AN AUDIT OF MANAGEMENT OF DIFFERENTIATED THYROID CANCERS

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ABSTRACT

OBJECTIVE: Management of differentiated thyroid cancers (DTC) remains controversial with a wide variation in clinical practice. The aim of this audit was to find out strength and weakness of treatment strategy being used at a tertiary care hospital. **PATIENTS AND METHOD:** Patients with DTC enrolled from January 2006 till May 2009 were reviewed. Histopathology, extent of surgery, measurement of serum markers, I-^{131} ablation, use of various imaging techniques and follow up rate at 1 year was evaluated. **RESULTS:** One hundred and six patients (M:F 36:72 with mean age of 40.55 ±16 years) were enrolled and papillary (72%) followed by follicular carcinomas (15%) were the most common tumors. Total or completion thyroidectomies were performed in 78 and 22 patients respectively while 6 had partial thyroidectomies. Serum TSH and thyroglobulin level with antibodies were measured in all patients at baseline and 1 year follow up. Radioiodine-^{131} (I-^{131}) was given (50-200 mCi) to every patient at a mean TSH level of 55.11 ± 31mU/L. Diagnostic whole body iodine scan (DWBIS) was performed in 36/106 (34%) patients at baseline and 30/48 (63%) at follow up. Therapeutic WBIS (TWBIS) was performed in 103/106 (97%) patients at baseline and 23/25 (92%) at follow up. Neck ultrasound was performed in 25% and 27% patients at baseline and follow up. Follow up failure of 55% was seen at 1 year. **CONCLUSIONS:** This audit regarding the management of DTC at KIRAN reveals adequacy of extent of surgery, use of I-^{131} ablation, TWBIS and measurement of clinical markers are in good agreement with recommended guidelines. However, this audit shows over utilization DWBIS, under-utilization of neck ultrasound and dismal follow-up at 1 year and these need to be addressed properly.
Keyword: Thyroid Cancer, thyroglobulin, ablation, whole body iodine scan, thyroidectomy.

Introduction

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (90%) of all thyroid cancers which is less than 1% of all malignancies.[1] Papillary and follicular carcinomas have a good prognosis, although tumor recurrence occurs in about 30% cases and cancer related deaths in 10%.[2] Surgery, radioioidine-^{131} ablation (I-^{131}) and life long L-Thyroxin suppression therapy are the major therapeutic options available. As thyroid cancer is uncommon there have been no prospective trails examining these treatment options. There are, however, large and well documented retrospective series which have provided good evidence for importance of adequate surgery, use of post-operative I-^{131} ablation and long term L-Thyroxin therapy in improving prognosis.[3,4] Since 1996 till late 2009, the American thyroid Association has published three treatment guidelines for thyroid nodule and DTC because of controversies in many areas like extent of surgery in small cancer, use of I-^{131} ablation after thyroidectomy and appropriate use of L-Thyroxin therapy and also robust advances in the diagnostic and therapeutic arenas. Another important fact to consider is relatively less aggressive approach recommended by United Kingdom and European

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Societies guidelines than American counterpart.

Because of the complexity of decision making in treatment of DTC, many centers in world follow their own protocols agreed by team of surgeons, endocrinologist and oncologist.[5] In Pakistan, there has been a similar trend of locally agreed protocols based on various international guidelines for the management of DTC in major cities. We have audited the treatment of DTC at Karachi Institute of Radiotherapy And Nuclear Medicine (KIRAN) Karachi, which is the largest tertiary cancer care hospital in public sector with 4 radio-iodine treatment suites. The objectives of this audit were to find out the extent of surgery, I-^{131} ablation, use of serum thyroglobulin, thyroid antibodies, diagnostic/post-ablative scans and ultrasound neck during initial visit and follow up, use of L-Thyroxin to suppress TSH and also to find out the pattern of follow up of treated patients after 1 year.

Patients and Methods

This audit included all patients with diagnosed DTC (papillary, follicular or follicular variant of) who were registered to Nuclear Medicine Department of Karachi Institute of Radiotherapy And Nuclear Medicine (KIRAN), Karachi from January 2006 till May 2009. These patients were referred from various public and private sector hospitals where thyroid surgery was performed.

Data collected include age, gender, type of cancer, type of thyroid surgery, estimation of TSH, serum thyroglobulin and thyroid antibodies level, use of ultrasound neck, whole body I-^{131} scan (diagnostic and post-ablative) prior and after I-^{131} treatment. We also collected data about the average time of I-^{131} ablation after surgery, dose of I-^{131} and discrepancies between diagnostic and post-ablative whole body scans (DWBIS, TWBIS). We also gathered data regarding dose of L-Thyroxin and patients los to follow up.

