Intensity Modulated Radiation Therapy (IMRT) for Thyroid Cancer

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Abstract. **Objective:** To evaluate outcomes and toxicities in patients with thyroid cancer treated with intensity-modulated radiation therapy (IMRT). **Methods:** This was a single institution retrospective review of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center between May 2001 and June 2008. The median age was 69 years. Among the 10 patients, seven had papillary carcinoma, two had T3 and 8 had T4 disease, eight had N1 disease, and two had distant metastases. Radioactive iodine was given to all patients, while the median radiotherapy (RT) dose was 60 Gy. **Results:** Median follow up was 28.5 months (range: 4.5-to-50.6 months). The Kaplan-Meier estimates of 3-year local control, locoregional control, and overall survival rates 90%, 90%, and 80%, respectively. Nine patients had grade 2 skin toxicity, 10 had grade 2 pharyngitis/esophagitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis. Few grade 2 or 3 late toxicities were observed. **Conclusions:** IMRT is effective in the postoperative setting for the postoperative treatment of thyroid cancer. Long-term follow-up is still needed to assess the incidence of late toxicities.

Keywords. • IMRT • Thyroid cancer • Radio-iodine therapy • RT toxicities

Introduction

Surgical resection with or without radioactive iodine therapy (RAI) is the typical management of differentiated thyroid cancer. The role of external beam radiation therapy is controversial. The NCCN guidelines currently recommend postoperative radiation therapy (PORT) for T4 disease with extra-thyroidal extension and when the patient's age is more than 45 years. Local failures occur in the thyroid bed, the surrounding target volume, and regional lymph nodes. The irregular shape of this target volume and the wide extent of lymph node stations at risk mean that delivering doses beyond 50 Gy (5,000 rad) by conventional methods of radiation technique is difficult.

Intensity-modulated radiation therapy (IMRT) provides better dose coverage to the target volume.[1,2] To date, there is limited published data available with only 33 cases reported in the literature using IMRT[3-5] to treat thyroid cancer. We report the local control rates and toxicities in a series of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center (FCCC).

Materials and Methods

The FCCC institutional review board approved this retrospective review. Between November 2002 and September 2007, 11 patients with thyroid cancer were treated at FCCC with IMRT. One patient was excluded from analysis because of the development of distant metastases during a course of radiation for an inoperable anaplastic thyroid carcinoma. Among the remaining patients, five were treated with postoperative radiation therapy (PORT) followed by

RAI, while five were treated with RAI then PORT (Table 1). PORT is recommended at FCCC for patients older than 60 years of age with T4 disease, extra thyroid extension, gross residual disease, and multiple positive lymph nodes with extra capsular extension.

regions included the thyroid bed, levels II-to-VI lymph nodes, and the superior mediastinum lymph nodes.

IMRT was delivered with 7 or 8 fixed beams. The planning target volume (PTV) was prescribed to 60 Gy in 30 fractions, 2 Gy per fraction, one fraction per day. Normal tissue constraints were as follows: Spinal

Table 1. Study group characteristics (n = 10)

Variable (%)	Number. of patients	Variable (%)	Number. of patients
Age, median, in years (range)	69 (51-85)	**Type of surgery**	
< 70	4 (40)	Subtotal thyroidectomy	2 (20)
≥ 70	6 (60)	Total thyroidectomy	8 (80)
Sex		**Resection status**	
Male	5 (50)	Complete	5 (50)
Female	5 (50)	Incomplete	5 (50)
T stage		**Margin status**	
T3	2 (20)	Positive	10 (100)
T4	8 (80)	**Grade**	
N stage		Well differentiated	5 (50)
N0	2 (20)	Papillary with Tall cell features	2 (20)
N1	8 (80)	Papillary with follicular features	1 (10)
M stage		Papillary with anaplastic features	1 (10)
M0	7 (70)	Poorly differentiated	1 (10)
M1	3 (30)	**Neck dissection**	
Overall stage		Yes	4 (40)
III	1 (10	**Lymph nodes (LN)**	
IV A	6 (60)	Positive	8 (80)
IV B	0 (0)	≥ 2 LN positive	6 (60)
IV C	3 (20)	Extra nodal extension positive	1 (10)
III/ IV A	7 (70)	**Treatment details**	
IV B/ C	3 (30)	Sx +PORT + RAI	5 (50)
Histology		Sx + RAI + PORT	5 (50)
Papillary	7 (70)	**RAI dose (mCi)** 10 (100)	
Follicular	1 (10)	50-100	1 (10)
Insular	1 (10)	100-150	3 (30)
Anaplastic	1 (10)	> 150	4 (40)
Path size primary		**Missing dose details**	2 (20)
≤ 4 cm	7 (70)		
≥ 4 cm	3 (30)		
Multifocality			
Yes	4 (40)		
No	6 (60)		
Extrathyroid extension, positive	9 (90)		

