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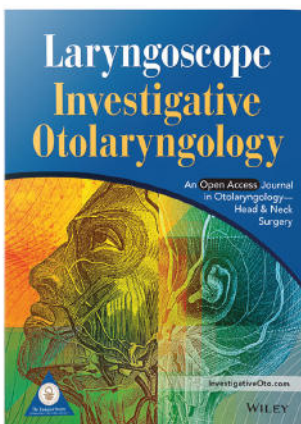


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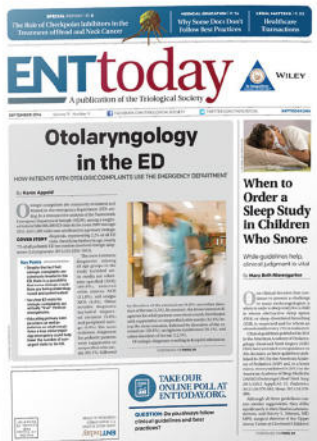


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# Dysphagia, hypothyroidism, and osteoradionecrosis after radiation therapy for head and neck cancer

Pihla Ranta MD<sup>1</sup>  | Eero Kytö MD<sup>1</sup>  | Linda Nissi MD<sup>2</sup> |  
Ilpo Kinnunen MD, PhD<sup>1</sup> | Tero Vahlberg MSc<sup>3</sup> | Heikki Minn MD, PhD<sup>2</sup>  |  
Eeva Haapio MD, PhD<sup>1</sup> | Lassi Nelimarkka MD, PhD<sup>4</sup> | Heikki Irjala MD, PhD<sup>1</sup> 

<sup>1</sup>Department of Otorhinolaryngology – Head and Neck Surgery, Turku University and Turku University Hospital, Turku, Finland

<sup>2</sup>Department of Oncology and Radiotherapy, Turku University and Turku University Hospital, Turku, Finland

<sup>3</sup>Department of Clinical Medicine, Biostatistics, Turku University and Turku University Hospital, Turku, Finland

<sup>4</sup>Department of Endocrinology, Division of Medicine, Turku University and Turku University Hospital, Turku, Finland

## Correspondence

Pihla Ranta, Department of Otorhinolaryngology—Head and Neck Surgery, Turku University and Turku University Hospital, Turku, Finland; Department of Otorhinolaryngology, Turku University Hospital, Kiinamylynkatu 4-8, PO Box 52, 20521 Turku, Finland.  
Email: pihla.m.ranta@utu.fi

## Abstract

**Objectives:** To analyze the long-term side effects of radiation therapy (RT) for head and neck cancer (HNC).

**Methods:** Retrospective chart analysis of all 688 HNC patients treated during 2010–2015 at Turku University Hospital, Finland. All patients who survived for more than a year after RT/chemoRT were included ( $n = 233$ ). Intensity modulated RT (IMRT) with standard fractionation was applied in each case.

**Results:** One hundred and six patients (45%) reported persisting dysphagia, for which neck RT increased risk. Definitive neck RT to high-risk volume did not increase late toxicity risks compared to elective neck RT. Radiation-induced hypothyroidism (29%,  $n = 67$ ) was more common among younger patients and females. Osteoradionecrosis (12%,  $n = 29$ ) was more common in the oral cavity cancer group (20.7%,  $n = 92$ ) compared to all other subsites.

**Conclusions:** Late toxicities of RT for HNC are common. Age, gender, tumor subsite, and neck RT affect susceptibility to long-term side effects.

**Level of evidence:** 4.

## KEYWORDS

dysphagia/swallowing, neoplasia/malignancy, radiation therapy

## 1 | INTRODUCTION

The incidence of tobacco-related head and neck cancer (HNC) is decreasing in many countries, but the incidence of human papilloma virus (HPV)-related HNC is rising rapidly.<sup>1</sup> The overall 5-year relative survival of HNC patients has increased from 54.7% in 1992–1996 to 65.9% in 2002–2006.<sup>2</sup> At present, HNC patients constitute 3% of all cancer survivors,<sup>3,4</sup> raising the pressure to focus on minimizing the long-term side effects of HNC treatment.

Current treatments for some HNCs may be more intensive than necessary.<sup>5</sup> There is evidence that single modality treatment is superior to combined treatment regarding quality of life (QOL).<sup>6,7,8,9</sup> However, there is no consensus on whether a surgical approach or primary oncological treatment is superior. In a recent meta-analysis, overall survival with surgical treatment was not significantly different from nonsurgical treatment.<sup>10</sup> Still, for early-stage disease, single modality treatment is recommended, whereas for locally advanced HNC a combination of surgery and (chemo)radiotherapy remains the standard treatment.<sup>11</sup>

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At present, most HNC patients receive radiation therapy (RT) as a single modality or part of a multimodality treatment.<sup>12,13</sup> Known long-term RT toxicities are xerostomia, hypothyroidism, swallowing difficulties, chronic skin changes, neck fibrosis, dental caries, osteoradionecrosis, trismus, and pharyngoesophageal stenosis.<sup>14,15</sup> Most HNC patients also report high pain scores in the first year after diagnosis, especially those who received RT.<sup>16</sup>

Our objective was to analyze the long-term side effects of RT for HNC. We also aimed to find treatment-related and patient-related factors that have an impact on those late toxicities. Moreover, we assessed how the side effects were treated. This knowledge may help to develop more individualized treatment strategies for HNC patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

This study is a single-center retrospective chart analysis of all HNC patients treated between 2010 and 2015 at Turku University Hospital, Finland. A more detailed description of RT techniques and use of cisplatin or cetuximab enhanced chemoradiotherapy (CRT) is given by Nissi et al.<sup>17</sup> In September 2020, a list of survivors was collected from the Finnish Population Register Centre. Data on all patients who survived for more than a year was collected from patient files between September and December 2020. This study was approved by the local Clinical Research Centre (record number: T06/049/20), and study permission was granted.

