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Toxicity and Quality of Life After Locoregional Radiotherapy in Patients With Thyroid Cancer

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ABSTRACT

Background: Locoregional external beam radiotherapy (EBRT) is selectively used in thyroid cancer patients to induce locoregional control. However, despite technological advances, EBRT remains associated with toxicities. We evaluated thyroid-cancer specific toxicities and long-term Quality of Life (QoL) post-EBRT.

Methods: EBRT-treated thyroid cancer patients at Universal Medical Centre Groningen (2007–2023) were retrospectively evaluated ($n = 66$). Acute (< 6 weeks) and late (≥ 3 months) toxicities and QLQ-H&N35 results, prospectively collected as standard patient care, were analyzed (available in 24/66). Additionally, 17/66 living patients cross-sectionally completed the QLQ-H&N43 [renewed QLQ-H&N35] and SF-36-RAND-36.

Results: In 24/66 patients who completed questionnaires during EBRT treatment, most severe acute toxicities occurred around week 6 (91% dermatitis, 74% pain, 70% hoarseness, 65% dysphagia). Late toxicities included persisting acute toxicities and fibrosis. Six months post-treatment, only QLQ-H&N35 domains "social eating" ($p = 0.031$) and "dry mouth/sticky saliva" ($p = 0.025$) were affected, in comparison to pre-radiation. In the 10/17 patients who completed the QLQ-H&N35 6 months post-radiation and the cross-sectionally performed QLQ-H&N43, no long-term mitigation of assessed domains was identified in a longitudinal analysis. The most advanced EBRT technique was associated with better QLQ-H&N43 scores ($p = 0.047$).

Conclusions: EBRT causes acute and late toxicities in most thyroid cancer patients and may be associated with a decreased QoL. As these patients generally survive for multiple years, there is a compelling need to minimize toxicities with more refined radiation techniques, such as proton therapy.

1 | Introduction

While most thyroid cancer patients have a good prognosis with standard-of-care treatment, some require additional treatments like systemic therapy or external beam radiotherapy (EBRT) to reach disease control [1]. EBRT is typically used after surgery to reduce recurrence in patients with high-risk tumors and in palliative setting to obtain locoregional control [2].

Unfortunately, EBRT is associated with acute and late toxicities, due to detrimental effects on healthy tissue [3]. Throughout the years, there have been significant technological advancements

in the field of radiotherapy. Intensity-modulated radiotherapy (IMRT) allows improved sparing of organs at risk, compared with traditional two-dimensional and three-dimensional conformal radiotherapy (3DCRT). Volumetric intensity modulated arc therapy (VMAT) has optimized IMRT further by varying the rotation speed, dose rate and beam shape dynamically during treatment delivery, which is associated with improved organ-at-risk doses, monitor units and treatment times [4, 5].

In contrast to other head and neck cancers, there is limited data on thyroid cancer-specific toxicities of EBRT. In addition, to date, no studies have been conducted on the long-term toxicity and Quality of Life (QoL) after EBRT in those thyroid cancer patients with an extended survival period. Prior research showed a median survival of EBRT-treated ATC patients ranging from 1.97 to 6.77 months [6]. In differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC) patients treated with EBRT, a 4-year and 5-year disease specific survival of respectively 76% and 82% was observed [7, 8]. Therefore, more knowledge is needed about the late radiation-induced side effects for thyroid cancer patients treated with EBRT, as well as their long-term impact on the patients' QoL.

The present study was initiated to describe both acute and late toxicities, as well as to assess the long-term general and head-and-neck specific QoL in patients with thyroid cancer, treated with EBRT. Additionally, we evaluated the correlation between long-term QoL, EBRT and other treatment characteristics.

2 | Materials and Methods

2.1 | Design

This study of thyroid cancer patients, treated with EBRT in the University Medical Center of Groningen (UMCG) between 2007 and June 2023, consists of a retrospective, prospective, cross-sectional, and longitudinal part.

2.2 | Retrospective—Clinical Characteristics (Part A)

Eligible patients were identified by reviewing all patients with a thyroid cancer diagnosis-treatment code and radiotherapeutic treatment in the electronic patient files. This was cross-checked with a list of the Department of Radiotherapy of thyroid cancer patients visiting the department between January 2007 and June 2023.

Patients were eligible for inclusion when diagnosed with thyroid cancer and treated with EBRT for the primary tumor and/or cervical lymph node metastases at the UMCG between 2007 and June 2023. Exclusion criteria encompassed: radiation for distant metastasis only, radiotherapy not yet completed or radiated in the last three months of the inclusion period, and discontinuation of radiotherapy (Figure S1). After patient selection, patient and treatment characteristics were collected from patient files. Follow-up time was defined as the time between the last radiation session and the last out-patient visit. We defined primary EBRT treatment as the first treatment after diagnosis, adjuvant EBRT included both post-operative and post-radioactive iodine (RAI) EBRT, while salvage EBRT treatment defined radiation for recurrent and persistent lesions. EBRT with 33 or 35 fractions of 2 Gy with either curative or palliative intent were classified as radical curative or radical palliative intent, respectively. Those receiving lower doses were categorized as non-radical palliative intent.