Abbreviations: T = tumor, N = nodal stage, M = metastasis, cm = centi meters, % = percentage, Sx = surgery, PORT = postoperative radiation therapy, RAI = Radio-iodine ablation, mCi = milli Curies.

Radiotherapy. Patients were simulated using CT simulation with an Aquaplast mask (WFR/Aquaplast Corp, Avondale, PA) to improve daily reproducibility. Axial images were obtained every 3 mm from the top of the head to 5 cm below the carina. The treatment

cord dose was limited to less than 45 Gy, brain stem to < 54 Gy, brachial plexus to < 62 Gy, and parotid glands limited to 26 Gy. The Corvus inverse treatment planning system was used for the majority of patients (version 3.0, NOMOS Corp., Cranberry Township,

PA). For an ideal plan, 95% of PTV should receive 60 Gy with at least PTV getting 93% of the prescribed dose and hot spots should be less than 120%.

Table 2. Radiation therapy details (n = 10)

Variable	Number. of patients (%)
Type of treatment	
PORT	8 (80)
PORT + CT	2 (20)
RT dose (Gy)	
56	1 (10)
60	5 (50)
68	1 (10)
70	3 (30)
PTV1 in Gy, median, range	60 (56-70)
PTV2 in Gy, median, range	57 (40-70)
No of beams, median, range	7 (7-8)
No of fractions, median, range	32 (28-35)
RT duration in months, median, range	1.54 (1.22- 1.74)
Interval between surgery and RT, mo	3.45 (0.82-32.10)
Chemotherapy	
Yes	2 (20)
Doxorubicin based	2 (100)

Abbreviations: PTV1, 2 = planning target volume one and two, Gy = gray, PEG = percutaneous endoscopic gastrostomy, CT = chemotherapy, RT = radiation therapy.

Radio-iodine therapy. At FCCC, all patients were evaluated with ^{123}I scan postoperatively to assess for potential residual disease or residual normal thyroid tissue. For patients with residual disease/thyroid tissue, ^{131}I ablation was performed to eliminate tissue/disease and enable thyroglobulin monitoring for recurrence. The doses used were 100 mCi (milli Curies) to the thyroid bed and 150 mCi in the presence of positive lymph nodes. One hundred seventy-five mCi ^{131}I were administered for lung and 200 mCi for bone metastases. Thyroid hormonal suppression was instituted in all patients post-ablation.

Statistical analysis. Descriptive data of diagnostic and treatment factors were obtained for all patients. Three-year actuarial rates of overall local relapse free and local-regional relapse free survivals were obtained via Kaplan-Meier estimation method. All the analyses were performed using the statistical analysis systems (SAS institute, Cary, NC). Acute and late toxicity were recorded as per the Radiation Therapy Oncology Group6 (RTOG) toxicity criteria.

Results

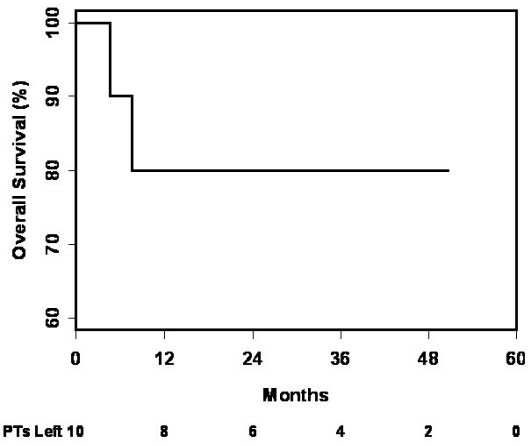
Median follow-up was 28.5 months (range: 4.5-to-50.6 months). Patient, tumor, and treatment-related characteristics are shown in Tables 1 and 6. Median age was 69 years (range: 51-to-85 years) with 4 patients ≥ 70 years old. There were 5 men and 5 women. Four patients had a prior history of goiter.