The following well defined points of good practice (based upon published guidelines with recommendation ratings [Tab. 1]) were evaluated:

1. Prevalence of disease as per age and gender of patients.
2. Extent of thyroid surgery: Near total or total thyroidectomy, completion thyroidectomy, or lobectomy. Increased extent of primary surgery may improve survival for high risk patients[6,7] and low risk patients.[8,9] Similarly Bilimoria et al[8] reported that patients underwent lobectomy for small (1-2 cm) tumors, had high risk of recurrence and mortality.
3. Histopathology: Papillary (PC), follicular (FC), follicular variant of papillary (FVPC), Hurtle cell (HC) or well differentiated tumor of uncertain malignant potential (WDUMP).
4. Serum TSH, thyroglobulin (Tg) and thyroid antibodies (Tab): Time of assays measurement from date of surgery, TSH level at time of I-^{131} ablation, average time off-thyroxin measurement of Tg and TAb at follow-up. Adequate TSH level of > 30 mU/l was defined as adequate for DWBIS, measurement of Tg and TAb and I-^{131} ablation.[10] A serum Tg level <2 ng/ml (with negative TAb) has a negative predictive value (NPV 98.4%) for recurrence.[11]
5. Radioiodine-^{131} Ablation: Post-operative ablation of remnant tissue using I-131 is being increasingly used as it facilitates the early detection of recurrence using Tg and WBIS and also reduces recurrence. Revised ATA guidelines recommend a dose of 30-100 mCi for low risk and 100-200 mCi for high risk patients.[19] Although there is a trend of higher ablation rates with higher activities.[12]
6. Use of ultrasound neck, DWBIS and TWBIS: Absence of thyroid tissue, nodes in neck or elsewhere in body on TWBIS was considered as an indicator of successful ablation. Cervical ultrasound is highly sensitive and can detect nodal metastases even when TSH stimulated Tg is undetectable.[13] DWBIS due to its limited accuracy and possibility of stunning is not recommended during follow up of low risk patients.[14,15] TWBIS has higher sensitivity and may detect disease not seen on DWBIS.[16,17]
7. TSH Suppression with L-Thyroxin: There has been an association between thyroid hormone suppression therapy and reduction in major adverse event.18 In high risk patients a serum TSH level <0.1 mU/L and 0.1-0.5 mU/L for low risk patients

Table 1. American Thyroid Association 2009 guidelines ratings and definitions based on Available Evidence.

Rating	Definition
A	Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes. Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
B	Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.
C	Recommends. The recommendation is based on expert opinion.
D	Recommends against. The recommendation is based on expert opinion.
E	Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
F	Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits. Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Adapted from the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality.[20]

has been recommended by revised American Thyroid Association guidelines.[19]

8. Follow-Up: DTCs have a good prognosis, although tumor recurrence occurs in about 30% cases and cancer related deaths in 10%.[2] Therefore, lifelong follow up and surveillance using stimulated Tg level and neck ultrasound is recommended as early detection of recurrence is not only cost effective but also ensures better outcome too.

Results

During the study period 106 cases were registered to Nuclear Medicine Department of KIRAN. Mean age of the population was 40.55 ±16 years, 72 females and 36 were males. Total thyroidectomy was the most common surgical procedure (as per surgical notes/referral letters) seen in 78/106 (73%), followed by completion thyroidectomy in 22/106 (21%) and partial thyroidectomy in remaining 6/106 (6%). Histopathology revealed PC 76 (72%), FC 16 (15%), FVPC 10 (9%), HC 1 (1%) and 3 (3%) WDUMP.

Serum TSH, Tg and TAb were estimated in all patients at mean 26 days (17-37days) from date of surgery from the same laboratory on same sample. Mean TSH level before I^{-131} ablation was 55.11 ± 31mU/L while in 70 patients Tg level (pre-ablative) was >2 ng/ml (857.96 ±2246) with negative TAb in 68 (in 2 patients TAb were positive). In remaining 36 patients Tg level (pre-ablative) was <2 ng/ml (0.2-2l) with negative TAb in 31 (in 5 patients TAb were positive). The incidence of TAb samples in studied population (pre-ablative) was 7%.

At fist year follow up (48 patients), average off-thyroxin period for estimation of TSH, Tg and TAb was 19 days (14-29 days). Mean TSH level at follow up was 77.80 ± 29 mU/L while in 22 patients Tg level (at follow up) was >2 ng/ml (936.96 ±41.66) with negative TAb in 19 (in 3 patients TAb were positive). In remaining 26 patients Tg level (follow up) was <2 ng/ml (0.2-2 ng/ml) with negative TAb in 24 (in 2 patients TAb were positive). The incidence of TAb samples in studied population (follow up) was 10%.

Radioioidne-131 ablation was performed in 106 patients with an average dose of 108.8 mCi (50 -200 mCi). 50 mCi was given to patients with partial thyroidectomies, 100 mCi to total thyroidectomies, 150 mCi in patients with evidence of nodal metastasis and 200 mCi for patients with distant metastases. Average time between surgery and ablation was 5 weeks (26-41 days). All patients were admitted in radionuclide therapy suite for 48-72 hr and were released when radiation dose was in safe limits.

