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The Role of Radiotherapy for Patients With Thyroid Cancer in the Modern Era

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Abstract. *Background/Aim: Thyroid cancer (TC) is a relatively rare malignancy. The mainstay treatment is surgery followed by radioactive iodine (RAI) and medical systemic treatments. The role of external beam radiotherapy (EBRT) in TC is controversial regarding the survival benefits. The aim of this study was to analyse the effectiveness of EBRT for different forms of TC in different stages. Patients and Methods: Between January 1990 and 2016, 75 patients underwent 255 radiotherapy (RT) courses at our Institution. Local control (LC) and progression-free survival (PFS) were analyzed. Results: The cohort consisted of 22 patients who received curative RT and 53 patients who received RT in a palliative setting. The estimated 5-year LC for the curative group was 92±8% and the palliative group 78±7%. The estimated 5-year PFS for the curative group was 27±9% and for palliative group 31±6%. Conclusion: The addition of RT in TC seems to be safe and effective. Our analysis showed an excellent local control (median >15 years) regardless of the treatment setting.*

Thyroid cancer (TC) is a relatively rare malignancy; it is responsible for 567,000 cases worldwide which makes it the ninth most common malignancy according to 2018 data. It is three times more common in females than in males (1). Ionizing radiation is the most common risk factor for TC, especially when exposure happens early in childhood (2, 3), other risk factors were reported such as obesity, smoking and iodine intake (4, 5). The increasing incidence of TC is mostly due to overdiagnosis, particularly in the era of advanced diagnostic techniques (6). Most thyroid cancers originate from epithelial cells and are classified according to their histological differentiation into papillary (PTC), follicular (FTC), poorly differentiated (PDTC), anaplastic (ATC), and medullary thyroid carcinomas (MTC) (7).

The mainstay treatment for TC is surgery (hemi- or total thyroidectomy) followed by radioactive iodine (RAI) with or without recombinant human thyroid stimulating hormone for PTC, FTC and PDTC and chemotherapy or immunotherapy for PDTC, MTC and ATC (8-14). The effectiveness of external beam radiotherapy (EBRT) in TC is controversially discussed; however, several reports found that adjuvant EBRT may improve locoregional disease control in different histological types (15-30). As yet, the existing literatures are rare and well-conducted prospective clinical trials are lacking.

We investigated the treatment outcomes of patients with different histological types of TC treated with EBRT in curative or palliative settings at the Department of Radiation Oncology, University Hospital of Muenster.

Patients and Methods

Patients. Between January 1990 and 2016, seventy-five patients underwent 255 RT courses at our Institution, Department of Radiation Oncology, University Hospital of Muenster. Patient characteristics are summarized in Table I. We divided the whole cohort into two major groups. Curative group (n=22); patients with no known metastasis for whom radiotherapy (RT) was received as primary therapy within thyroid region after surgery. Palliative group (n=53); patients with known distant metastases, this group was further divided into group A, where RT was delivered to both thyroid region and metastases (n=15) and group B, where RT was delivered to metastasis only (n=38). All our patients were discussed in a multidisciplinary tumor board in order to provide the suitable radiation fractions. Indications for lung metastases SBRT at our

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Key Words: Thyroid cancer, curative, palliative setting, stereotactic radiotherapy.

Table I. *Patient and treatment characteristics*.