The histological pattern was papillary in 7 patients, follicular in 1, insular in 1, and anaplastic cancer in 1. There were 2 patients with stage T3 and 8 patients with stage T4. Eight patients had stage N1 and three presented with metastatic disease (stage IV C).

Subtotal thyroidectomies were performed in 2 patients and 8 underwent total thyroidectomies. Neck dissection (central compartment) was performed in 4 patients. Seven patients had tumor size ≤ 4 cm and multifocal disease was seen in 4 patients. Extrathyroid extension was seen in 9 patients and all 10 patients had positive margins. Six patients had > 2 lymph nodes positive at resection. None of the patients had gross residual disease. Among patients with papillary carcinoma, two had tall cell features, one had associated follicular, and one had anaplastic component. RAI was done in all patients with ^{123}I scans prior to ablation. All but one patient received > 100 mCi of ^{131}I .

The median dose to PTV was 60 Gy (range: 56-to-70 Gy) over a duration of 1.54 months (range: 1.22-to-1.74 months), 2 Gy per fraction, one fraction per day. The median-time between surgery and the initiation of radiation therapy (EBRT) was 3.45 months (range: 0.82- to-32.10 months, Table 2). Two patients were treated with concurrent chemotherapy with dox-

Figure 1: Overall survival rates for all 10 patients



orubicin 15 mg/m^2, weekly over 7 weeks during radiation therapy. Chemotherapy was given to a patient who had an anaplastic spindle cell carcinoma associated with a multifocal tall cell papillary thyroid carcinoma. Two of 3 lymph nodes were positive for metastatic disease. The second patient had high-grade multifocal papillary carcinoma with anaplastic features with 8 of 73 lymph nodes demonstrating metastatic disease.

Table 3. Incidence of grade 2 and 3 acute and late toxicities

	Grade 2, N (%)		Grade 3, N (%)	
	Acute	**Late**	**Acute**	**Late**
Skin	9 (90)	0 (0)	0 (0)	0 (0)
Mucosa	5 (50)	0 (0)	1 (10)	0 (0)
Pharynx/ Esophagitis	10 (100)	2 (20)	0 (0)	1 (10)
Larynx	2 (20)	2 (20)	3 (30)	0 (0)
Taste changes	6 (60)	—	0 (0)	—
Xerostomia	6 (60)	4 (40)	0 (0)	0 (0)
Hematological	1 (10)	0 (0)	0 (0)	0 (0)

Abbreviations: N = number of patients.

The Kaplan-Meier estimates of 3-year local and locoregional control rates were 90%, 90%, and the overall survival was 80% for all patients (shown in Figures 1, 2A, 3A). The distant metastasis free-rate

Figure 2A: Local control rates for all 10 patients

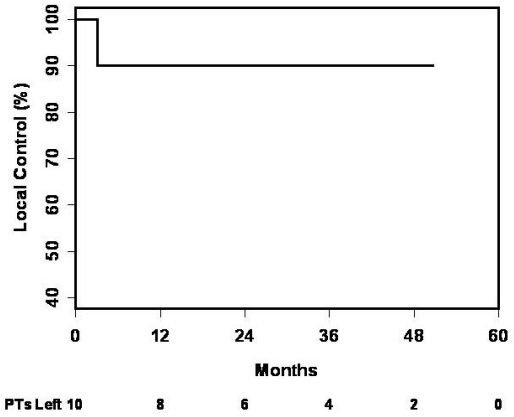
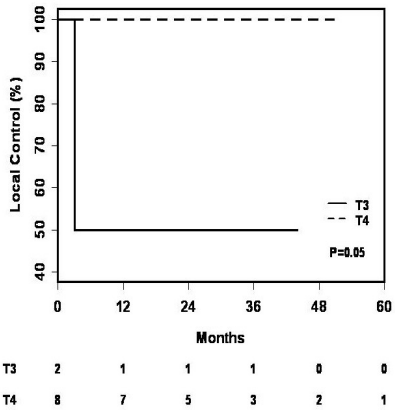