### 2.2 | HPV status

HPV status was determined by p16 immunohistochemistry. The tumor was regarded as p16 positive if more than 70% of the tumor cells were strongly immunopositive.

### 2.3 | Smoking

Participants were divided into groups of never smoker, early quitter (cessation 1 year or earlier before diagnosis of HNC), recent quitter (cessation less than 1 year before or after diagnosis of HNC), and current smoker.<sup>18</sup>

### 2.4 | Heavy alcohol use

Heavy alcohol use was defined as consuming >16 drinks/week for women and >24 drinks/week for men. In addition, alcohol use was considered heavy if there was a mention of heavy alcohol use or alcohol use disorder in the participant's medical report.

### 2.5 | Dysphagia, hypothyroidism, and osteoradionecrosis

All patients were questioned about dysphagia on regular follow-up. Possible dysphagia was recorded on the patient charts by clinicians. Hypothyroidism was defined as plasma thyroid-stimulating hormone (TSH) concentrations above and thyroxine concentrations below the normal reference range. Osteoradionecrosis was defined as the presence of mucosal breakdown in the gingiva, or failure of healing in previously irradiated areas, resulting in bone exposure and necrosis of the overlying bone. The diagnosis of osteoradionecrosis was clinical, but radiology was often used for confirmation and evaluation of the extent of bone involvement.

### 2.6 | Statistical methods

IBM SPSS Statistics version 27 was used in the statistical analyses. Crosstabs, Chi-Square test and Fisher's exact test were used to assess whether there was a difference in RT side effect incidence between smoking, gender, alcohol consumption, primary tumor site, cancer stage, p16, surgery modality, neck RT, and chemotherapy drug groups. One-way ANOVA was used to assess how age at diagnosis impacted RT side effect incidence. Mann-Whitney *U* test and Kruskal-Wallis test were used to assess whether the radiation dose or fraction were different in groups of hypothyroidism, dysphagia, dietary change, dysphagia treatment, osteoradionecrosis, and osteoradionecrosis treatment. Radiation dose and fraction were skewed, but age at diagnosis was normally distributed according to the histograms. The trend in median TSH levels between time points was tested with linear regression. A *p* value of less than .05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Study population

The total number of HNC patients within our study period was 688, of whom 307 received RT (44.6%). The RT modality was intensity-modulated radiotherapy (IMRT). All patients who survived for over a year after RT were included in this study ( $n = 233$ , 75.9%). Of the participants, 39 received RT and 194 chemoRT. An overview of participants is presented in Table 1.

### 3.2 | Long-term side effects of treatment

#### 3.2.1 | Dysphagia

Of the patients, 106 (45%) reported dysphagia that continued for more than a year after RT; 101 of them had changed their diet as a result. Common dietary changes included avoiding hard and crunchy foods, moistening and mechanically mincing all food, or only

TABLE 1 Overview of participants

Sample characteristic		% (n)
Follow-up length		
Survivor group	5 years of regular examinations by a head and neck surgeon	63.9 (149)
Group of participants who died before September 2020	Median 30.34 months (IQR 30.11 months, mean 37.10 months)	36.1 (84)
Combined total	Median 5 years (IQR 1.12 years), mean 4.31 years	100 (233)
Age at diagnosis (mean $\pm$ SD)	61.4 $\pm$ 10.1	
Gender	Female	26.6 (62)
	Male	73.4 (171)
Primary tumor site	Oral cavity	39.5 (92)
	Oropharynx	26.2 (61)
	Nasopharynx or nasal cavity	5.6 (13)
	Hypopharynx	1.7 (4)
	Larynx	21.0 (49)
	Parotid gland	0.9 (2)
	Paranasal sinuses	0.4 (1)
	Multiple head and neck primary tumors	0.4 (1)
	Neck metastasis	4.3 (10)
Stage <sup>a</sup>	I	10.7 (25)
	II	21.0 (49)
	III	22.3 (52)
	IVa + IVb	38.6 (90)
	Information missing (unknown primary)	7.3 (17)
Human papillomavirus (p16) status	Positive	9.9 (23)
	Negative	6.4 (15)
	Information missing	83.6 (195)
Treatment modality	Definitive radiation therapy (RT)	9.0 (21)
	Definitive RT, concomitant chemotherapy	41.6 (97)
	Preoperative RT	1.3 (3)
	Postoperative RT	6.4 (15)
	Preoperative RT + chemotherapy	16.7 (39)
	Postoperative RT + chemotherapy	23.2 (54)
	Palliative RT $\pm$ chemotherapy	1.8 (4)
Radiation therapy of the neck	No	6.0 (14)
	Ipsilateral	5.2 (12)
	Bilateral	88.8 (207)

(Continues)

TABLE 1 (Continued)

Sample characteristic		% (n)
Chemotherapy drug	Cisplatin	86.0 (166)
	Cetuximab	8.3 (16)
	Paclitaxel	0.5 (1)
	Information missing	5.2 (10)
Smoking	Current smoker	32.2 (75)
	Earlier quitter (cessation 1 year or earlier before diagnosis of head and neck cancer)	22.7 (53)
	Recent quitter (cessation less than 1 year earlier or after diagnosis of head and neck cancer)	21.5 (50)
	Never smoker	22.3 (52)
	Information missing	1.3 (3)
Heavy alcohol use <sup>b</sup>	Never	58.4 (136)
	Before	10.7 (25)
	Yes	19.3 (45)
	Information missing	11.6 (27)

<sup>a</sup>Stage was classified according to International Union Against Cancer (UICC) TNM Classification of Malignant Tumors, 7th Edition.

<sup>b</sup>See Materials and Methods for definition of heavy alcohol use.

consuming pureed foods. All dysphagia patients received nutritional therapy and counseling. Of all dysphagia patients, 22 (21%) had undergone esophageal upper sphincter dilatations. The number of dilatations needed per patient varied between one and 14 (median 1, interquartile range IQR 3, mean 2.54). Time between dilatations varied from 1 month to 3 years (median 3 months, IQR 3 months, mean 3.45 months). Twenty-four patients had become permanently dependent on a percutaneous gastrostomy tube (PEG); 20 of them were able to swallow some purees and liquids, 3 could only swallow small amounts of liquids, and 1 was not able to swallow at all.