Characteristic	N (% or range)	Curative	Palliative	*p*-Value
Patients	75 (100%)	22 (29%)	53 (71%)	
Age (Median)	66 (14-85)	66 (23-85)	65 (14-83)	0.6
Gender	F: 43 (57%)	14 (64%)	29 (55%)	0.6
	M: 32 (43%)	8 (36%)	24 (45%)	
Thyroid region RT	37 (49%)	22 (100%)	15 (28%)	**<0.001**
Others	38 (51%)	0 (0%)	38 (72%)	
T				0.09
1	3 (4%)	1 (4%)	2 (4%)	
2	8 (11%)	0 (0%)	8 (15%)	
3	25 (33%)	5 (23%)	20 (38%)	
4	38 (51%)	16 (73%)	22 (42%)	
Unknown	1 (1%)	0 (0%)	1 (1%)	
N				0.3
0	27 (36%)	6 (27%)	21 (40%)	
1	45 (60%)	16 (73%)	29 (55%)	
Unknown	3 (4%)	0 (0%)	3 (5%)	
M				**<0.001**
0	22 (29%)	22 (100%)	0 (0%)	
1	53 (71%)	0 (0%)	53 (100%)	
Resection margin				**<0.001**
0	60 (80%)	10 (45%)	50 (94%)	
1	9 (12%)	9 (41%)	0 (0%)	
2	6 (8%)	3 (14%)	3 (6%)	
Relapse pattern				0.3
Yes	35 (46%)	7 (32%)	28 (53%)	
Local alone	3 (4%)	0 (0%)	3 (9%)	
Distant alone	22 (29%)	5 (23%)	17 (32%)	
Both	10 (13%)	2 (9%)	8 (15%)	
No	40 (54%)	15 (38%)	25 (47%)	
Histology				**<0.001**
Papillary	28 (37%)	9 (41%)	19 (36%)	
Follicular	27 (36%)	1 (5%)	26 (49%)	
Medullary	9 (12%)	5 (22%)	4 (8%)	
Anaplastic	8 (11%)	4 (18%)	4 (7%)	
PDTC	3 (4%)	3 (14%)	0 (0%)	
Differentiation				**<0.001**
Well differentiated	55 (73%)	10 (45%)	45 (85%)	
Others	20 (27%)	12 (55%)	8 (15%)	
Event				0.2
Died	45 (60%)	15 (68%)	30 (57%)	
Live without relapse	12 (16%)	5 (23%)	7 (13%)	
Live with relapse	13 (17%)	2 (9%)	11 (21%)	
Lost to follow	5 (7%)	0 (0%)	5 (9%)	
RT technique				0.3
IMRT	63 (84%)	17 (77%)	46 (87%)	
3D conformal	12 (16%)	5 (23%)	7 (13%)	
Systemic therapy				**0.05**
No	13 (17%)	8 (11%)	5 (6%)	
CTx	1 (1%)	0 (0%)	1 (1%)	
TKI	4 (5%)	1 (1%)	3 (4%)	
RAI	48 (64%)	12 (16%)	36 (48%)	
RAI +CTx	1 (1%)	0 (0%)	1 (1%)	
RAI +TKI	6 (8%)	0 (0%)	6 (8%)	
CTx+TKI	2 (4%)	1 (2%)	1 (2%)	
All	0 (0%)	0 (0%)	0 (0%)	
Radiation dose	55.8 (30-72.6)	63 (50-72.6)	50 (30-70)	**0.05**

RT, Radiation therapy; M, male; F, female; IMRT, intensity modulated RT; RAI, radioactive iodine; CTx, chemotherapy; TKI, tyrosine kinase inhibitors; PDTC, poorly differentiated thyroid cancer. Bold values indicate statistical significance.

institution are: i) metastases diameter ≤3 cm; ii) ≤5 lungs metastases; iii) ECOG 0-2 with life expectancy >6 months. The fractionation schemata are either 3×12.5 Gy or 5×7 Gy based on location of the metastasis. Patients with bone metastases were treated with normal fractionation 10×3 Gy or 20×2 Gy. All patients especially those with PTC and FTC had received PET-CT, either whole body scan (WBS) or single photon emission computerized tomography/computerized tomography (SPECT/CT) as planning CT to define our gross tumour volume (GTV) or planning target volume (PTV). Recently was published the role of SPECT/CT in PTC staging in comparison to WBS (31).

Ethical approval and consent to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis. All statistical analyses were conducted with SPSS version 25.0 software (IBM, Armonk, NY, USA). Differences were considered statistically relevant at a p-value<0.05. Overall survival (OS) was calculated from the first day of RT. Progression-free survival (PFS) was calculated from the initiation of RT until the time of documented relapse or death. Local control (LC) was calculated from the initiation of RT until the time of documented local relapse. Time-dependent event curves were calculated using the Kaplan-Meier method and were compared using the log-rank test.

