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Results of Intensity Modulated Radiation Therapy in Patients with Well Differentiated Thyroid Carcinoma: Experience of King Fahad Medical City

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Abstract

Background: We aimed to evaluate the outcomes and toxicity profile in patients with well differentiated thyroid carcinoma (WDTC) treated with intensity modulated radiation therapy (IMRT).

Materials and methods: Between June 2007 and July 2011, 18 patients with WDTC received postoperative IMRT with mean radiation dose 66Gy (60-66) delivered with 7 dynamic beams. Median age was 50.5 years (23-66); of whom 10 were males (55.6%) and 8 were females (44.4%). Predominant histology was papillary in 17 patients (94.4%) and predominant T stage was T4 in 15 patients (83.3%). RAI therapy was given to all patients.

Results: Median follow up was 53 months (6-55). At 48 months, the Kaplan-Meier estimates of locoregional control, distant control and overall survival were 88.9%, 83.2% and 89.4% respectively. Incomplete surgery, presence of lymphovascular invasion (LVI), and number of >4 positive lymph nodes were found as poor prognostic factors (0.0001). Acute grade 3 Mucositis was experienced in one patient (5.5%) and grade 3 skin toxicity was seen in 1 patient (5.5%). Late toxicities were few and of grade 2.

Conclusion: Postoperative IMRT offers excellent locoregional and distant control rates and overall survival with minimal toxicity profile in the treatment of WDTC.

Keywords: Well differentiated thyroid carcinoma; Postoperative intensity modulated radiation therapy; locoregional and distant control; Overall survival; Toxicity profile

Introduction

The incidence of thyroid carcinoma varies according to age, gender, ethnicity and geographic region. It ranks 12th most common cancer worldwide. However, in Saudi Arabia annual incidence of thyroid carcinoma is 5.0 per 100,000, ranking 4th common cancer in men and 2nd common cancer in women second to breast cancer. Majority of these patients present with localized or locoregional disease and with well differentiated (papillary and follicular) as predominant histological type (83.3%) [1,2]. For these patients surgery with or without radioactive iodine ^{131}I therapy remains as a standard curative option [3]. The role of external beam radiation therapy (EBRT) has remain controversial; however recent studies recommend its use in patients with extrathyroid extention or residual disease and patients with age above 50 years [4,5]. However, irregular shape of target volume and multiple nodal sites pose problems to deliver radiation dose beyond 50 Gy by conventional and conformal radiation therapy techniques, which results poor locoregional control and low survival rates [6,7]. Intensity modulated radiation therapy (IMRT) has shown better dose coverage to the target volume.

However, role of IMRT in differentiated thyroid carcinoma has not been widely evaluated; to date few studies have been published in literature using postoperative IMRT [8,9,10]. We aimed to evaluate the efficacy, safety and impact of IMRT in patients with differentiated thyroid carcinoma on locoregional control, distant control and overall survival.

Materials and Methods

After approval from Institutional Ethical Review Board (IRB) committee, between June 2007 and July 2011, eighteen patients with differentiated thyroid carcinoma were treated in our center with postoperative IMRT after primary surgery and RAI therapy after written consent.

A complete medical history, physical examination, hematology, serum chemistry, thyroid profile, thyroid scintigraphy, neck ultrasound, computed tomography and central pathology review were performed to for accurate evaluation of extent of primary and nodal status and for assessment of resectability of any gross residual before starting EBRT.

Eligibility

- Histolopathogical confirmed well differentiated carcinoma (papillary and follicular)
- T3 and T4 disease with confirmed sternothyroid muscle invasion or extra-capsular invasion
- Post RAI therapy gross residual disease
- Patients with metastatic disease were excluded

Treatment Protocol

All patients were simulated using Siemens Emotions 6 CT simulator with thermoplastic mask (Aquaplast Corp, Avondale PA). Contrast enhanced axial images of 3 mm slice thickness were obtained from the top of head to 5 cm below the level of carina. After the acquisition of CT data, delineation of contouring of thyroid bed, GTV [gross tumor