Figure 2B: Local control rates for all 10 patients based on T stage



was 87% at 1-year and 58% at 3-years. Only one patient had persistent disease 3 months following ra diation therapy to 70 Gy. He was a 77-year-old male with poorly differentiated insular carcinoma treated with EBRT for local recurrence 3 years after surgery and RAI. One patient developed supraclavicular lymph node metastases (in-field failure). Two patients developed distant metastases. At last follow-up, 8 patients were alive and 2 were dead.

On univariate analysis including age (< 70 versus > 70 years), gender (male versus female), N-stage (N0 versus N1), overall stage (III/IVa versus IV b/c), number of lymph nodes positive (< 2 versus > 2) or extra nodal extension (yes versus no) and addition of chemotherapy (yes versus no), only T stage (T3 versus T4) and type of surgery (partial versus total thyroidectomy) were significant for local failure (p = 0.05, 0.05, respectively Table 4, Figures 2B, 3B). Al-

Figure 2C: Local control rates for all 10 patients based on type of surgery

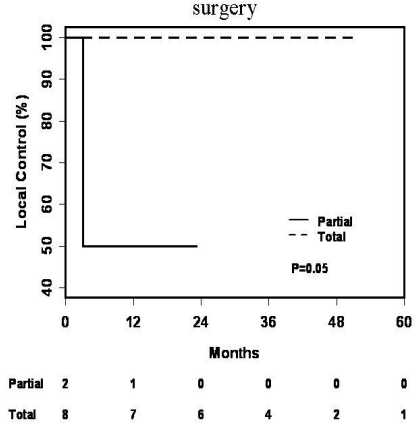


Table 4. Univariate analysis of variables on the clinical outcomes

Variable	OS*	LC rate*	LRC rate*	DM free rate*
Age (<70 vs ≥ 70 years)	0.06	0.22	0.22	0.56
Gender (male vs. female)	0.94	0.32	1.00	0.81
T stage (T3 vs T4)	0.18	0.05	0.05	0.01
N stage (N0 vs N1)	0.46	0.62	0.64	0.52
M stage (M0 vs M1)	0.58	0.51	0.77	0.52
Overall stage (III/Iva vs IVb/c)	0.58	0.51	0.77	0.52
Type of surgery (subtotal vs total thyroidectomy)	0.18	0.05	0.05	0.71
Resection status (complete vs incomplete)	0.94	0.32	0.16	0.23
LN positive (< 2 vs ≥ 2)	0.23	0.41	0.89	0.81
Extra nodal extension (yes vs no)	0.63	0.74	0.30	0.35
Size of tumor (< 4 vs ≥ 4 cm)	0.44	0.13	0.13	0.08
Multifocality	0.23	0.41	0.41	0.32
Extra thyroid extension (yes vs no)	0.63	0.74	0.74	0.71
Chemotherapy (yes vs no)	0.46	0.62	0.62	0.36
Dose of I^{-131}	0.03	—	—	0.39

Abbreviations: LN = lymph nodes, I^{-131} = iodine, cm = centimeters, vs = versus. *p value < 0.05 is considered statistically significant.

so, for locoregional failure, the T stage and type of surgery were statistically significant (p = 0.05, 0.05, Figures 2C, 3C). T stage was the only significant factor for the distant metastases free rate (p = 0.01). No factor except the dose of RAI was significant for the overall survival (p = 0.03).

RT toxicities. Nine patients had grade 2 skin toxicity. Five patients developed grade 2 mucositis, and one had grade 3 mucositis. All patients developed grade 2 pharyngitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis (shown in Table 3). Two patients developed grade 2 and one grade 3 pharyngitis.

