–44 Gy, 31% of patients developed hypothyroidism while 1.9% developed hyperthyroidism [6]. Within that cohort, the actuarial risk of both overt and subclinical hypothyroidism after 20 years was 44% in patients who received > 30 Gy, 27% who received 7.5–30 Gy, and 2% who received 0 Gy. Another study found that patients with mean thyroid dose greater than 45 Gy have five times increased risk of developing hypothyroidism

compared to those who didn't [19]. Other studies found that radiation-induced thyroid complications can be seen with doses as low as 6–12 Gy [20]. Additional risk factors associated with radiation-induced thyroid problems include older age at diagnosis, being female, and concurrent chemotherapy treatment [9]. It is hypothesized that women are at higher risk due to their predisposition for autoimmune thyroid diseases (Hashimoto's, Graves' disease), as well as having lower thyroid gland volume reserves than men [21]. Some studies have estimated a 5%-7% decreased risk of hypothyroidism when thyroid volume increases by 1 cc [15,22].

According to the 2019 NCCN guidelines, it is recommended that patients undergo biannual/ annual monitoring of thyroid function tests post radiation [23]. However, there is no official guideline stating when the ideal time frame is to begin monitoring thyroid levels post radiotherapy, or when to initiate treatment. In the study by Garcia et al. where they found that 60% of their patients developed hypothyroidism within 5 years post radiotherapy, they recommended serial monitoring of TSH levels every 6 months for the first 5 years, and yearly afterward [24]. In addition, they suggested beginning treatment for any patient with a TSH greater than 4.5 mIU/L even in the absence of symptoms. However, since TSH testing techniques and reference values vary per lab, we cannot give a specific cut-off level to recommend therapy initiation. Thus, it is crucial that treating providers address this by establishing a follow-up protocol for patients after radiotherapy.

Three primary goals for treating hypothyroidism include: resolving patients' signs and symptoms of hypothyroidism, normalizing serum TSH and thyroid hormones, and avoiding overtreatment that can lead to thyrotoxicosis [25]. The mainstay treatment for hypothyroidism