Disease extent was determined using the 8th edition of the Tumor Node Metastases (TNM) classification system, following the American Joint Committee on Cancer (AJCC) guidelines. Histopathological parameters were retrospectively extracted from pathology reports of experienced thyroid pathologists. Radicality of the resection was defined as microscopic (R1) or macroscopic (R2) presence of tumor at the margins.

2.3 | Prospective—Toxicity and Quality of Life (Part B)

From 2007 onward, toxicity and QoL data of part of the EBRT-treated thyroid cancer patients was recorded by the Department of Radiotherapy in the prospective ProTRAIT database (Figure 1). Patients receiving palliative care are not routinely included, and some patients choose not to participate.

2.4 | Toxicity

Toxicity was assessed across various domains including xerostomia, mucositis, dermatitis, hoarseness, dysphagia, and neck fibrosis and was evaluated utilizing the RTOG/EORTC Radiation Morbidity Scoring Criteria [9, 10]. Throat and mouth pain and aspiration were evaluated by UMCG criteria, while sticky saliva, taste alterations, dental caries, acneiform rash, soft tissue necrosis, and laryngeal edema were assessed by CTCAE criteria [11]. Osteoradionecrosis was scored per Glanzmann criteria [12].

Baseline toxicities were measured prior to the first radiation session (week 0) while acute toxicities included those occurring < 6 weeks of starting EBRT, with weekly assessments documenting adverse effects and reporting the highest severity grade. Late toxicity was defined as toxicity present ≥ 3 months after the last administered EBRT fraction, including any persistent acute toxicity. We evaluated this late toxicity after 3, 6, and 12 months, employing the same methodology utilized during EBRT. Patients who died < 12 months of their last radiation dose were excluded from the toxicity analysis. Moreover, only patients receiving radiation with radical curative or radical palliative intent were included.

2.5 | Quality of Life

Outcomes of the Organization for Research and Treatment of Cancer Head and Neck Specific Quality of Life Questionnaire—35 items (EORTC QLQ-H&N35) were also

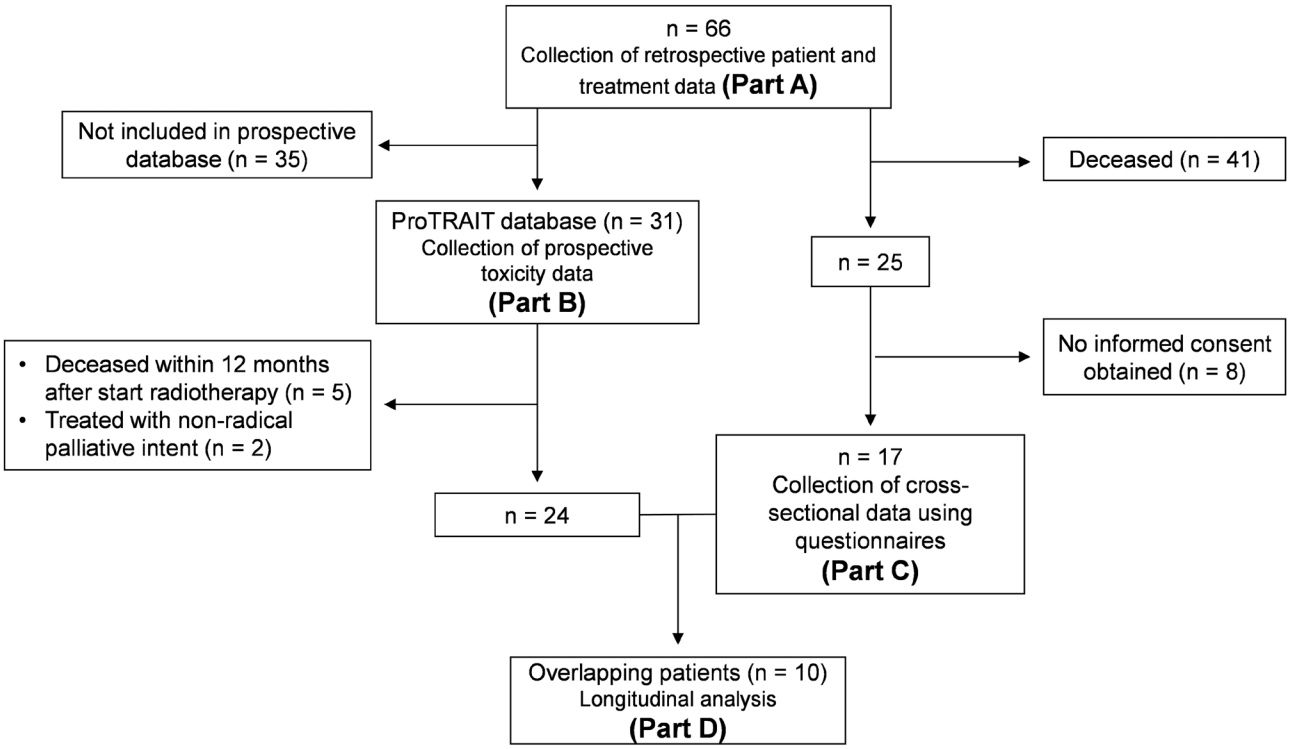

FIGURE 1 | Flow diagram displaying patient selection.

documented in the prospective database and analyzed in the current study. This data encompasses baseline radiotherapy assessments and evaluations 6 months after the last radiotherapy treatment.