Results

The cohort consisted of 43 females and 32 males with a median age of 66 years. The median follow-up of all patients was 33 months (IQR=54%). There was a significant longer follow-up for the palliative group in comparison with the curative group (median 39 vs. 16 months, p=0.036). The median radiation within the thyroid region was 63 Gy (range: 50-72.6 Gy) with a median fraction dose of 1.8 Gy (range=1.8-2 Gy) and for metastases 40 Gy (range=30-66.6 Gy) with a median fraction dose of 2.5 Gy (range=1.8-12.5 Gy). RT was delivered to lymphatic drainage of thyroid (bilateral neck and superior mediastinum) in the curative group. EBRT was delivered using 3D conformal RT in 12 patients and intensity modulated RT (IMRT) in 63 patients. A total of 37 patients received RT in the thyroid region (22 curative and 15 palliative). Six patients in the curative group have been treated with upfront RT, while 16 patients received salvage RT.

Radiotherapy intent. In the curative group, the median of LC, PFS, and OS were 187, 13, and 14 months, respectively. The estimated 3- and 5-year LC, PFS, and OS were 92±8%, 27±9%, and 32±9%, respectively. On the other hand, in the palliative group the median of LC, PFS, and OS were 205, 24, 62 months, respectively. The estimated 3- and 5-year LC, PFS, and OS were (83±6% and 78±7%), (40±7% and 31±6%), and (62±7% and 52±7%), respectively. In palliative subgroup analysis, we could not detect any relevant

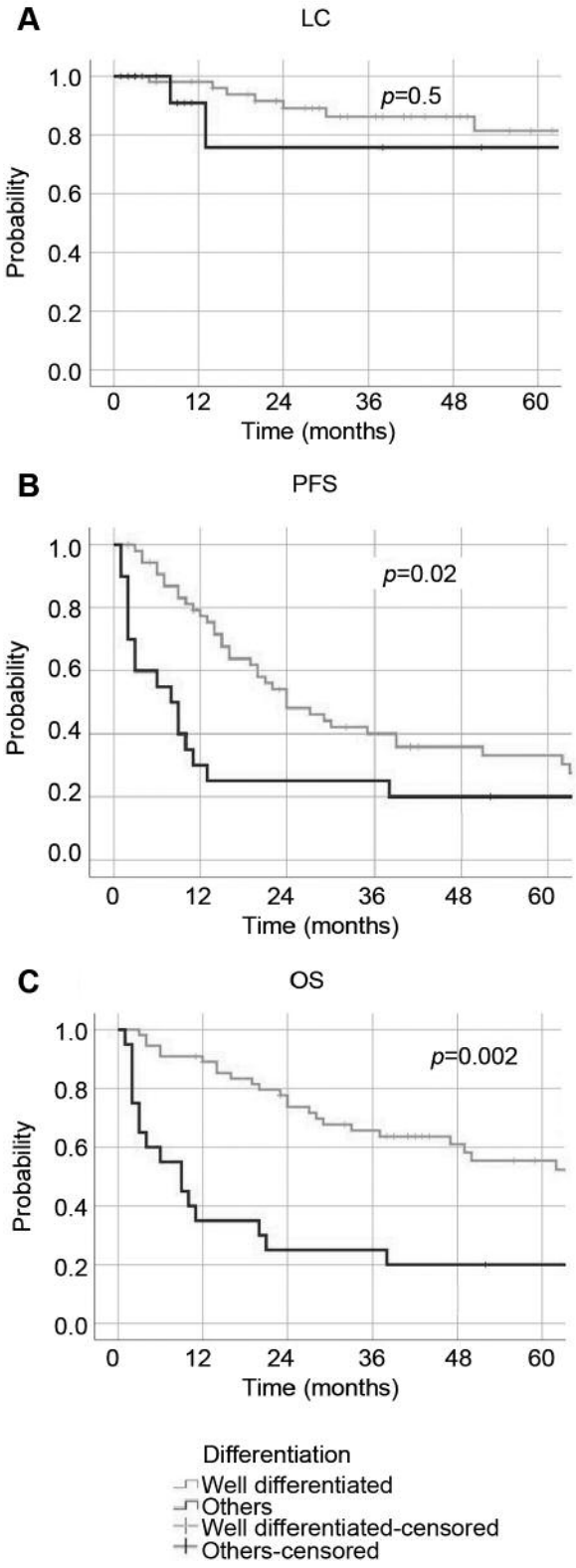

Figure 1. *Kaplan–Meier estimates of local control (A), progression-free survival (B) and overall survival (C) according to histologic differentiation in whole cohort.*