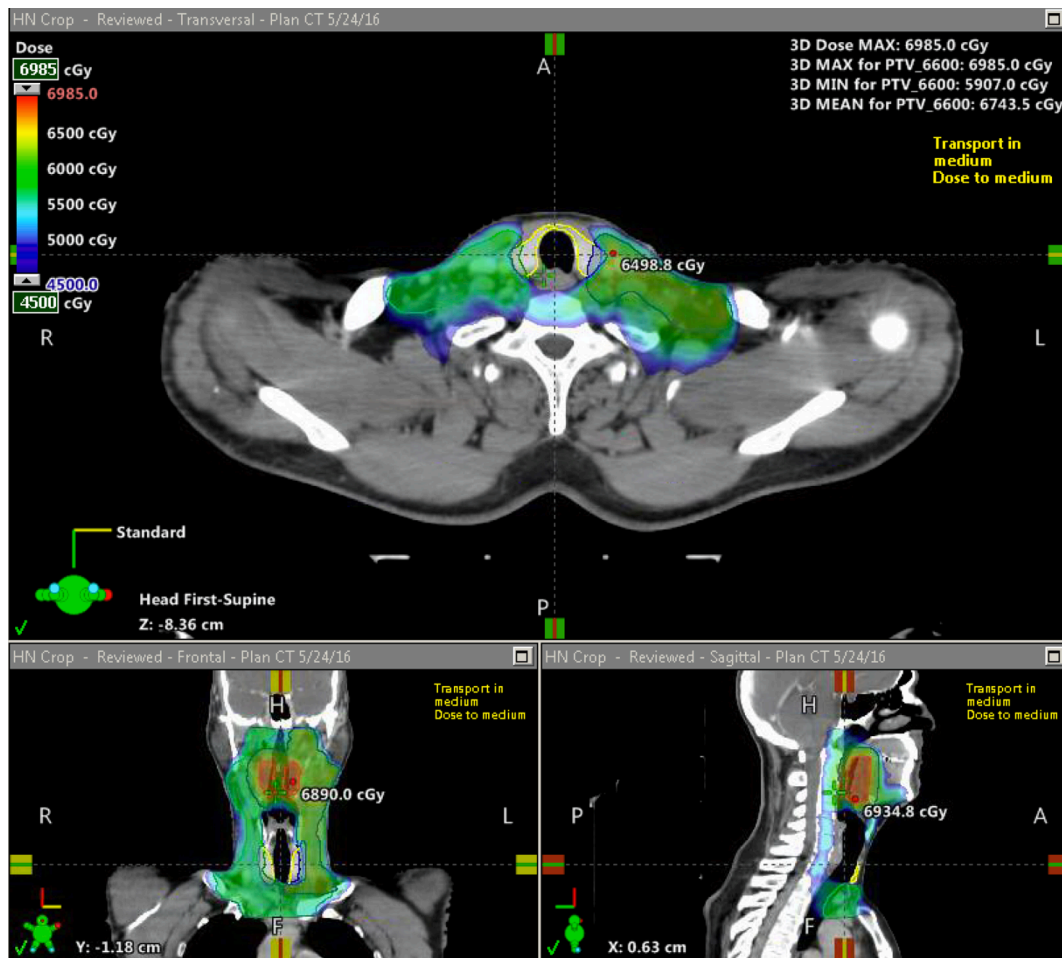


Fig. 1c. Model II - Thyroid sparing plan (TS-IMRT).

**Table 2**  
Thyroid dose and coverage for 3 plans.

	Initial – TNO-IMRT	Model I – TO-IMRT	Model II – TS-IMRT
Mean Dose (cGy)	5,580	4,325	3,154
Range (cGy)	4,922–5,966	4,037–4,573	2,873–3,537
V100% PTV low/int	97.3%/95.6%	94%/93.9%	96%/94%
V95% PTV low/int	101.3%/100.2%	99.3%/99.6%	100%/100%

involves putting patients on lifelong levothyroxine supplements. Levothyroxine is a prohormone of T4 that gets converted to the active metabolite T3, thus effectively addressing the symptoms caused by low T3 and T4 levels [26]. The starting dose of levothyroxine varies depending on age and presence of other comorbidities, but typically begins at 25–50 µg daily and then raised by 25–50 µg at 6 to 8 week intervals until TSH is within therapeutic range [27]. TSH is considered the most reliable marker for thyroid hormone replacement treatment, with a target goal in the range of 0.4–4.0 mIU/L [25].

Nearly all patients diagnosed with overt hypothyroidism are started on levothyroxine, whereas the approach for subclinical hypothyroidism is under debate and provider dependent due to the perceived, milder nature of the condition. In a meta-analysis of patients with subclinical hypothyroidism, it was found that there was a significant increase in risk of cardiovascular mortality and morbidity in individuals with TSH levels > 10 mIU/L, whereas minimal TSH elevations were not associated with an increased risk [28]. While there is no established guideline on

how to approach subclinical hypothyroidism, many physicians give levothyroxine to subclinical patients out of concern of progression to worse clinical outcomes.

While hypothyroidism is relatively straightforward to treat with thyroxine supplements, it is a condition that requires lifelong hormone replacement, routine laboratory monitoring, and extra healthcare costs [9]. While levothyroxine toxicity is usually asymptomatic, symptoms can include tachycardia, agitation, nervousness, or progress to severe features such as respiratory failure, seizures, arrhythmia, and coma [29]. In addition, long term levothyroxine supplementation may be associated with increased mortality rates in patients with heart failure [30]. Especially with head and neck cancer patients, it is optimal for physicians to minimize the side effects and comorbidities that may result from radiotherapy treatment. Our study results show that it is possible to achieve thyroid sparing by contouring it and optimizing the planning system to minimize thyroid dose while maintaining adequate PTV coverage. We however, do not recommend such optimization for patients with gross tumor in proximity to the thyroid gland.