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volume], CTV [clinical target volume], PTV1 [planning target volume included GTV+ CTV + level II to level IV lymph nodes+ superior mediastinal lymph nodes], PTV2 [included GTV + 1 cm margins] and critical structures (spinal cord, esophagus, larynx lungs and parotids) was performed using Varian Eclipse Contouring software by two radiation Oncologists. After contouring treatment planning for IMRT was carried out by two medical physicists. IMRT plans were made using 5 or 7 dynamic beams. The PTV1 was prescribed to 50 Gy in 25 fractions, 2 Gy per fraction, one fraction per day and PTV2 was prescribed to 60-66Gy. Efforts were made to receive 60-66Gy to 95% of PTV2 and to reduce hot spots less than 120%. During planning, the mean dose to the parotid gland was constrained to < 26 Gy, and the total doses to the spinal cord, larynx, esophagus and lungs were constrained to< 45Gy, < 60Gy, < 60 Gy and 20 Gy respectively (Figure 1).

Toxicity and response evaluation

During radiation therapy (IMRT), patients were evaluated every week for weight, performance status, hematology/chemistry and side effects. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were used to score acute radiation toxicity (≤90 days from start of radiation therapy). The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity persisting beyond 90 days from the completion of radiotherapy.

After completion of therapy, periodic follow ups were carried out every 3 months for first two years and every 6 months subsequent 3rd to 5th year with thyroid profile (T3, T4, TSH, thyroglobulin and calcium) and ^{123}I scan. All patients were instituted on thyroid hormonal suppression.

Statistical analysis

The primary endpoints were the efficacy of IMRT in terms of safety profile, response rates and locoregional and distant control. Secondary endpoints were overall survival and prognostic factors affecting locoregional and distant control. The times to last follow up evaluation, appearance of local and distant relapse and death were calculated from date of starting treatment. Disease free survival (DFS) was defined as the duration between the entry date and the date of documented disease reappearance, death from cancer and/or last follow-up (censored). Overall survival (OS) was defined as the duration between the entry date and the date of patient death or last follow-up (censored). Probabilities of locoregional and distant control, disease free and the overall survival were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using log rank test

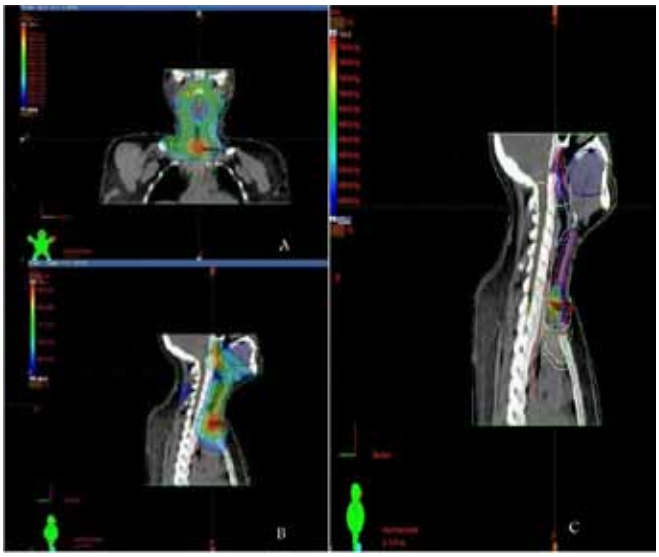

Figure 1: Intensity modulated radiotherapy technique incorporated with 5-7 beamlets showing isodose distribution in axial, saggital and coronal images of phase 1 (A, B) and boost(C) in saggital and coronal views of MPR (multiplanar reconstructed radiographs).