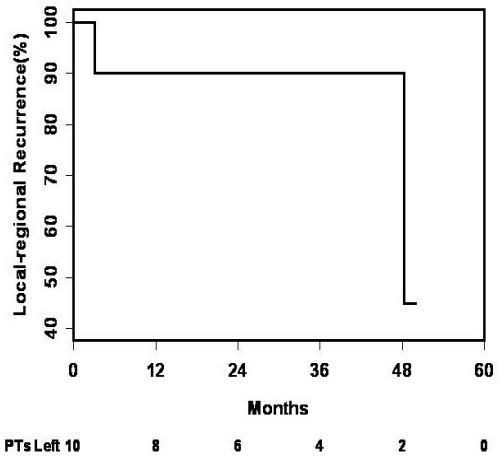
Two had grade 2 laryngitis. Four patients had grade 2 xerostomia. One patient developed respiratory distress during the course of radiation therapy and underwent tracheotomy. Also, he developed swallowing difficulty with placement of a PEG (percutaneous endoscopic gastrostomy) tube and still requires both at 3-year follow up. Another patient needed a tracheostomy tube at the time of the completion of thyroidectomy and retained the tracheotomy at the last visit (2 years and 4 months).

Table 5. Comparisons of Loco regional control rates

Authors	Patients (n)	Loco regional control rate, 2 years (%)	Distant metastasis free rate, 2 years (%)
Rosenbluth et al, 2005[3]	20	85%	46%
Urbano et al, 2007[4]	13	85%	NA
Our study	10	90%	87%

Abbreviations: NA= not available.

Figure 3A: Loco regional control rates for all 10 patients

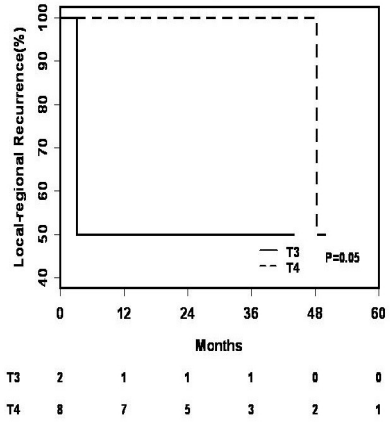


Discussion

Currently, the indications for radiation therapy in the management of thyroid cancer are controversial. The University of Florida indications[7] for PORT for differentiated thyroid cancer are in adults over 45 years of age with one of the following poor prognostic variables: positive margins, more than minimal extrathyroid extension (T4), multiple positive nodes with extracapsular extension, and disease resistant to ^{131}I.

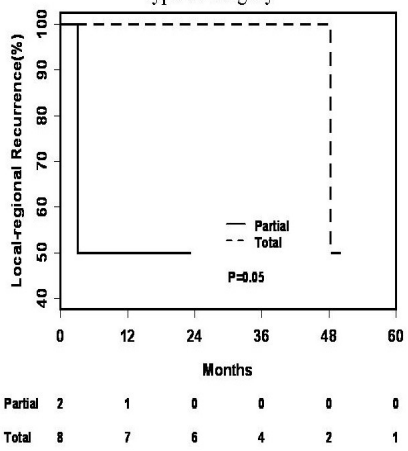
Given the complexity of treating this target volume, IMRT offers an excellent method to deliver radiotherapy adequately. IMRT for the treatment of thyroid cancer has been compared to conventional techniques in two studies.[1,5] Nutting et al[1] evaluated the potential role of IMRT in the treatment of thyroid cancer in 6 patients treated with EBRT. Conventional plans (3 fields: direct anterior and paired anterior-oblique wedge fields) were generated for each patient and compared with the 3D-CRT and IMRT plans. IMRT produced improved target coverage while reducing the volume of irradiated normal tissue ($p = 0.01$) and maximum dose to the spinal cord ($p = < 0.01$). Posner et al[5] demonstrated similar results. All the treatment plans were able to deliver a minimum dose of 60 Gy to the 95% of the gross tumor volume, while keeping the maximum spinal cord dose at or below 45 Gy.