Some limitations of our study include that cropping PTVs and avoiding the thyroid can potentially increase the risk of nodal failures in the immediate vicinity. Since we do not have laboratory studies for these patients, it is possible that none of the patients analyzed actually developed thyroid toxicity. There are other research studies evaluating the omission of postoperative radiation to the neck in N0 patients that have demonstrated promising control rates in the unirradiated neck without long-term adverse effects on quality of life measures [31]. In addition, while we presumed that the modeled plans would pass standard QA due to the comparable MU's from the original and modeled

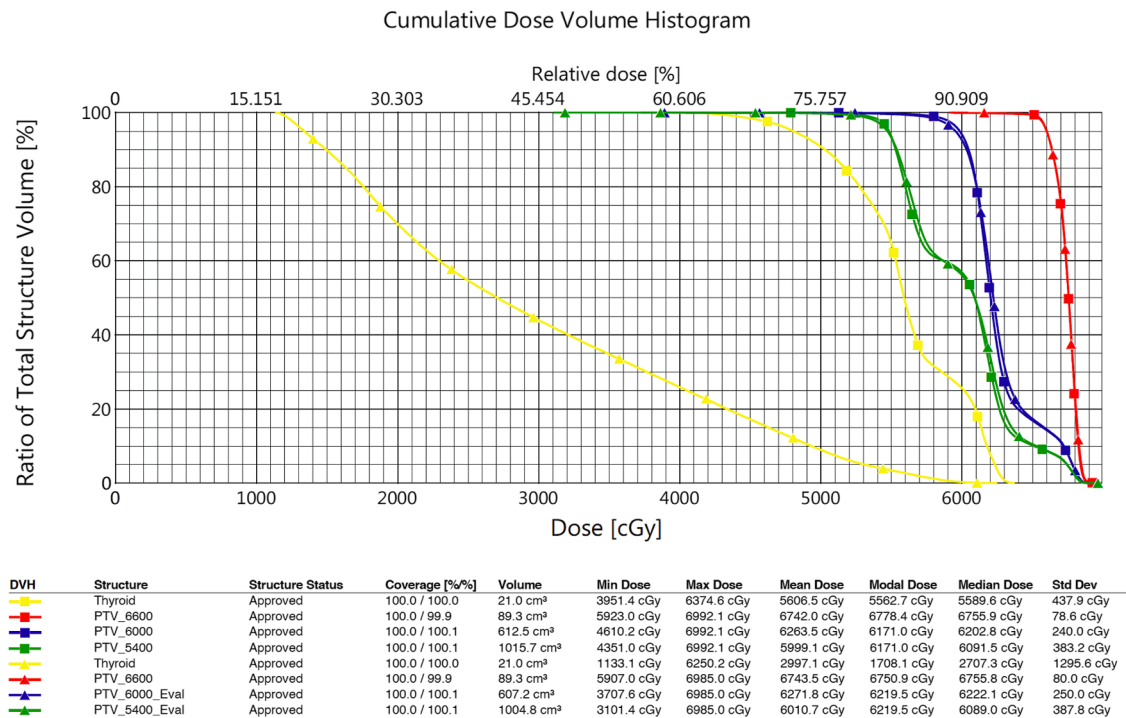


Fig. 2a. Initial vs. Model I Dose Volume Histogram.