2.6 | Cross-Sectional—Toxicity and Quality of Life (Part C)

To study the long-term effects cross-sectionally, patients who were still alive at the time of data collection and capable to participate, filled in two questionnaires, after written consent, concerning long-term effects of EBRT (Figure 1). The EORTC QLQ-H&N–43 items and the Short Form-36-Research and Development-36 (SF-36-RAND-36) questionnaires were used. The QLQ-H&N43 measures the QoL in patients with head and neck malignancies [13]. In this questionnaire, a value of 0 conveys an optimal state of health. The SF-36-RAND-36 measures general health, with a score of 100 reflecting perfect health [14]. For patients who completed these questionnaires, the follow-up period was defined as the time between the last radiation session and the date of questionnaire submission.

2.7 | Longitudinal—Toxicity and Quality of Life (Part D)

To allow a longitudinal analysis, patients with data from both the QLQ H&N35 (part B) and the QLQ H&N43 (part C) were identified. The QLQ H&N35 overlapped with the QLQ H&N43 across seven domains (pain in the mouth, swallowing, problems with senses, trouble with social eating, problems opening mouth, coughing, and dry mouth and sticky saliva). The remaining domains speech, trouble with social contact, problems with teeth, and weight loss consisted of different questions and therefore could not be compared statistically. Other domains were unique for each of the questionnaires and therefore not compared.

2.8 | Treatment Characteristics Analysis (Part E)

Finally, we assessed correlations between the median scores of the QLQ-H&N43 and SF-36-RAND-36 and the number of surgeries, number of RAI treatments, total RAI dose, systemic treatment, follow up-time, total radiation dose, and EBRT technique.

2.9 | Ethics

The Medical Ethics Committee of the UMCG approved this study (register number: 10880). Approval for the prospective ProTRAIT database was obtained from the same ethics committee (register number: 4775). Written informed consent was obtained where required. All study procedures were performed in accordance with the Declaration of Helsinki.

2.10 | Statistics

Descriptive statistics were used to describe patient and clinical characteristics. We used the Wilcoxon signed-rank test to compare paired, non-normally distributed continuous data. Spearman's rho identified significant correlations between non-normally distributed variables. Differences between groups

TABLE 1 | Part A: Patient, tumor, and treatment characteristics.

	Part A ($n=66$) n (%) or median (IQR)	Part B ($n=24$) n (%) or median (IQR)	Part C ($n=17$) n (%) or median (IQR)
Female sex	32 (49)	7 (29)	8 (47)
Age at start radiotherapy	71 (61–77)	68 (56–73)	66 (57–71)
Alive	25 (38)	17 (71)	17 (100)
Histologic subtype			
Follicular cell-derived	50 (76)	16 (67)	10 (59)
DTC/Oncocytic	29 (44)	13 (55)	8 (47)
Poorly differentiated	3 (5)	2 (8)	0 (0)
Anaplastic	18 (27)	1 (4)	2 (12)
C-cell derived	16 (24)	8 (33)	7 (41)
T stage			
TX	5 (8)	0 (0)	0 (0)
T0	1 (1)	1 (4)	0 (0)
T1-2	6 (9)	5 (21)	1 (6)
T3-4b	54 (82)	18 (75)	16 (94)
N stage			
NX	6 (9)	0 (0)	0 (0)
N0	17 (25)	8 (33)	6 (35)
N1a/b	43 (65)	16 (67)	11 (65)
M stage			
MX	5 (8)	0 (0)	0 (0)
M0	47 (71)	22 (92)	13 (76)
M1	14 (21)	2 (8)	4 (24)
Surgery	49 (74)	21 (88)	15 (88)
Total thyroidectomy	30 (61)	15 (71)	10 (67)
Hemithyroidectomy	11 (23)	5 (24)	3 (20)
Other thyroid surgery	8 (16)	1 (5)	2 (13)
Surgical margins[a]			
Positive (R1/R2)	37 (76)	13 (62)	10 (67)
Negative (R0)	11 (22)	7 (33)	5 (33)
Unknown	1 (2)	1 (5)	0 (0)
Total number of surgeries			
1	23 (47)	11 (52)	9 (60)
2	14 (29)	5 (24)	2 (13)
≥ 3	12 (24)	5 (24)	4 (27)
LND	38 (58)	20 (83)	12 (71)
RAI	27 (41)	12 (50)	7 (41)
Number of RAI treatments	2 (2–3)	2 (1–3)	2 (1–2)

(Continues)

TABLE 1 | (Continued)

	Part A ($n=66$) n (%) or median (IQR)	Part B ($n=24$) n (%) or median (IQR)	Part C ($n=17$) n (%) or median (IQR)
Cumulative dose (mCi)	300 (255–450)	300 (150–413)	300 (150–300)
Systemic treatment	13 (20)	6 (25)	5 (29)
Tyrosine kinase inhibitors[b]	13 (86)	7 (100)	5 (100)
Chemotherapy[b]	1 (7)	0 (0)	0 (0)
Immunotherapy[b]	1 (7)	0 (0)	0 (0)
EBRT	66 (100)	24 (100)	17 (100)
Primary	17 (26)	3 (13)	2 (12)
Adjuvant	23 (35)	12 (50)	9 (53)
Salvage	26 (39)	9 (37)	6 (35)
Re-irradiation	4 (6)	1 (4)	0 (0)
EBRT technique[c]			
3D-CRT	4 (6)	0 (0)	0 (0)
IMRT	20 (29)	3 (12)	3 (18)
VMAT	36 (51)	22 (88)	14 (82)
Unknown	10 (14)	0 (0)	0 (0)
Intention EBRT[c]			
Radical curative	32 (46)	20 (80)	11 (65)
Radical palliative	8 (11)	4 (16)	1 (6)
Non-radical palliative	30 (43)	1 (4)[d]	5 (29)
Total radiation dose (Gy)[c]	66 (39–70)	70 (66–70)	67 (50–70)
Fractions[c]	33 (13–35)	33 (33–35)	35 (16–35)
Follow-up (months)	22 (6–50)	25 (15–49)	33 (22–60)