Figure 3B: Loco regional control rates for all 10 patients based on T stage



In our series, the 3-year rates of overall survival, local control, and freedom from distant metastases were 80%, 90%, and 58%, respectively. These results are comparable with the other 2 small single institution series (Table 5). Rosenbluth[3] and Urbano[4] demonstrated locoregional control rates of 85% at 2 years. Urbano et al[4] evaluated the toxicity results of a phase I study in 13 patients treated with IMRT in locally advanced thyroid cancer. The mean PTV dose delivered to 95% of the volume was 56.4 Gy in 28 fractions (2.1 Gy per fraction, 5 fractions per week).

Figure 3C: Loco regional control rates for all 10 patients based on type of surgery



The mean elective nodal dose was 46.4 Gy in 28 fractions (1.8 Gy per fraction). Grade 2 and 3 skin changes were seen in 31% and 38.5% of patients, while 53% and 8% developed grade 2 and 3 mucositis. No grade 4 toxicities were observed. Thirty percent of patients developed L'Hermitte's syndrome. All patients had complete responses to treatment but 3 patients developed recurrence. One had a local recurrence at 36 months, a second in the mediastinum and the lungs at 7 months, and a third had bone and lung metastases 3 months later.

Rosenbluth[3] et al treated 20 nonanaplastic thyroid cancer patients with IMRT. Most of their patients had T4N1 disease. The doses of RT were 54 Gy for low-risk microscopic disease, 59.4-to-63 Gy to the high risk areas, 63-to-66 Gy for positive margins, and 63-to-70 Gy to gross disease. Fourteen patients were treated with accelerated hyperfractionated RT, 1.6 Gy per fraction, twice daily. The 2-year local progression-free rate was 85%, with 2 local failures and the 2-year overall survival rate was 60%. Grade 3 acute mucositis and pharyngitis were seen in 7 and 3 patients, respectively. Only 2 patients had symptomatic grade 3 acute skin toxicity and 2 had grade 3 acute laryngeal toxicity. No significant radiation-related late effects were reported.

In the present study, the percent incidence of both and late toxicities were comparable to the reported studies in the literature. Due to the small number of patients in our series (Table 4), we could not further evaluate by multivariate analysis the influence on the outcomes of standard risk factors such as age, gender, T, N-stage, overall stage, type of surgery, margin status, number of lymph nodes positive, extra nodal extension, RAI therapy, and the addition of chemotherapy.

Conclusions

IMRT offers excellent local control rates with minimal acute side effects in the treatment of differentiated thyroid cancer in the postoperative setting. Long-term follow up is needed to assess the incidence of late toxicities. Declaration of interest: None of the authors has any financial or other potent conflict of interest. Funding: this research did not receive grants from the funding agencies.

Author Contributions

All the authors were involved in the preparation of

Table 6. Clinical characteristics and patterns of failure of 10 patients

S. No	Age year	Gender	Histology	Treatment Method	RT dose (Gy)	Type of x surgery	Status at last visit
1	52	Female	Papillary ca	SX+RAI+PORT	56	Subtotal thyroidectomy	NED
2	61	Male	Papillary ca	SX+RAI+PORT +CTX	60	Total thyroidectomy	Hilar LN and lung nodules
3	77	Male	Anaplastic ca	SX+PORT+RAI +CTX	68	Total thyroidectomy	NED
4	56	Male	Papillary ca	SX+PORT+RAI	70	Total thyroidectomy	NED
5	74	Female	Papillary ca	SX+PORT+RAI	70	Total thyroidectomy	NED
6	69	Male	Papillary ca	SX+PORT+RAI	60	Total thyroidectomy	NED
7	85	Female	Papillary ca	SX+RAI+PORT	60	Total thyroidectomy	Bone
8	69	Female	Follicular ca	SX+PORT+RAI	60	Total thyroidectomy	NED
9	77	Male	Insular ca	SX+RAI+PORT	70	Subtotal thyroidectomy	Residual disease (in-field)
10	51	Female	Papillary ca	SX+RAI+PORT	60	Total thyroidectomy	Supraclavicular LN

Abbreviations: as described in the other tables, ca = carcinoma, NED = no evidence of disease.

the manuscript. Statistical analyses were done by the biostatistician at the Fox Chase Cancer Center.

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