For comparison, we analyzed only surgically treated stage III–IV patients who had not received RT, and who survived at least 1 year after the operation ( $n = 8$ ). The main reason not to combine (chemo) radiation after surgery among patients with advanced stage disease was comorbidity burden. The primary tumor subsites in these patients were oral cavity ( $n = 7$ ) and larynx ( $n = 1$ ). There was no acute or late treatment-related dysphagia. One oral cavity cancer patient, who had been treated only surgically, suffered from dysphagia related to Parkinson's disease prior to the HNC diagnosis and was therefore excluded from further analyses.

### 3.2.2 | Hypothyroidism

There were 67 cases (29%) of hypothyroidism diagnosed after HNC treatment. The median time between the end of RT and starting thyroxine medication was 2.5 years (IQR 2.9 years), the

earliest time being 15 days and the latest 9.1 years after the end of RT. Additionally, 18 participants had already been treated for hypothyroidism before the RT. In all the patients, TSH values trended upwards after treatment ( $\beta = 0.22$  for trend in median TSH levels between time points, 95% CI 0.11–0.33,  $p = .001$ ) Figure 1A,B.

### 3.2.3 | Osteoradionecrosis

Of the participants, 29 (12%) were diagnosed with osteoradionecrosis. Thirteen of them were treated by a dental specialist in local anesthesia, whereas 10 underwent a larger operation under general anesthesia. In addition to surgical interventions, 6 participants were treated with hyperbaric oxygen. Three patients received parenteral antibiotics and nine were treated only with oral antibiotics. Two patients with very minor osteoradionecrosis received no treatment interventions but were followed up by a dental specialist until the necrotized area had healed (Figure 2A,B).

## 3.3 | Patient- and treatment-related risk factors for long-term side effects of treatment

### 3.3.1 | Age

Hypothyroidism was more common in younger patients ( $p = .01$ ); those diagnosed with hypothyroidism after HNC treatment had a mean age of 58.4 years (SD 9.8). The mean age of the other participants was 62.2 (SD 9.8). Age did not have any statistically significant impact on the incidence of dysphagia, dietary change, dysphagia treatment modality, osteoradionecrosis, or its treatment.

### 3.3.2 | Gender

Hypothyroidism was more common in females ( $p < .001$ ), being diagnosed in 52.8% of females ( $n = 28$ ) after HNC treatment but only in 23.5% ( $n = 38$ ) of males. Gender did not have a statistically significant impact on the incidence of dysphagia, dietary change, dysphagia treatment modality, osteoradionecrosis, or its treatment. The mean age of females and males was similar, 61.7 (SD 11.3) and 61.5 years (SD 9.5) respectively ( $p = .889$ ).

### 3.3.3 | Cancer stage

In this RT-treated cohort, 60.9% of patients had stage III–IV disease (see Table 1). Nevertheless, a higher stage did not have a statistically significant impact on the incidence of hypothyroidism, dysphagia, dietary change, dysphagia treatment modality, osteoradionecrosis, or its treatment.

### 3.3.4 | RT of the neck

RT of the neck increased the risk of dysphagia ( $p < .001$ ). Of the participants who did not receive neck radiation ( $n = 14$ ), none reported persisting dysphagia or a need for dietary changes. Both ipsilateral and bilateral RT-treated patients reported persisting dysphagia, 66% ( $n = 12$ ) and 47% ( $n = 207$ ), respectively ( $p = .241$ ). Neck RT did not have a statistically significant impact on the incidence of hypothyroidism, dysphagia treatment modality, osteoradionecrosis, or its treatment.

### 3.3.5 | Definitive and elective neck radiation

A total of 219 participants received neck RT. Of them, 63.4% received definitive RT to metastatic areas of the neck (median dose 65 Gy, IQR 3 Gy), whereas 36.6% received only elective neck RT (median dose 50 Gy, IQR 0 Gy). There were no statistically significant differences between definitive and elective neck RT groups with regard to dysphagia, hypothyroidism, or osteoradionecrosis (Table 2).

### 3.3.6 | Primary tumor site

Osteoradionecrosis was more common in the oral cavity tumor group (20.7%,  $n = 92$ ) compared to a group of all other primary tumor sites (7.2%,  $n = 141$ ) ( $p = .003$ ). The primary tumor site did not have a statistically significant impact on the incidence of hypothyroidism, dysphagia, dietary change, or dysphagia treatment modality.