Abbreviations: 3D-CR = three-dimensional conformal radiation therapy; Ci = millicurie; EBRT = external beam radiotherapy; Gy = gray; IMRT = intensity modulated radiotherapy; IQR = interquartile range; LND = lymph node dissection; R0 = no residual tumor; R1 = microscopic residual tumor; R2 = macroscopic residual tumor; RAI = radioactive iodine; VMAT = volumetric modulated arc therapy.
[a]Surgical margins of the first operation.
[b]Including the cases of two systemic treatments.
[c]Including the cases of re-irradiation.
[d]Prospective toxicity analyses was performed before this re-irradiation.

were identified with the chi-square test or fisher's exact test (in case of < 5 observations) for categorical data, and with the Mann Whitney U test for continuous data. A p-value < 0.05 was considered statistically significant. SPSS version 29 was used for all statistical analyses.

3 | Results

3.1 | Retrospective—Clinical Characteristics (Part A)

A total of 220 patients were primarily identified in the hospital registration, of which 66 met the inclusion criteria for the retrospective analysis (Figure 1). The majority of excluded patients had radiotherapy before 2007 ($n=56$) or only for metastatic lesions ($n=59$) (Figure S1). Of the total of 66 included patients (Table 1), the median age at the start of the radiotherapy was 71 (IQR, 61–77). Surgical intervention was the initial treatment for 49 (74%) patients, with a majority undergoing multiple neck surgeries. RAI was administered to 27 (41%) patients and systemic treatment was provided to 13 (20%) patients. The median interval between the last radiation treatment and the last follow up was 22 (IQR, 5.8–49.8) months.

Of the 66 patients receiving EBRT, 17 (26%) patients received EBRT as primary treatment to obtain locoregional control, while 23 (35%) patients underwent adjuvant EBRT. The remaining 26 (39%) patients underwent EBRT as salvage treatment. Notably, 4 (6%) patients underwent re-irradiation with palliative intent. The median radiation dose was 66 (IQR, 39.0–70.0) Gray. VMAT technique was most commonly used (51%), compared to IMRT (29%) and 3D-CRT (6%). The radiation technique was not reported in 14% of patients.