Variables	Number (%)
Age Age < 50 years Age > 50 years	Mean 50.5 years (range:23-66) SD12.01 10 (55.6%) 8 (44.4%)
Gender Male Female	 10 (55.6%) 8 (44.4%)
T Stage T3 T4	 3 (16.7%) 15 (83.3%)
N Stage N0 N1 N1a N1b	 4 (22.2%) 14 (77.8%) 8 (44.4%) 6 (33.3%)
Histology Papillary Follicular	 17 (94.4%) 1 (5.6%)
Pathological T size Less than 4cm More than 4cm	 8 (44.4%) 10 (55.6%)
Multifocality Yes No	 10 (55.6%) 8 (44.4%)
Lymphovascular invasion Yes No	 7 (38.9%) 11 (61.1%)
Surgical margin status Positive Negative	 14 (77.8%) 4 (22.2%)
Extrathyroid extention Yes No	 17 (94.4%) 1 (5.6%)
Type of surgery Total thyroidectomy Subtotal thyroidectomy	 16 (88.9%) 2 (11.1%)
Neck dissection Yes No	 7 (38.9%) 11 (61.1%)
Before IMRT Tg level (ng/ml)	59.7 (1-248.9) SD 83.9
^{131}I therapy cumulative dose (mCi)	159± 30.9

SD= standard deviation, Tg= serum Thyroglobulin, mCi= milliCurie

Table 1: Patient characteristics.

Toxicity	Grade 2 n (%)		Grade 3 n (%)	
	Acute	Late	Acute	Late
Skin	5 (27.8%)	1 (5.5%)	1 (5.5%)	0
Mucositis	4 (22.2%)	0	1 (5.5%)	0
Esophagitis (dysphagia)	4 (22.2%)	1 (5.5%)	1 (5.5%)	0
Laryngitis (hoarseness)	5 (27.8%)	0	0	0
Taste change	3 (16.7%)	1 (5.5%)	0	0
Xerostomia	2 (11.1%)	1 (5.5%)	0	0

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

Variable	Locoregional Control	Distant Metastasis Control	Overall Survival
Age (< 50 vs. > 50 years)	0.33	0.66	0.71
Gender(Female vs. male)	0.98	0.90	1.00
T stage (T3 vs. T4)	0.03	0.02	0.23
N stage (N0 vs. N1)	0.77	0.66	0.56
Type of surgery (total vs, subtotal)	0.02	0.90	0.23
Neck dissection (yes vs. no)	0.90	1.00	1.00
LN positive (< 4 vs. > 4)	0.85	0.03	0.56
LVI (no vs. yes)	0.03	0.90	0.60
Margin status (negative vs. positive)	0.75	0.44	0.70
ETE (no vs. yes)	0.45	0.45	0.56
Multifocality (no vs. yes)	0.55	0.40	0.33

T= tumor, N= stage, M= metastasis, LN= lymph nodes, LVI= lymphovascular invasion, ETE= extra thyroid extension

Table 3: Univariate analysis of variables on locoregional control, distant control and overall survival.

and Cox regression analysis. Statistical analyses were performed using the computer program SPSS version 16.0.

Results

Median follow up was 53 months (range: 6-55 months). Patients' characteristics are shown in Table 1. Majority of study cohort was aged above 50 years (10 patients, 55.6%) and male predominant (10 patients, 55.6%). Papillary carcinoma was predominant histological pattern (17 patients, 94.4%). According to stage, T4 was in 15 patients (83.3%), T3 in remaining 3 patients (16.7%) and node positive (N1) disease in 14 patients (77.8%). Majority of patients underwent total thyroidectomies (16 patients, 88.9%). However neck dissection was carried out in 7 patients (38.9%).

Median time between surgery and IMRT was 4.45 months (range: 1.3-6.2 months). The median dose to PTV1 was 50 Gy (range: 49-55Gy) and PTV2 was 66 Gy (range: 64-70Gy) in 33 fractions (range: 32-35) and IMRT duration was 1.53 months (range: 1.33-1.60 months).

Toxicity profile

Treatment was generally well tolerated by all patients with grade 2 and 3 side effects (Table.2). No grade 4 side effects or hospitalization or treatment related death was seen.

Locoregional control, distant control and overall survival rates

The Kaplan-Meier estimates of 1, 2 and 4 year local control rates were 100%, 95% and 88.9% respectively. Two patients developed local recurrences (in-field). One patient developed right level III neck node at 21 months of completions of IMRT and other developed left supraclavicular node at 43 months of completion of IMRT.