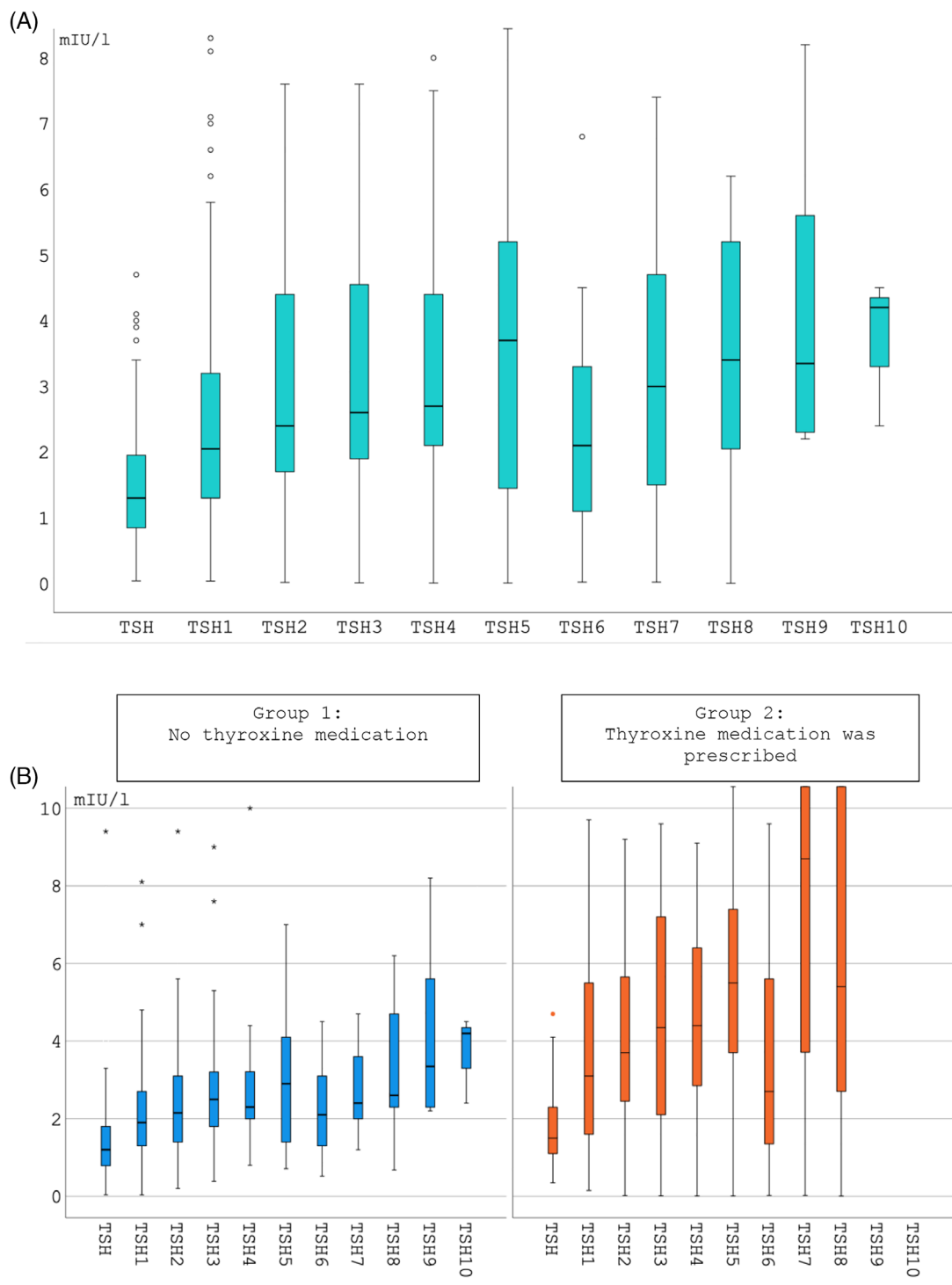
### 3.3.7 | Surgery as a part of treatment

Of the 233 patients in our RT-treated cohort, a total of 39.9% ( $n = 93$ ) received no surgical treatment. In addition to RT, 65 participants (27.9%) received planned neck dissection and planned surgery for the primary tumor, 22 (9.4%) received planned surgery for the primary tumor, and 46 (19.7%) were treated with planned neck dissection. Moreover, seven patients (3.0%) underwent salvage surgery on the primary tumor.

Surgical treatment modalities as a part of treatment did not increase the incidence of dysphagia ( $p = .247$ ), hypothyroidism ( $p = .673$ ), or osteoradionecrosis ( $p = .563$ ).

### 3.3.8 | Radiation dose and radiation fraction impact

Radiation dose (median 63.7 Gy, IQR 7.0 Gy) or radiation fraction (median 2.0 Gy, IQR 0.2 Gy) did not have a statistically significant impact on the incidence of hypothyroidism, dysphagia, dietary change, dysphagia treatment modality, osteoradionecrosis, or its treatment.



**FIGURE 1** Plasma thyroid stimulating hormone levels: (A) a follow-up of all patients. TSH = plasma thyroid stimulating hormone level before the end of radiation therapy (RT). TSH1 = plasma thyroid stimulating hormone level after RT. TSH2-TSH10 = plasma thyroid stimulating hormone follow-up levels. Mean time between TSH1 and TSH: 389 days ( $n = 167$ ). Mean time between other follow-up time-points (TSH2 and TSH1, TSH3 and TSH2, ... TSH10 and TSH9): 297 days. The longest thyroid stimulating hormone follow-up period (TSH to TSH10) was 8 years. The trend in median TSH levels between time points was significant ( $\beta = 0.22$ , 95% CI 0.11–0.33,  $p = .001$ ). (B) Plasma thyroid stimulating hormone levels; a comparison between patients not treated with thyroxine and patients who started thyroxine medication. Group 1: No thyroxine medication was prescribed. Group 2: Thyroxine medication was prescribed. Median time between the end of radiation therapy (RT) and starting thyroxine medication was 2.5 years (IQR 2.9 years), the earliest time point being 15 days and the latest 9.1 years after the end of RT. The trend in median TSH levels between time points was significant in group 1 ( $\beta = 0.20$ , 95% CI 0.10–0.30,  $p = .001$ ) and group 2 ( $\beta = 0.53$ , 95% CI 0.04–1.01,  $p = .037$ )

### 3.3.9 | Chemoradiotherapy

Chemotherapy itself, the drug used (cisplatin vs. cetuximab) or the number of cycles did not have a statistically significant impact on the incidence of hypothyroidism, dysphagia, dietary change, dysphagia treatment modality, osteoradionecrosis, or its treatment.

### 3.3.10 | Alcohol consumption, smoking, and p16

In the group of heavy alcohol users, hypothyroidism was less common (19.0%) compared to the group of participants with no history of

heavy alcohol use (31.1%), and to the group with a history of heavy alcohol use before the HNC diagnosis (48.0%) ( $p = .045$ ). Alcohol consumption did not have a statistically significant impact on the incidence of dysphagia, dietary change, osteoradionecrosis or its treatment. For smoking and p16, there was too much missing data and/or the late toxicity subgroups were too small for reliable analyses.