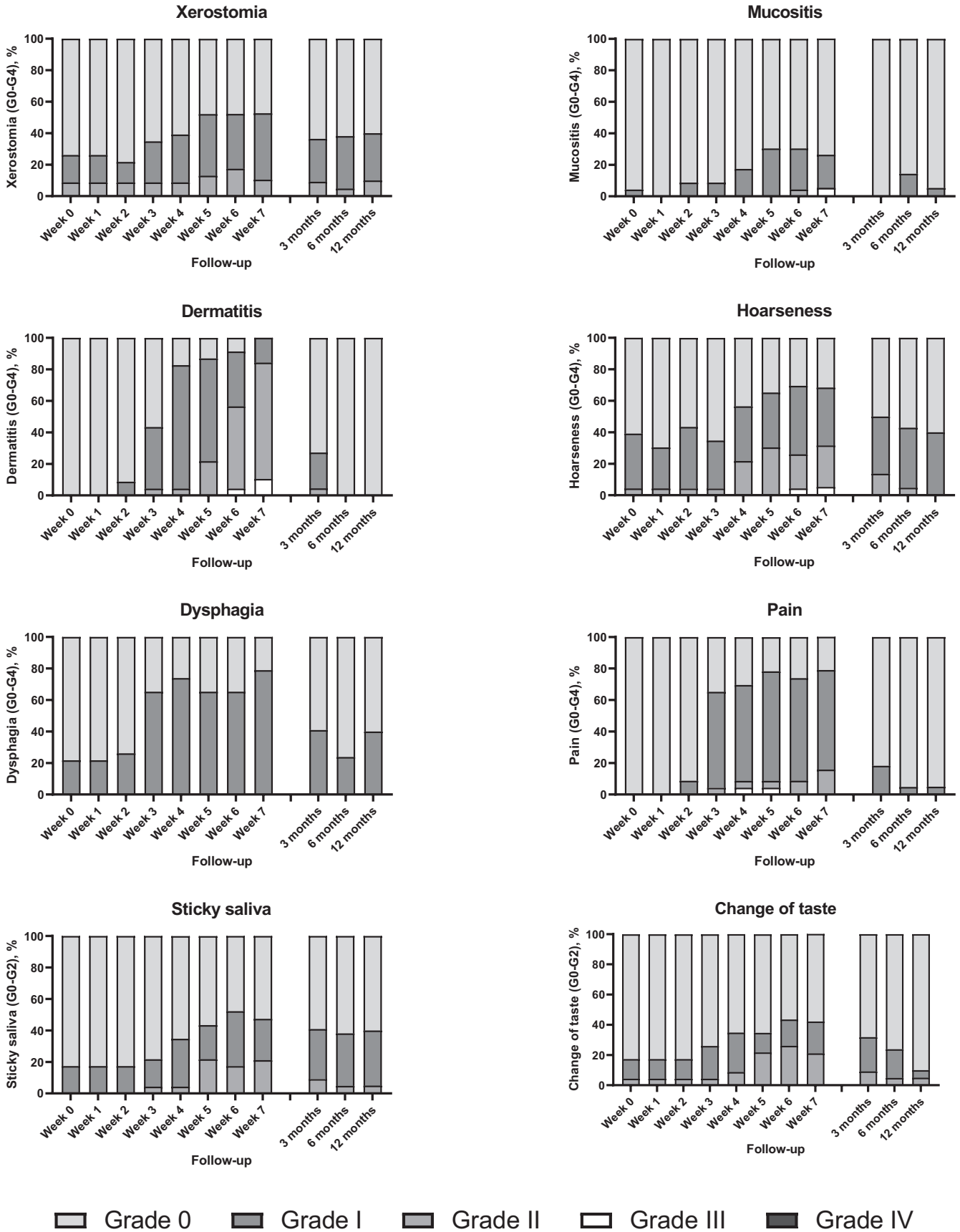

FIGURE 2 | Legend on next page.

3.2 | Prospective—Toxicity (Part B)

Among the cohort of 66 patients in part A, prospective toxicity and QoL data was available for 31. To ensure a minimum 12-month follow-up after last radiation treatment, 5 patients were excluded from the toxicity analysis. Two more patients were excluded due to radiation with non-radical palliative intent (Figure 1). Patient and treatment characteristics of the remaining 24 patients, included in the toxicity analysis, are shown in Table 1. None of 24 patients were treated with systemic treatment prior to or in the 12 months after radiotherapy. RAI was administered to 11/24 patients prior to radiotherapy. One patient received a second RAI dose during the 12 months following radiotherapy. The median time between the last RAI dose and the first radiation treatment was 10.5 (IQR, 1.3–21.3) months. In comparison to the other 42 patients, these 24 patients had more favorable characteristics, reflecting the methodology where those treated with palliative intent were not routinely included in the prospective survey of toxicity (Table S1).

In the 24 patients, most toxicities presented between the third and seventh weeks of radiation (Figure 2). At the six-week mark, a substantial proportion of patients experienced dermatitis (91%), pain (74%), hoarseness (70%), dysphagia (65%), sticky saliva (52%), xerostomia (52%), change of taste (44%), and mucositis (30%) (Table 2). Grade III mucositis, dermatitis and hoarseness were each reported once and grade III pain twice. Notably, there were no instances of grade IV toxicity. No patient experienced acute acneiform rash.

Three months post-radiation, a significant proportion of patients continued to experience persistent hoarseness (50%), dysphagia (41%), sticky saliva (41%), xerostomia (36%), change of taste (32%), dermatitis (27%), and pain (18%). Only for mucositis (0%), a notable reduction in incidence was observed. Fibrosis was reported at 6 and 12 months, with respective frequencies of 71.4% and 70%, predominantly grade I. No instances of grade III or IV fibrosis were observed. Osteonecrosis, soft tissue necrosis, Lhermitte's sign and laryngeal edema were not observed.

3.3 | Cross-Sectional—Toxicity and Quality of Life (Part C)

Of the 66 patients included in part A, 25 individuals were alive at time of data collection, and 17 filled in the questionnaires for cross-sectional evaluation (Table 1). These 17 patients had comparable characteristics with the rest of the cohort ($n=49$), except that this group had a younger age ($p=0.01$), more often received VMAT ($p=0.003$), and a longer follow-up ($p=0.02$) (Table S2). The younger age and increased utilization of VMAT among these 17 patients can mostly be attributed to more recent administration of radiotherapy, with the median year of initial radiation being 2020 (IQR, 2017–2020) compared to 2015 (IQR, 2009–2018).

Seven of 17 patients received RAI prior to the surveys. Median time between RAI and the part C surveys was 55.0 (IQR, 35.0–88.0) months. Four patients were receiving TKI treatment when the surveys were conducted, while another patient stopped TKI treatment 7 months priorly. Both the QLQ-H&N43 (Table 3, median: 12.0, IQR: 8.7–30.7) and SF-36-RAND-36 (Figure 3, median: 67.5, IQR: 54.2–80.7) demonstrated a wide range of scores. The respondents completed the questionnaires after a median follow-up period of 35 (IQR, 23.5–61.0) months.

3.4 | Longitudinal—Toxicity and Quality of Life (Part D)

Table 3 presents the results of the QLQ-H&N35 at baseline and after six months, alongside the longitudinal outcomes of the QLQ-H&N43. At the six-month mark, significant deterioration was observed solely in the domains "trouble with social eating" ($p=0.031$) and "dry mouth and sticky saliva" ($p=0.025$) relative to the baseline results. Ten patients completed both the QLQ-H&N35 6 months post-radiation and the cross-sectionally performed QLQ-H&N43. No significant differences were observed between the outcomes of these questionnaires.