Table II. *Histological differentiation according to systemic therapy (N=56).*

Histology	Systemic therapy							Total
	RAI only	CTx only	TKI only	RAI+TKI	CTx+TKI	RAI+CTx	No	
Papillary	22	0	1	2	0	0	3	28
Follicular	22	0	1	3	0	1	0	27
Medullary	1	0	1	1	1	0	5	9
Anaplastic	0	1	1	0	1	0	5	8
Others	3	0	0	0	0	0	0	3
Total	48	1	4	6	2	1	13	75

RAI, Radioactive iodine; CTx, chemotherapy; TKI, tyrosine kinase inhibitors.

differences between group A and B regarding LC (p=0.9), PFS (p=0.3), and OS (p=0.2).

Histologic differentiation. In terms of histology for the whole cohort, LC was not significant between (PTC and FTC) and others (p=0.5), in contrast to PFS and OS which were both significant (p=0.02, p=0.002, respectively). In subgroup analysis we observed a trend in LC (p=0.08) and significant PFS (p<0.001) difference between different histological entities in the curative setting. In the palliative group, LC did not present significant differences between the different histologies (p=0.99) while PFS was significantly different (p=0.03). In the curative group the median PFS in PTC was 29 months, in FTC it was 15 months, in MTC it was 11 months, and in ATC it was 2 months. In subgroup analysis for patients with palliative RT indications, the median PFS in FTC was 30 months, followed by PTC 16 months, MTC 9 months and ATC only 2 months. In OS analysis, we observed a significant difference between histological entities in both groups (curative p<0.001, palliative p<0.001); in the curative group the median OS in PTC, FTC, MTC, and ATC was not reached. In the palliative group, patients with PTC had the longest median OS with 83 months followed by FTC with 65 months, MTC with 20 months, and ATC with 2 months.

Due to different TNM classification and staging systems, we excluded the ATC (N=8) and PDTC (N=3) patients from the cohort and re-analysed the LC, PFS and OS (Table I). The median LC in the curative group was 187 months and in the palliative group was 205 months (p=0.2). The median PFS in the curative group was 19 months, while 24 months in the palliative group (p=0.7). The median OS in the curative group was 29 months, while 65 months in the palliative group (p=0.8). The LC, PFS and OS were not significantly different between PTC, FTC and MTC in the curative and palliative groups (p>0.05).

Systemic therapies. Various systemic therapies were administered in 56 patients (Table II). In the whole cohort, patients who received systemic treatment in addition to RT had significantly longer PFS in comparison to those who received RT alone (p<0.001). Regarding OS, there was a significant impact of systemic therapies in the curative group (p=0.04) and palliative group (p<0.001). There was no significant impact of systemic treatment on LC (p=0.8).

The longest PFS and OS in the curative group has been observed with RAI patients (15 and 21 months, respectively). While in the palliative group the longest PFS and OS has been detected in patients received tyrosine kinase inhibitors (TKI) agents such as lenvatinib and cabozantinib (51 and 83 months, respectively) and RAI (24 and 77 months, respectively). In patients treated with RT alone, the median PFS and OS was 11 months in the curative group and 6 months in the palliative group.

Local ablative and bone irradiation. In this cohort, there were 53 stereotactic body radiation therapy (SBRT) courses delivered on 21 patients with lung metastasis at different doses. SBRT was decided on the basis of radioactivity in the PET-CT scan, symptoms or progress restaging. Following SBRT, the median OS was 245 months, median PFS was 16 months and median LC was 187 months. In addition, 34 patients with bone metastasis were treated with RT, they had a median OS of 50 months, median PFS of 24 months, and a median LC of 98 months.