### 3.4 | Residual and recurrent tumors

Eight participants (3.4%) were diagnosed with a residual tumor, 35 (15.0%) with a local recurrent tumor, and nine (3.9%) with both residual and local recurrent tumors. Neck recurrence was found in 11 patients (4.7%), a distant metastasis in 22 patients (9.4%), and both neck recurrence and distant metastasis in four (1.7%) patients.

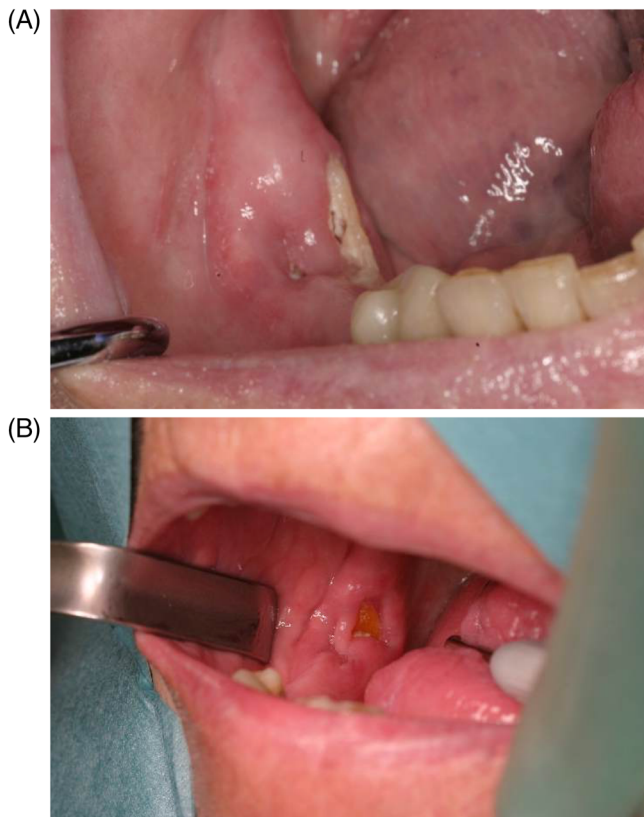
### 3.5 | Secondary malignancies

There were 24 second primary tumors (10.3%). The most common site for the second primary tumor was the lung (9). Other sites were colorectal (4), tongue (3), tonsil (2), urinary bladder (2), trachea (1), lip (1), adrenal gland (1), and kidney (1).

## 4 | DISCUSSION

This study is a retrospective chart analysis of the long-term side effects of RT for HNC. Our cohort included all HNC patients who received RT between 2010 and 2015 in our center and who survived at least 1 year after the RT ( $n = 233$ ). Median follow-up was 5 years. We found a rather high incidence of dysphagia, hypothyroidism, and osteoradionecrosis. We also found that age, gender, tumor subsite, and neck RT affect susceptibility to long-term side effects.

In line with previous literature, we found that nearly half of HNC patients report persistent dysphagia.<sup>19,20,21,22</sup> Dysphagia is less common in patients treated only surgically than in those who have received (chemo)RT.<sup>19</sup> Irradiation causes soft tissue deformities such as upper sphincter stricture, mucosal injuries, damage to connective tissue, and xerostomia, all of which impair bolus movement during swallowing.<sup>23</sup> Dysphagia has been shown to greatly affect QOL.<sup>24</sup> Especially PEG dependency impairs QOL.<sup>6</sup> Greco et al. demonstrated



**FIGURE 2** (A) Photograph of a patient with mandibular osteoradionecrosis. The patient was symptom-free. The necrotic area was treated surgically under local anesthesia and oral antibiotics were prescribed. (B) Improvement was visible 3 months later

**TABLE 2** Dysphagia incidence and its treatment within treatment modality groups

	Dysphagia incidence (n = 106)	PEG tube dependence (n = 24)	Esophageal dilatations (n = 22)	Nutritional therapy only (n = 60)
Only surgery, stage III-IV (n = 7)	0	—	—	—
Only primary tumor radiated (n = 15)	13.3%	0	6.7%	6.7%
Neck radiated, elective dose (median 50 Gy, n = 79)	46.8%	10.1%	11.4%	25.3%
Neck radiated, definitive dose (median 65 Gy, n = 139)	48.2%	11.5%	8.6%	28.1%
<i>p</i>	.004	.420	.769	.123

that behavioral swallowing interventions improve the swallowing function in HNC patients who have dysphagia secondary to RT.<sup>25</sup> Moreover, esophageal dilatations performed <1 year after RT have been shown to improve the subjective swallowing function.<sup>26</sup> Esophageal strictures secondary to RT have a high long-term recurrence rate of up to 33%.<sup>27</sup> A recent systematic review summarized that esophageal dilatations in HNC patients have a pooled success rate of 72.9% and an overall complication rate of 10.6%, and thus the use of dilatations is generally supported.<sup>28</sup>

Baudelet et al. found that the severity of dysphagia was higher in patients with a higher T classification, and that older patients had higher dysphagia scores.<sup>29</sup> They also found that dysphagia does not appear to be stable over time; however, in line with our findings, dysphagia remains highly prevalent at very late follow-up of 5–8 years. In our data, no correlation between age or cancer stage and dysphagia was found. A significant treatment-related factor behind dysphagia cases in our data was neck RT. Gharzai et al. have suggested that late progressive dysphagia correlates with a higher ipsilateral hypoglossal nerve dose to 1 cc, with no significant differences in ipsilateral mean or contralateral doses.<sup>30</sup> Contrary to our results, there is also evidence that ipsilateral irradiation would reduce dysphagia.<sup>31,32</sup> On the other hand, Chin et al. found that dysphagia scores were not significantly different in unilateral and bilateral IMRT groups.<sup>33</sup> A recent review stated that ipsilateral RT is usually appropriate for a tonsil-confined tumor with a minimal burden of nodal disease. Ipsilateral RT was not recommended for other patient groups. The conclusion was that further research is needed on the optimal selection of patients for ipsilateral RT.<sup>34</sup> Several researchers consider current bilateral elective neck irradiation strategies to be overtreatment and show growing interest in a unilateral nodal irradiation in selected HNC patients.<sup>35</sup>