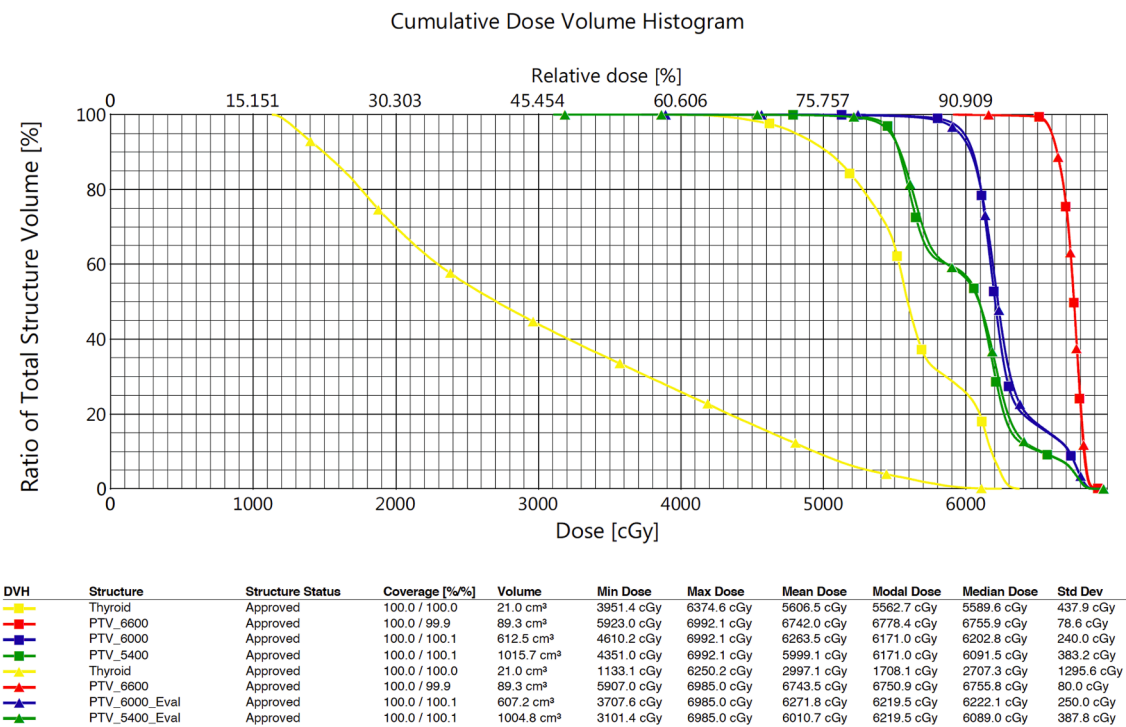


Fig. 2b. Initial vs. Model II Dose Volume Histogram.

plans, unfortunately we were unable to actually run a simulated IMRT QA to assess if this was true. Lastly, the development of newer radiotherapy delivery techniques, like proton therapy, may make it even easier to avoid the thyroid. Despite these limitations, to the best of our knowledge, our study is the first to propose feasibility of thyroid-optimized and thyroid-sparing IMRT [32].

### Conclusion

In select patients with no gross disease in proximity of the thyroid gland, such as NO-N2a oral cavity and oropharyngeal cancers, mean dose to the thyroid can be significantly reduced using either a thyroid-optimized or thyroid-sparing approaches while maintaining adequate target coverage. In our study, the mean doses to the thyroid gland were significantly reduced by 22.5% (TO-IMRT) and 43.5% (TS-IMRT) while

maintaining acceptable PTV coverage. Since the aim of this retrospective, feasibility study was to identify a patient population with low-risk of disease of the thyroid, we limited our inclusion criteria to oral cavity and oropharynx cases who did not have nodal disease in the mid- to lower-neck around the thyroid area. For the proof of concept, the current patient numbers appear sufficient for our purposes. A prospective, larger clinical study or trial with adequate follow-up and TSH measurements would be needed to identify a cohort that would clinically benefit from thyroid sparing techniques without increased risk of recurrence in the thyroidal area. In addition, a prospective study could further assess the safety and feasibility of this approach and its ultimate clinical effect on lowering the incidence of radiation-induced hypothyroidism.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Meeting Presentations

2018 AAMD – Poster Presentation

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