Prognostic factors with Cox proportional hazards model. Several parameters have been included in Cox proportional hazards model (Table III). There were no significant factors for LC. In univariate analysis, age (p=0.07), histological differentiation (p=0.03), and systemic therapy administration (p=0.01) had a possible impact on PFS. Similarly, histological differentiation (p=0.002), systemic therapy administration (p=0.01) and SBRT (p=0.03) had an impact on OS.

In multivariate analysis, only age (p<0.001) and histological differentiation (p=<0.001) affected PFS. In the subgroup analysis regarding intent of RT, age (p=0.05) and histological differentiation (p=0.006) remained significant in

Table III. *Univariate and multivariate analyses for LRC, PFS, and OS (N=75).*

Risk factor	LRC			PFS			OS		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Univariate model									
Age (years)	1.024	0.974-1.076	0.4	1.020	0.998-1.042	**0.07**	1.015	0.991-1.040	0.2
Gender (female)	2.054	0.597-7.056	0.3	0.813	0.478-1.384	0.4	0.855	0.464-1.571	0.6
Nodal radiation (yes)	0.631	0.183-2.172	0.5	0.952	0.560-1.618	0.9	0.801	0.483-1.466	0.5
Histology (differentiated)	0.646	0.164-2.533	0.5	0.531	0.299-0.945	**0.03**	0.386	0.207-0.720	**0.002**
Primary *vs*. secondary (primary)	0.653	0.190-2.241	0.5	0.894	0.528-1.513	0.7	1.024	0.565-1.855	0.9
Curative *vs*. palliative (curative)	0.614	0.131-2.881	0.5	1.263	0.713-2.235	0.4	1.623	0.868-3.034	**0.1**
RT technique (IMRT)	2.620	0.327-20.932	0.4	1.300	0.664-2.543	0.4	0.971	0.472-1.999	0.9
SBRT (yes)	0.625	0.165-2.366	0.5	1.266	0.726-2.209	0.4	0.446	0.213-0.934	**0.03**
Systemic therapy administration (yes)	0.793	0.168-3.740	0.8	0.653	0.358-1.181	0.15	0.453	0.238-0.864	**0.01**
Multivariate model									
Age (years)	--	--	--	1.045	1.02-1.07	**<0.001**	--	--	--
Histology (differentiated)	--	--	--	.235	0.119-0.464	**<0.001**	0.431	0.230-0.808	**0.009**
SBRT (yes)	--	--	--	--	-	-	0.504	0.237-1.071	**0.08**

LRC, Locoregional control; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiation therapy. Bold values indicate statistical significance.

the curative group, while patients in the palliative group had better PFS with systemic therapy and RT administered sequentially (p=0.002). Regarding OS, only histological differentiation (p=0.009) seemed to be significant. In subgroup analysis regarding intent of RT, histological differentiation (p=0.02) remained significant in the curative group. On the other hand, in the palliative group only the age was significant with OS (p=0.04).

Toxicities. RT was well tolerated in our cohort without significant adverse events (AEs). During RT courses, almost all patients had grade 1 AEs (N=45, 60%) and 36% of patients experienced grade 2 AEs (N=27). Only four patients (5%) had grade 3 AEs. Most common AEs were erythema, xerostomia, and mucositis. There were no severe radiation-related toxicities or deaths.

Discussion

This retrospective analysis investigated the role of radiotherapy in TC at our Institution. Surgery is standard treatment for TC, complete resection is sometimes infeasible in locally advanced cancer where there is invasion to the surrounding structures (10-14, 31). Several studies have found that RT has a significant effect on LC and OS especially for PTC and FTC with high-risk features (32-34). In addition, the PDTC and ATC have worse prognosis without RT (6-15).