The incidence of radiation-induced hypothyroidism in HNC patients at 3-year follow-up has varied from 25.8% to 56.6%.<sup>36,37,38,39,40</sup> Our result (29%) is in line with these findings. Known risk factors for radiation-induced hypothyroidism are female sex, younger age, small thyroid size, previous neck surgery, and higher radiation dose.<sup>41</sup> In our data, the impact of female sex and younger age in hypothyroidism was visible, but a higher radiation dose did not correlate with a higher incidence of hypothyroidism. Individual thyroid gland doses were not available for analyses. Nevertheless, IMRT limits the thyroid gland dose effectively.<sup>41</sup>

We found that TSH levels rise after radiation (Figure 1A,B). However, TSH distribution and reference limits shift to higher concentrations with age,<sup>42</sup> and thus we concluded that this finding is not of further significance.

De Felice et al. summarized that the incidence of mandibular osteoradionecrosis (MORN) secondary to IMRT for HNC ranges from 0% to 14%, which is also true in our data (12%).<sup>43</sup> They also stated that MORN is influenced by both RT-related parameters (such as total dose, fractionation scheme, type of energy, treatment field size) and patient-related factors (old age, smoking, poor oral hygiene, general health). Aarup-Kristensen et al. found that surgery to the mandible, pre-RT tooth extraction, smoking, and treatment dose were associated with the development of

osteoradionecrosis.<sup>44</sup> In line with our findings, oral cavity cancer patients are shown to be at higher risk of developing MORN.<sup>45,46</sup> In our data, only a small number of patients were diagnosed with osteoradionecrosis ( $n = 29$ ), which might explain why we could not find other significant correlations.

A meta-analysis by Haussmann et al. found that classic high-grade toxicities (xerostomia, dysphagia, or subcutaneous, bone, and skin toxicity) appear not to be worsened by the addition of chemotherapy given concurrently with hyperfractionated RT.<sup>47</sup> Our data suggest similar conclusions. Haussmann et al. also discussed that many chemotherapy-specific side effects like hematological adverse events, nausea and vomiting were not often reported, as they hardly occur in non-chemotherapy treatment modality groups. The typically smaller than standard 2 Gy fraction size applied in hyperfractionated regimens may in fact protect late reacting tissues such as peripheral nerves and vasculature.

Many de-intensification strategies have been investigated. In the field of surgery, transoral robotic surgery (TORS) has been shown to have less intraoperative and postoperative complications, with no difference in survival rate, compared to open surgery for HNC.<sup>48</sup> There is also firm evidence that IMRT reduces the risk of xerostomia compared to conventional two-dimensional and/or three-dimensional radiotherapy in curative-intent management of HNC.<sup>49</sup> In addition, IMRT has shown superior outcomes compared to conventional radiotherapy in early-stage glottic cancer.<sup>50,51</sup> Nonetheless, in our IMRT-treated patients, side effects were common. Moreover, both p16 positive and negative HNC recur in high-risk RT, and thus biomarkers predicting radioresistance should be characterized before embarking on de-escalated CRT protocols.<sup>17</sup> However, molecular imaging-guided RT, adaptive therapy, and proton beam therapy could potentially decrease the long-term complications of RT.<sup>52,53,54</sup>

There are some limitations to this study. For analyses of risk factors for osteoradionecrosis, our sample was small. There was also a lack of systematic information on weight changes secondary to dysphagia. Moreover, p16 information was missing in most cases.

More research and prospective, randomized studies are needed to assess which interventions will minimize the long-term side effects of HNC treatment.

## 5 | CONCLUSION

Late toxicities of RT for HNC are common. The most frequent persisting complications are dysphagia and hypothyroidism. Hypothyroidism is more common in females and younger patients. RT of the neck increases the risk of dysphagia. Neither a combination of chemotherapy, nor definitive neck radiation to high-risk target volume for metastatic areas compared to elective neck radiation, seem to increase the risk of late toxicities of RT. Surgical interventions did not increase the incidence of dysphagia, hypothyroidism, or osteoradionecrosis in our data. Oral cavity cancer patients are more likely to develop osteoradionecrosis.



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## CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