The Kaplan-Meier estimates of 1, 2 and 4 year distant metastasis control rates were 100%, 88% and 83.2% respectively. Two patients developed lung metastases at 18 months after IMRT completion, of whom one patient had local recurrence after 3 months of distant metastasis. Third patient developed bone metastasis at 43 months of completion of IMRT.

The Kaplan-Meier estimates of 1, 2 and 4 year survival rates were 100%, 95% and 89.4% respectively.

Further Univariate analysis was carried out in Table 3. It was found that T stage, type of surgery and LVI were significant prognostic factors for locoregional failure (0.03, 0.02 and 0.03 p respectively) Figure 2. For distant failure, T stage and number of nodes were significant prognostic factors (p 0.02 and 0.03 respectively). For overall survival no significant prognostic factor was found.

Discussion

Role of EBRT has remained controversial in the management of differentiated thyroid carcinoma because of no mere survival benefit; however strategy based on survival benefit would ignore the associated problems with locoregional failure (anaplastic transformation of long standing locoregional disease, increased risk of multiple surgeries, extensive follow ups with cost of tests and airway compromise and death by locoregional disease) [3]. Various studies have supported the use of EBRT in high risk differentiated thyroid carcinoma (pT4, nodal involvement, extra-nodal extension, extensive extrathyroid extension and gross residual disease not amenable for surgery).

In our study, IMRT resulted in the 4 year locoregional control, distant control and overall survival rates of 88.9%, 83.2% and 89.4% respectively in differentiated thyroid carcinoma. These results were found comparable or superior with other similar studies utilizing

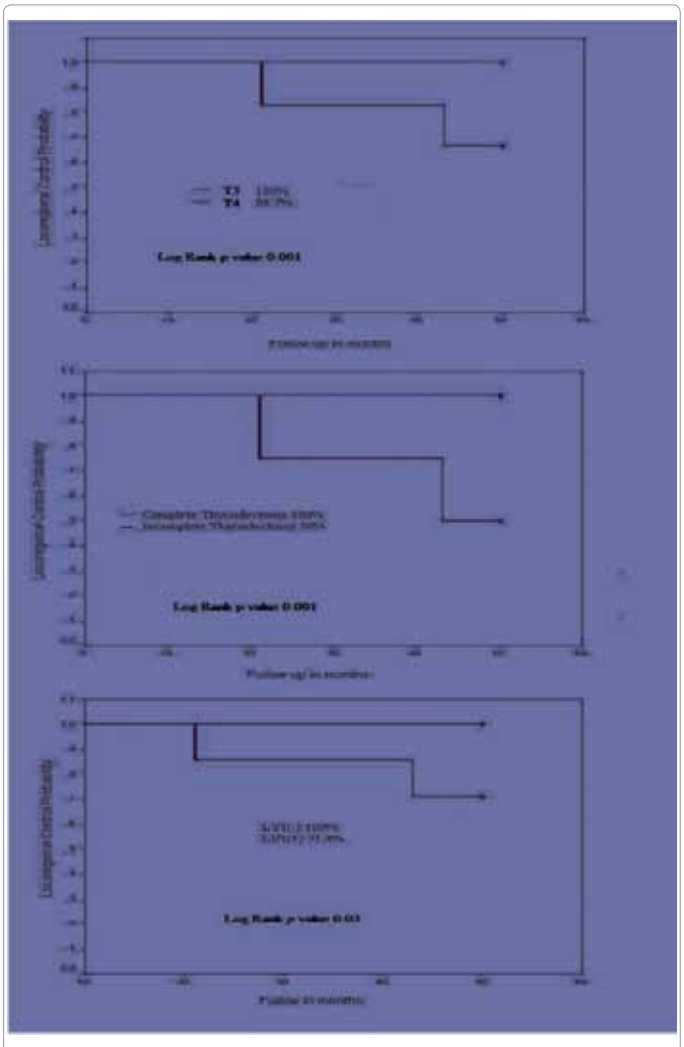

Figure 2: Cumulative locoregional control according to (a) T stage,(b) type of surgery and (c) presence of lymphovascular invasion (LVI).