3.5 | Treatment Characteristics Analysis (Part E)

No statistically significant correlations were found between the total number of surgeries, number of RAI treatments, total RAI dose, administration of systemic treatment, follow-up time, total radiation dose and the median QLQ-H&N43 ($p=0.455$, $p=0.107$, $p=0.107$, $p=0.897$, $p=0.207$, $p=0.710$, respectively) or SF-36-RAND-36 ($p=0.956$, $p=0.183$, $p=0.183$, $p=0.661$, $p=0.679$, $p=0.811$, respectively) score. Patients treated with VMAT had a significantly better median QLQ-H&N43 score than IMRT treated patients (VMAT 7.89 vs. IMRT 14.17, $p=0.047$). This was not the case for the median SF-36-RAND-36 score (VMAT 9.23 vs. IMRT 5.33, $p=0.239$).

4 | Discussion

This is the first study of thyroid cancer patients reporting acute and late toxicities and QoL after EBRT. According to our results, EBRT seems to result in acute and late toxicities in the majority of thyroid cancer patients. Moreover, our data demonstrates that the impaired QoL 6 months post-radiation does not seem to improve during long-term follow-up. We also note that VMAT was associated with a better long-term QoL than IMRT, possibly a result of more precise radiation.

FIGURE 2 | Acute and late toxicities Xerostomia; Grade 0 = No complaints, Grade I = Symptomatic—no change of eating behavior, Grade II = Symptomatic—change of eating behavior, Grade IV = SV/PEG sonde necessary. Mucositis, Dermatitis, Hoarseness, Dysphagia, Pain; Grade 0 = No complaints, Grade I = Mild complaints, Grade II = Moderate complaints, Grade III = Severe complaints, Grade IV = Ulceration/necrosis/bleeding (mucositis/dermatitis), whispered speech (hoarseness), complete obstruction (dysphagia), unbearable pain (pain). Sticky saliva, change of taste; Grade 0 = No complaints, Grade I = mild complaints, Grade II = Severe complaints.

TABLE 2 | Part B: Prospectively scored toxicity of 31 patients at baseline, 6 weeks, 3, and 6 months.

	Grade 0 *n* (%)	Grade I *n* (%)	Grade II *n* (%)	Grade III *n* (%)	Grade IV *n* (%)
Xerostomia[a]					
Baseline	17 (74)	4 (17)	2 (9)	—	0 (0)
6 weeks	11 (48)	8 (35)	4 (17)		0 (0)
3 months	14 (64)	6 (27)	2 (9)		0 (0)
6 months	13 (62)	7 (33)	1 (5)		0 (0)
Mucositis					
Baseline	22 (96)	1 (4)	0 (0)	0 (0)	0 (0)
6 weeks	16 (70)	6 (26)	1 (4)	0 (0)	0 (0)
3 months	22 (100)	0 (0)	0 (0)	0 (0)	0 (0)
6 months	18 (86)	3 (14)	0 (0)	0 (0)	0 (0)
Dermatitis					
Baseline	23 (100)	0 (0)	0 (0)	0 (0)	0 (0)
6 weeks	2 (9)	8 (35)	12 (52)	1 (4)	0 (0)
3 months	16 (73)	5 (23)	1 (4)	0 (0)	0 (0)
6 months	10 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Hoarseness					
Baseline	14 (61)	8 (35)	1 (4)	0 (0)	0 (0)
6 weeks	7 (30)	10 (44)	5 (22)	1 (4)	0 (0)
3 months	11 (50)	8 (36)	3 (14)	0 (0)	0 (0)
6 months	12 (57)	8 (38)	1 (5)	0 (0)	0 (0)
Dysphagia					
Baseline	18 (78)	5 (22)	0 (0)	0 (0)	0 (0)
6 weeks	8 (35)	15 (65)	0 (0)	0 (0)	0 (0)
3 months	13 (59)	9 (41)	0 (0)	0 (0)	0 (0)
6 months	16 (76)	5 (24)	0 (0)	0 (0)	0 (0)
Pain[b]					
Baseline	23 (100)	0 (0)	0 (0)	0 (0)	0 (0)
6 weeks	6 (26)	15 (65)	2 (9)	0 (0)	0 (0)
3 months	18 (82)	4 (18)	0 (0)	0 (0)	0 (0)
6 months	20 (95)	1 (5)	0 (0)	0 (0)	0 (0)
Sticky saliva[c]					
Baseline	19 (83)	4 (17)	0 (0)	—	—
6 weeks	11 (48)	8 (35)	4 (17)		
3 months	13 (59)	7 (32)	2 (9)		
6 months	13 (62)	7 (33)	1 (5)		
Change of taste[c]					
Baseline	19 (83)	3 (13)	1 (4)	—	—
6 weeks	13 (57)	4 (17)	6 (26)		
3 months	15 (68)	5 (23)	2 (9)		
6 months	16 (76)	4 (19)	1 (5)		

Note: Xerostomia; Grade 0 = No complaints, Grade I = Symptomatic—no change of eating behavior, Grade II = Symptomatic—change of eating behavior, Grade IV = SV/PEG sonde necessary. Mucositis, Dermatitis, Hoarseness, Dysphagia, Pain; Grade 0 = No complaints, Grade I = Mild complaints, Grade II = Moderate complaints, Grade III = Severe complaints, Grade IV = Ulceration/necrosis/bleeding (mucositis/dermatitis), whispered speech (hoarseness), complete obstruction (dysphagia), unbearable pain (pain). Sticky saliva, Change of taste; Grade 0 = No complaints, Grade I = mild complaints, Grade II = Severe complaints.