## ORCID

Pihla Ranta  <https://orcid.org/0000-0003-3211-2018>

Eero Kytö  <https://orcid.org/0000-0002-2567-5931>

Heikki Minn  <https://orcid.org/0000-0002-5878-4333>

Heikki Irjala  <https://orcid.org/0000-0003-3054-4677>

## REFERENCES

- Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surg Oncol Clin N Am*. 2015;24(3):379-396. doi:10.1016/j.soc.2015.03.001
- Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. *Oncologist*. 2010;15(9):994-1001. doi:10.1634/theoncologist.2009-0289
- Mifsud M, Eskander A, Irish J, et al. Evolving trends in head and neck cancer epidemiology: Ontario, Canada 1993–2010. *Head Neck*. 2017;39(9):1770-1778. doi:10.1002/hed.24829
- Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289. doi:10.3322/caac.21349
- Cramer JD, Burtneß B, Le QT, Ferris RL. The changing therapeutic landscape of head and neck cancer. *Nat Rev Clin Oncol*. 2019;16(11):669-683. doi:10.1038/s41571-019-0227-z
- Ranta P, Kinnunen I, Jouhi L, et al. Long-term quality of life after treatment of oropharyngeal squamous cell carcinoma. *Laryngoscope*. 2020;131:E1172-E1178. doi:10.1002/lary.29042
- Xu MJ, Plonowska KA, Gurman ZR, et al. Treatment modality impact on quality of life for human papillomavirus-associated oropharynx cancer. *Laryngoscope*. 2019;130:E48-E56. doi:10.1002/lary.27937
- Amit M, Hutcheson K, Zaveri J, et al. Patient-reported outcomes of symptom burden in patients receiving surgical or nonsurgical treatment for low-intermediate risk oropharyngeal squamous cell carcinoma: a comparative analysis of a prospective registry. *Oral Oncol*. 2019;91:13-20. doi:10.1016/j.oraloncology.2019.01.020
- Brogie MA, Soltermann A, Haile SR, et al. Quality of life of oropharyngeal cancer patients with respect to treatment strategy and p16-positivity. *Laryngoscope*. 2013;123(1):164-170. doi:10.1002/lary.23622
- Sinha P, Karadaghy OA, Doering MM, Tuuli MG, Jackson RS, Haughey BH. Survival for HPV-positive oropharyngeal squamous cell carcinoma with surgical versus non-surgical treatment approach: a systematic review and meta-analysis. 2018. doi:10.1016/j.oraloncology.2018.09.018
- Lo Nigro C, Denaro N, Merlotti A, Merlano M. Head and neck cancer: improving outcomes with a multidisciplinary approach. *Cancer Manag Res*. 2017;9:363-371. doi:10.2147/CMAR.S115761
- Schlichting JA, Pagedar NA, Chioreso C, Lynch CF, Charlton ME. Treatment trends in head and neck cancer: surveillance, epidemiology, and end results (SEER) patterns of care analysis. *Cancer Causes Control*. 2019;30(7):721-732. doi:10.1007/s10552-019-01185-z
- Bhide SA, Newbold KL, Harrington KJ, Nutting CM. Clinical evaluation of intensity-modulated radiotherapy for head and neck cancers. *Br J Radiol*. 2012;85(1013):487-494. doi:10.1259/bjr/85942136
- Hamilton SN, Arshad O, Kwok J, et al. Documentation and incidence of late effects and screening recommendations for adolescent and young adult head and neck cancer survivors treated with radiotherapy. *Support Care Cancer*. 2019;27(7):2609-2616. doi:10.1007/s00520-018-4559-5
- Brook I. Late side effects of radiation treatment for head and neck cancer. *Radiat Oncol J*. 2020;38(2):84-92. doi:10.3857/roj.2020.00213
- Allen-Ayodabo CO, Eskander A, Davis LE, et al. Symptom burden among head and neck cancer patients in the first year after diagnosis: association with primary treatment modality. *Oral Oncol*. 2019;99:104434. doi:10.1016/j.oraloncology.2019.09.026
- Nissi L, Suilamo S, Kytö E, Vaittinen S, Irjala H, Minn H. Recurrence of head and neck squamous cell carcinoma in relation to high-risk treatment volume. *Clin Transl Radiat Oncol*. 2021;27:139-146. doi:10.1016/j.ctro.2021.01.013
- US Department of Health and Human Services. Smoking cessation: a report of the surgeon general.
- Pezdirec M, Strojani P, Boltezar IH. Swallowing disorders after treatment for head and neck cancer. *Radiol Oncol*. 2019;53(2):225-230. doi:10.2478/raon-2019-0028
- Kraaijenga SAC, Oskam IM, Van Der Molen L, Hamming-Vrieze O, Hilgers FJM, Van Den Brekel MWM. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. *Oral Oncol*. 2015;51(8):787-794. doi:10.1016/j.oraloncology.2015.05.003
- Martin A, Murray L, Sethugavalan B, et al. Changes in patient-reported swallow function in the long term after chemoradiotherapy for oropharyngeal carcinoma. *Clin Oncol*. 2018;30(12):756-763. doi:10.1016/j.clon.2018.06.013
- Patterson JM, McColl E, Carding PN, Wilson JA. Swallowing beyond six years post (chemo)radiotherapy for head and neck cancer; a cohort study. *Oral Oncol*. 2018;83:53-58. doi:10.1016/j.oraloncology.2018.06.003
- King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of radiation-induced dysphagia in head and neck cancer. *Dysphagia*. 2016;31(3):339-351. doi:10.1007/s00455-016-9710-1
- Carmignani I, Locatello LG, Desideri I, et al. Analysis of dysphagia in advanced-stage head-and-neck cancer patients: impact on quality of life and development of a preventive swallowing treatment. *Eur Arch Oto-Rhino-Laryngol*. 2018;275(8):2159-2167. doi:10.1007/s00405-018-5054-9
- Greco E, Simic T, Ringash J, Tomlinson G, Inamoto Y, Martino R. Dysphagia treatment for patients with head and neck cancer undergoing radiation therapy: a meta-analysis review. *Int J Radiat Oncol Biol Phys*. 2018;101(2):421-444. doi:10.1016/j.ijrobp.2018.01.097
- Cho AH, Caldito G, Nathan CAO. Timing of esophageal dilation for dysphagia in head and neck cancer patients receiving radiation therapy. *Laryngoscope*. Vol 120. Laryngoscope; 2010.
- Agarwalla A, Small AJ, Mendelson AH, Scott FI, Kochman ML. Risk of recurrent or refractory strictures and outcome of endoscopic dilation for radiation-induced esophageal strictures. *Surg Endosc*. 2015;29(7):1903-1912. doi:10.1007/s00464-014-3883-1
- Moss WJ, Pang J, Orosco RK, et al. Esophageal dilation in head and neck cancer patients: a systematic review and meta-analysis. *Laryngoscope*. 2018;128(1):111-117. doi:10.1002/lary.26618
- Baudelet M, Van den Steen L, Tomassen P, et al. Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy. *Head Neck*. 2019;41(10):3594-3603. doi:10.1002/hed.25880
- Gharzai LA, Li P, Schipper MJ, et al. Characterization of very late dysphagia after chemoradiation for oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2020;111:104853. doi:10.1016/j.oraloncology.2020.104853
- Jensen K, Overgaard M, Grau C. Morbidity after ipsilateral radiotherapy for oropharyngeal cancer. *Radiother Oncol*. 2007;85(1):90-97. doi:10.1016/j.radonc.2007.06.005