Our retrospective study showed improvement in LC, PFS and OS for patients in both curative and palliative groups. By further analysis, we found that PFS and OS were significant for PTC and FTC in the curative group, in contrast to the palliative group where only PFS was significant. Regarding cell differentiation, LC, PFS and OS were significantly better for patients with PTC and FTC who underwent adjuvant EBRT which is consistent with a previous report by Schwartz *et al*. who reported 73% OS and 79% LC at 4 years in patients who received RAI (16). Similarly, other reports showed improvement in 5-year disease-free survival from 43% to 57% when adding EBRT to RAI for patients with PTC and FTC (30). These reports, including ours, showed that patients with high-risk features will benefit the most; those high-risk features include metastatic disease, post-operative residual disease, high-risk histologies such as ATC, advanced age, and tumors with reduced iodine uptake (20, 29). In patients with PDTC and ATC, our data agrees with previous studies (23). PFS and OS were significantly improved by adjuvant EBRT with a median PFS of 8 months and OS of 9 months which is consistent with previous reports such as Chen *et al*. (23).

Regarding the radiotherapy dose, the median RT dose was 63 Gy (range=50-72.6 Gy) in the curative group for all histologies; for PTC and FTC the median dose was 66 Gy (range=59.4-70.2 Gy) and for others the median dose was 61.5 Gy (range=50-72.6 Gy). For patients with ATC the median RT dose was 59 Gy (range=44-66 Gy). Different dose concepts were analyzed in several reports for PTC and FTC (17, 35). In both reports the median EBRT dose was 60 Gy in 30 fractions. Glaser *et al*. (9) reported that high-dose RT (≥59.4 Gy) for patients with ATC resulted in improved

OS and Pierie *et al*. (36) found that adjuvant radiotherapy >45 Gy improves outcome compared to a lower dose in specific conditions or patient characteristics with ATC. The role of radiation in patients with ATC who received either no surgery or grossly incomplete resection was reported by Pezzi *et al*. (37), who found that higher RT dose (60-75 Gy) had improved OS.

In recent studies, the role of SBRT seems to improve the prognosis of patients with solid tumors (38-43). Owing to the high incidence of pulmonary metastasis in TC (34), there were 53 SBRT courses with different doses delivered on 21 patients with lung metastasis in our cohort. Following SBRT, the median OS was 245 months. Median PFS was 16 months and median LC was 187 months. Details of SBRT doses and patient and tumor characteristics for those patients are beyond the scope of this article and will be analyzed in a separate study.

Our analysis showed that adding systemic therapy sequentially to RT had a significant impact on PFS and OS in comparison to RT alone. Univariate analysis showed age and histological differentiation as possible factors affecting PFS. On the other hand, in multivariate analysis only age ($p<0.001$) and histological differentiation ($p<0.001$) affected PFS. Subgroup analysis showed consistent results in the curative group, while in the palliative group PFS was affected by administration of systemic treatment only. In subgroup analysis regarding intent of RT, age ($p=0.05$) and histological differentiation ($p=0.006$) remained significant in curative patients, in contrast to the palliative group, in which PFS was only significant with systemic treatments ($p=0.002$). In multivariate analysis, SBRT administration ($p=0.08$) and well differentiated ($p=0.009$) seems to be associated with longer OS Table III).

Advantages and disadvantages of the study. Our study was limited with its retrospective design and being conducted in a single centre which precludes definitive conclusions, although patient characteristics were reasonably distributed between the examined groups. Moreover, our data agree with previous reports and add to existing literature regarding the importance of RT in this rare malignancy. The limited number of the examined population especially in the curative group may have contributed to a better PFS and OS in the palliative group. The OS was shorter in the curative group probably due to the small sample size. That being said, a larger cohort and prospective randomized trials are needed to further confirm these results.

Conclusion

Using of RT in TC led to improved outcomes with acceptable toxicity profile. Our analysis showed an excellent local control reaching >15 years in palliative and curative groups. Age, histologic differentiation and addition of systemic therapies may improve PFS in a particular group of patients.

Conflicts of Interest

On behalf of all the Authors, the corresponding author states that there are no conflicts of interest to report.

Authors' Contributions

LS, JK, and KE was involved in formal analysis, research methodology and first manuscript drafting. All co-authors were involved in conceptualization of manuscript, and manuscript drafting and editing. HTE was the senior author who oversaw the project. All co-authors read and approved the final manuscript.

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