Study [references]	Duration study conducted	Radiation Techniques	Mean Radiation doses	Sample size (n)	Follow up period	Loco-regional Control	Freedom From Distant Metastasis	Overall survival	Grade 3 Acute toxicity incidence	Grade 3 Late toxicity
Schwartz DL [7]	1996-2005	74→3DCRT 57→IMRT	60Gy/30fr	131	4 years	79%	76%	73%	NA	2%
Rosenbluth BD[8]	2001-2004	IMRT	63Gy/30fr	20	2 years	85%	46%	60%	50%	None
Urbano TG [9]	2005-2006	IMRT	58.8Gy/28fr	13	2 years	90%	87%	NA	8-31%	NA
Turaka A [10]	2001-2008	IMRT	60Gy/30fr	10	2years	90%	87%	80%	10-30%	None
Our study	2007-2011	IMRT	66Gy/33fr	18	4 years	88.9%	83.2%	89.4%	5.5%	None

3DCRT= Three dimensional conformal Radiation therapy, IMRT= Intensity modulated Radiation Therapy, Gy=Grays, NA= not available

Table 4: Comparison various studies using IMRT of locoregional control, distant metastasis control and overall survival rates.

Study [references]	Duration study conducted	Radiation techniques	Sample size (n)	Follow up period	Locoregional Control	Freedom From Distant metastasis	Overall survival
Kim TH [4]	1981-1997	3DCRT	23	7 years	95.2%	NA	90%
Chen PV [5]	1973-2001	Conventional;3DCRT	44	7.8 years	93%	NA	90%
Tubiana M [6]	1943-1965	conventional	55	5 years	NA	53%	60.6%
MSDS trial	2003-2004	3DCRT	26	2.5 years	97%	NA	96%
Terezakis SA [12]	1989-2006	3DCRT	76	4 years	72%	NA	55%
Azrif M [13]	1990-2000	Conventional 3DCRT	49	5.4 years	81.4%		75.7%
Keum KC [14]	1990-2005	Conventional;3DCRT	25	10 years	89%	NA	NA
Meadows KM [15]	1999-2000	3DCRT	42	5 years	89%	60%	60%
Ford D [16]	1988-2001	Conventional;3DCRT	41	5 years	74%	NA	67%
Busutti L [17]	1982-1995	Conventional;3DCRT	243	5 years	93.7%	93.7%	93.7%
O'Connel ME [18]	1969-1991	conventional	103	4 years	81%	NA	27%-85%
Kim JH [19]	1979-1986	Conventional with doxorubicin	22	2 years	77%	NA	NA
Brierly J [20]	1958-1998	conventional	70	10 years	84.9%	87.3%	65.7%

3DCRT= Three dimensional conformal Radiation therapy, NA= not available

Table 5: Comparison of locoregional, distant control and overall survival rates in various retrospective and cohort studies using conventional radiation therapy and 3DCRT techniques.

IMRT, three dimensional conformal radiation therapy (3DCRT) and conventional radiotherapy for differentiated thyroid carcinoma Table 4 and Table 5. Reason for better locoregional and distant control in our study can be explained by three fold reasons, (i) median radiation dose was 66 Gy in our patients, (ii) all metastatic patients were excluded in our study and (iii) anaplastic and medullary thyroid carcinoma were not included in our study.

In present study, at median prescribed radiation doses of 66 Gy only 5.5% patients developed grade 3 acute skin and esophagitis and were self limiting, which were much lower as reported by other similar studies Table 4. None of patients required hospitalization or gastrostomy. No treatment related death was observed and none of patients developed severe late toxicity.

In conclusion, our results showed that postoperative IMRT offers excellent locoregional and distant control rates and overall survival with minimal toxicity profile in the treatment of well differentiated thyroid carcinoma. However large randomized controls are warranted.

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