32. Chen AM, Meshman J, Hsu S, Yoshizaki T, Abemayor E, John MS. Oropharynx-directed ipsilateral irradiation for p16-positive squamous cell carcinoma involving the cervical lymph nodes of unknown primary origin. *Head Neck*. 2018;40(2):227-232. doi:10.1002/hed.24906
33. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. *Cancer*. 2017;123(23):4594-4607. doi:10.1002/cncr.30931
34. Tsai CJ, Galloway TJ, Margalit DN, et al. Ipsilateral radiation for squamous cell carcinoma of the tonsil: American radium society appropriate use criteria executive summary. *Head Neck*. 2021;43(1):392-406. doi:10.1002/hed.26492
35. Nuyts S, Bollen H, Eisbruch A, et al. Unilateral versus bilateral nodal irradiation: current evidence in the treatment of squamous cell carcinoma of the head and neck. *Head Neck*. 2021;43(9):2807-2821. doi:10.1002/hed.26713
36. Huang CL, Tan HW, Guo R, et al. Thyroid dose-volume thresholds for the risk of radiation-related hypothyroidism in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy—a single-institution study. *Cancer Med*. 2019;8(16):6887-6893. doi:10.1002/cam4.2574
37. Lee V, Chan SY, Choi CW, et al. Dosimetric predictors of hypothyroidism after radical intensity-modulated radiation therapy for non-metastatic nasopharyngeal carcinoma. *Clin Oncol*. 2016;28(8):e52-e60. doi:10.1016/j.clon.2016.05.004
38. Ping ZR, Fang KF, Run DC, Su HC, Mei YH. Radiation-induced hypothyroidism after IMRT for nasopharyngeal carcinoma: clinical and dosimetric predictors in a prospective cohort study. *Oral Oncol*. 2017;68:44-49. doi:10.1016/j.oraloncology.2017.03.005
39. Fujiwara M, Kamikonya N, Odawara S, et al. The threshold of hypothyroidism after radiation therapy for head and neck cancer: a retrospective analysis of 116 cases. *Journal of Radiation Research*. 2014;56:577-582. doi:10.1093/jrr/rrv006
40. Lertbutsayanukul C, Kitpanit S, Prayongrat A, Kannarunimit D, Netsawang B, Chakkabat C. Validation of previously reported predictors for radiation-induced hypothyroidism in nasopharyngeal cancer patients treated with intensity-modulated radiation therapy, a post hoc analysis from a phase III randomized trial. *J Radiat Res*. 2018;59(4):446-455. doi:10.1093/jrr/rry036
41. Zhou L, Chen J, Tao CJ, Chen M, Yu ZH, Chen YY. Research progress of radiation-induced hypothyroidism in head and neck cancer. *J Cancer*. 2020;12(2):451-459. doi:10.7150/jca.48587
42. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. *J Clin Endocrinol Metab*. 2010;95(2):496-502. doi:10.1210/jc.2009-1845
43. De Felice F, Tombolini V, Musio D, Polimeni A. Radiation therapy and mandibular osteoradionecrosis: state of the art. *Curr Oncol Rep*. 2020;22(9):1-8. doi:10.1007/s11912-020-00954-3
44. Aarup-Kristensen S, Hansen CR, Fomer L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. *Acta Oncol (Madr)*. 2019;58(10):1373-1377. doi:10.1080/0284186X.2019.1643037
45. Moon DH, Moon SH, Wang K, et al. Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. *Oral Oncol*. 2017;72:98-103. doi:10.1016/j.oraloncology.2017.07.014
46. Kubota H, Miyawaki D, Mukumoto N, et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. *Radiat Oncol*. 2021;16(1):1. doi:10.1186/s13014-020-01701-5
47. Haussmann J, Tamaskovics B, Bölke E, et al. Addition of chemotherapy to hyperfractionated radiotherapy in advanced head and neck cancer—a meta-analysis. *Strahlentherapie Und Onkol*. 2019;195(12):1041-1049. doi:10.1007/s00066-019-01511-z
48. Roselló À, Albuquerque R, Roselló-Llabrés X, Marí-Roig A, Estrugo-Devesa A, López-López J. Transoral robotic surgery vs open surgery in head and neck cancer. A systematic review of the literature. *Med Oral Patol Oral y Cir Bucal*. 2020;25(5):e599-e607. doi:10.4317/medoral.23632
49. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic review and meta-analyses of intensity-modulated radiation therapy versus conventional two-dimensional and/or or three-dimensional radiotherapy in curative-intent management of head and neck squamous cell carcinoma. *PLoS One*. 2018;13(7):e0200137. doi:10.1371/journal.pone.0200137
50. Mohamed ASR, Smith BD, Smith JB, et al. Outcomes of carotid-sparing IMRT for T1 glottic cancer: comparison with conventional radiation. *Laryngoscope*. 2020;130(1):146-153. doi:10.1002/lary.27873
51. Berwouts D, Swimberghe M, Duprez F, et al. Intensity-modulated radiotherapy for early-stage glottic cancer. *Head Neck*. 2016;38:E179-E184. doi:10.1002/hed.23967
52. Grégoire V, Thorwarth D, Lee JA. Molecular imaging-guided radiotherapy for the treatment of head-and-neck squamous cell carcinoma: does it fulfill the promises? *Semin Radiat Oncol*. 2018;28(1):35-45. doi:10.1016/j.semradonc.2017.08.003
53. Morgan HE, Sher DJ. Adaptive radiotherapy for head and neck cancer. *Cancers Head Neck*. 2020;5(1):1. doi:10.1186/s41199-019-0046-z
54. Hayashi Y, Nakamura T, Mitsudo K, et al. Retrograde intra-arterial chemotherapy and daily concurrent proton beam therapy for recurrent oral cavity squamous cell carcinoma: analysis of therapeutic results in 46 cases. *Head Neck*. 2016;38(8):1145-1151. doi:10.1002/hed.24421

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