[a]Xerostomia does not exhibit a grade III classification within the RTOG criteria.

[b]Pain refers to pain in mouth and/or throat.

[c]Sticky saliva and change of taste are scored on a scale from grade 0 to grade II.

TABLE 3 | Part B, C, and D: QLQ-H&N35, and QLQ-H&N43.

	QLQ-H&N35		QLQ-H&N43		
	Part B	Part B	Part C	Part D	Part D
	$T = 0$ months ($n = 28$)	$T = 6$ months ($n = 25$)	$T = 35$ months (IQR, 23.5–61.0) ($n = 17$)	$T = 0$ versus $T = 6$ months ($n = 23$)	$T = 6$ versus $T = 35$ months ($n = 10$)
	Median (IQR)	Median (IQR)	Median (IQR)	*p*	*p*
Pain in the mouth	0 (0–8.3)	4.2 (0–4.2)	8.3 (0–20.8)	0.260	0.564
Swallowing	4.2 (4.2–4.2)	8.3 (0–8.3)	8.3 (0–25)	0.681	0.453
Problems with senses	0 (0–0)	0 (0–0)	0 (0–25)	0.457	0.713
Trouble with social eating	0 (0–8.3)	8.3 (0–16.7)	8.3 (0–37.5)	**0.031**	0.129
Problems opening mouth	0 (0–0)	0 (0–0)	0 (0–0)	0.157	1.000
Coughing	33.3 (0–33.3)	33.3 (8.3–58.3)	33.3 (0–83.3)	0.166	0.581
Dry mouth and sticky saliva[a]	16.7 (0–33.3)	33.3 (8.3–50)	33.3 (8.3–50)	**0.025**	0.887
Speech	16.7 (0–33.3)	11.1 (0–33.3)	13.3 (6.7–56.7)	0.336	
Trouble with social contact	0 (0–0)	0 (0–10)	0 (0–16.7)	0.798	
Problems with teeth	0 (0–0)	0 (0–0)	11.1 (0–22.2)	1.000	
Weight loss	0 (0–0)	0 (0–0)	0 (0–33.3)	1.000	
Weight gain	0 (0–0)	0 (0–0)	—	1.000	—
Felt ill	0 (0–33.3)	0 (0–33.3)	—	0.763	—
Pain killers	50 (0–100)[b]	0 (0–0)[c]	—	0.564[b]	—
Nutritional supplements	0 (0–75)	0 (0–0)	—	0.655	—
Feeding tube	0 (0–0)	0 (0–0)	—	1.000	—
Sexuality	—	—	0 (0–50)	—	—
Body image	—	—	0 (0–16.7)	—	—
Problems with shoulder	—	—	16.7 (0–16.7)	—	—
Skin problems	—	—	11.1 (0–22.2)	—	—
Fear of progression	—	—	33.3 (16.7–50)	—	—
Swelling in the neck	—	—	0 (0–33.3)	—	—
Problems with wound healing	—	—	0 (0–0)	—	—
Neurological problems	—	—	33.3 (0–66.7)	—	—

Note: These domains exhibit overlap within both questionnaires. However, they consist of different questions impeding statistical comparison.
Abbreviations: IQR = interquartile range; QLQ-H&N = The European Organization for Research and Treatment of Cancer head and neck specific Quality of Life Questionnaire; T = follow-up time.
[a]Originally two separate domains in QLQ-H&N35, but transformed into one domain.
[b]$n = 6$.
[c]$n = 12$.

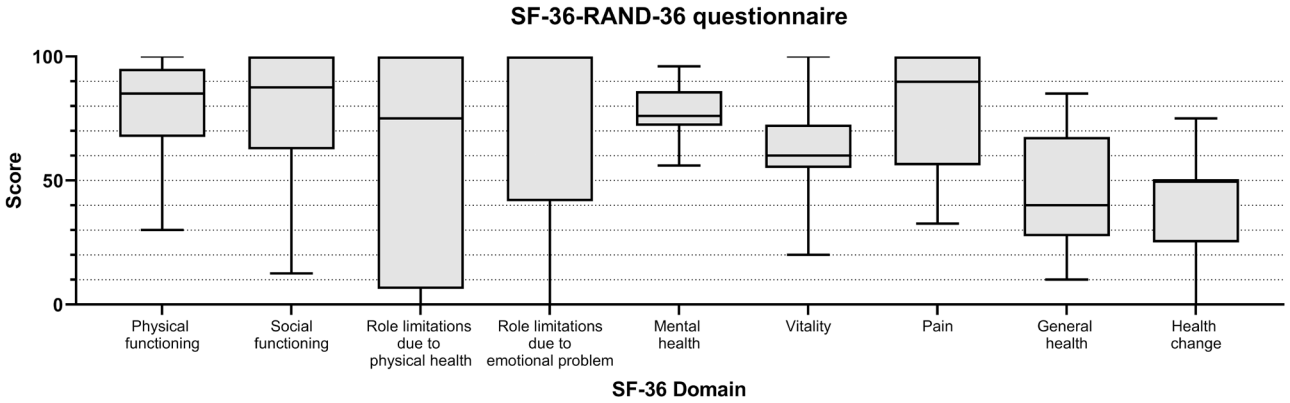

FIGURE 3 | SF-36-RAND-36 domain scores. The boxes display median score with interquartile range per domain.

The most frequent acute toxicities (dermatitis, hoarseness, dysphagia, and pain) and late toxicities (fibrosis in addition to persistent acute toxicities) in this study align with the scarce literature on thyroid cancer specific toxicities following EBRT [3, 8, 15–17]. However, prior studies had limited patient numbers and focused on the 3D-CRT and IMRT era, unlike our study which includes VMAT-treated patients, which are likely to experience less toxicities. In a non-thyroid head and neck cancer population, the acute and late toxicities of EBRT (including those experienced after VMAT) concur with our findings, except for osteoradionecrosis, sensorineural hearing impairment, laryngeal cartilage necrosis and dental and periodontal disease, complications that we did not observe [14, 18–20]. These differences in toxicity between thyroid cancer and other head and neck cancers are likely attributable to differences in primary tumor site and patterns of lymphatic spread, requiring a modified radiotherapeutic approach [21]. Future prospective research comparing toxicity following EBRT in thyroid cancer patients and those with other head and neck cancers could provide valuable insights.

The substantial amount of toxicity observed in patients in this study necessitates the adoption of more advanced radiation techniques. Photon therapy is associated with damage of healthy tissue, inherent with the physical properties of photons. Intensity modulated proton therapy (IMPT) is a more sophisticated technique, which allows for optimized dose distributions [22]. Prior research demonstrated that proton therapy in patients with head and neck cancer is associated with less patient-reported acute and late deterioration in multiple head and neck domains in comparison to photon therapy [22–24]. Studies on the toxicity of proton beam therapy in thyroid cancer patients showed similar types of toxicity to our results [25–27]. However, there are no thyroid-specific studies comparing the toxicity severity between VMAT and proton therapy.

The results of the SF-36-RAND-36 and the QLQ-H&N43 questionnaires provide unique insight into the effects of EBRT on the QoL. Prior research showed that significant differences in radiation specific QoL measures were observed among well differentiated thyroid cancer patients treated with (additional) EBRT in comparison to those treated solely with thyroidectomy and/or RAI [28]. However, QoL evaluation in the mentioned study occurred shortly after radiotherapy. Our study focusses on elucidating the persistent effects of EBRT over an extended period. In non-thyroid head and neck cancer patients, 12 months post-radiation, proton beam therapy exhibited enhancements in various QoL domains, notably in pain, xerostomia, and role function, as compared to VMAT [29]. Further research could focus on the potential thyroid cancer-specific enhanced long-term QoL and efficacy outcomes of proton therapy.

A limitation of this study is the small number of questionnaire respondents, attributable to the selective application of radiotherapy in thyroid cancer patients with aggressive tumors. Moreover, the median survival of ATC patients treated with EBRT is 1.97–6.77 months [6]. One could argue that the potential effects on long-term QoL and general health are less relevant in patients with this histological subtype. However, in patients with such a short remaining life, QoL is especially important and should not be disturbed by complications. An additional constraint stems from potential bias in the prospective database which included only patients treated with high radiation doses, potentially overestimating toxicities. Treatments prior to radiotherapy might also have influenced reported EBRT-toxicities. RAI treatment may have contributed to the reported xerostomia following radiotherapy, as 21% of patients experience chronic toxicity 12 months post-RAI [30]. However, other local effects are unlikely to have been caused by RAI. In addition, the long interval between RAI and the cross-sectional surveys in part C has minimized the likelihood of confounding. Lastly, TKI treatment during the survey in part C and D has potentially influenced questions about fatigue and appetite in the SF-36-RAND-36 and the QLQ-H&N43, as these are potential adverse events from TKI treatment. However, only four (part C) and two (part D) patients were on TKI treatment at the time the surveys conducted, and no correlation between the administration of systemic treatment and QoL outcomes was found. In addition, a recent study in a Lenvatinib-treated cohort showed that QoL is not significantly different before, during and 6 months after TKI treatment, further reducing the likelihood of significant confounding [31, 32].

Altogether, the current study underlines the high rate of acute and late toxicities after EBRT in thyroid cancer patients and suggests a significant impact on QoL during follow-up. In this small patient group, VMAT is associated with improved long-term QoL outcomes, suggesting that more specified radiation

techniques improve long-term toxicity outcomes. Since proton therapy is promising in further reducing toxicities in selected patients with head–neck cancer, additional research is warranted to identify which patients with thyroid cancer may benefit from such new treatment techniques to ultimately reduce long-term toxicity and enhance QoL [5, 23].

Author Contributions

Conceptualization, J.W.E. and E.C.J., methodology, J.W.E. and E.C.J.; formal analysis, J.W.E.; resources, H.H.G.V., T.P.L.; data curation, J.W.E. and E.C.J.; writing – original draft, J.W.E. and E.C.J.; writing – review and editing, J.W.E., E.C.J., H.H.G.V., E.O., L.J., A.H.B., W.T.Z., S.K., T.P.L.; visualization, J.W.E.; supervision, H.H.G.V. and T.P.L.

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The authors have nothing to report.

Ethics Statement

The Medical Ethics Committee of the UMCG approved this study (register numbers: 10880 and 4775).

Consent

All patients that filled in questionnaire gave written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.