Neck ultrasound was performed in 27/106 (25%) patients at initial work up with positive scans in 11/27 and 16/27 scans were negative. At 1 year follow up, neck ultrasound was done in 13/48 (27%) patients and all were negative for evidence of residual disease. DWBIS was performed at baseline (with 2 mCi of I-131 after 48 hr) in 36/106 (34%) patients and 33 scans were positive for functioning thyroid tissue over thyroid bed only (30 patients) and extra-thyroidal uptake as well (3 patients). Scan was negative in remaining 3/36 patients. TWBIS were performed (8 ± 2 days after ablative dose) in 103/106 (97%) patients while 3 patients did not turn up for scan. TWBIS was positive in 98 patients (thyroid bed only in 59 and extra-thyroidal as well in 39) while scan did not show evidence of functioning tissue in 5 patients. Comparing the DWBIS and TWBIS in 36 patients, data show complete concordance in 33 (94%) patients while discordance (-ve DWBIS but +ve TWBIS) was seen in 2 (6%) patients and 1 patient did not turn up for TWBIS. At 1 year follow DWBIS was performed (with 2 mCi of I-131 after 48 hr) in 30/48 (63%) patients and 10/30 scans were positive for residual disease over thyroid bed only (08 patients) and extra-thyroidal uptake as well (2 patients). Scan was negative in remaining 20/30 patients. TWBIS were performed at 1 year follow up (8 ± 2 days after a mean therapeutic I-131 dose of 125 ±25 mCi) in 23/25 (92%) patients given a therapeutic dose. TWBIS was positive in 18/23 patients (thyroid bed only in 08 and extra-thyroidal as well in 10) while it did not show evidence of functioning tissue in 5/23 patients. Comparing the DWBIS and TWBIS in 6 patients (ablation done in 6 patients with positive DWBIS and raised Tg level), complete concordance was seen in all patients.

Only 48/106 (45%) patients did follow after 1 year while 58/106 failed to turn up (55% turn up failure). (Tab. 2)

Table 2. Demographic data

Age	40.55 ± 16 years (mean ± SD)
Male : Female	34 (32%): 72 (68%)
Total WDTC	106
-PC	76 (72%)
-FC	16 (15%)
-FVPC	10 (9%)
-HC	1 (1%)
-WDUMP	3 (3%)
Thyroidectomies	106
-Total Thyroidectomy	78 (74%)
-Completion Thyroidectomy	22 (21%)
-Partial Thyroidectomy	06 (5%)
TSH level	
-Baseline	55.11 ± 31 mU/L
-Follow up	77.80 ± 29 mU/L
Thyroglobulin (Tg) level	
-Baseline	
>2 ng/ml	70 patients (857.96 ± 2246)
≤2 ng/ml	36 patients (0.2 ± 1.5)
-Follow up	
>2 ng/ml	22 patients (936.96 ± 41.66)
≤2 ng/ml	19 patients (0.4 ± 1.2)
Neck Ultrasound	
-Baseline	27/106 (25%)
-Follow up	13/48 (27%)
DWBIS	
-Baseline	36/106 (34%)
-Follow up	10/48 (21%)
TWBIS	
-Baseline	103/106 (97%)
-Follow up	23/48 (48%)
Follow up at 1 year	48/106 (45%)

SD= Standard Deviation
WDTC= Well Differentiated Thyroid Cancer
PC= Papillary Cancer
FC= Follicular Cancer
FVPC=Follicular Variant of Papillary Cancer
HC= Hurtle Cell Cancer
WDUMP= Well Differentiated tumor of Uncertain Malignant Potential
DWBIS=Diagnostic Whole Body Iodine Scan
TWBIS=Therapeutic Whole Body Iodine Scan

Discussion

This audit was conducted to find out points of good practice (based upon published guidelines) in the management of DTC at KIRAN hospital.

Extent of Surgery: This audit shows an aggressive surgical approach in term of total thyroidectomy (as one step or 2 steps) in 94% patients. Due to lack of surgical/histopathological notes in all patients, we can not ascertain whether this approach was biased or based on size of primary lesions as recommended in recent guidelines. However, on the basis of available complete information in 47 patients, decision was based on size of lesions detected on pre-operative ultrasounds or histopathological findings as recommended by most of published guidelines[19] (recommendation rating A).[19,20]

Measurement of TSH, Tg and TAb at Initial work-up: Adequate time was given for measurements of these parameters as mean TSH was 55.11 ± 31 mU/L at initial work-up and 77.80 ± 29 mU/L at 1 year follow-up. This again is in good compliance of recommended guidelines (recommendation rating B).[19]

Radioiodine-^{131} Ablation: Ablation was done in all patients. In 47 patients lesions was >2 cm while in remaining patients due to lack of complete information about the size of lesion, rational for I-^{131} ablation could not be ascertained (recommendation rating B and C).[19] Ablative dose of I-^{131} used in these patients also in accordance with published guidelines (recommendation rating B and C).[19] Sufficient time period between surgery and ablation was practiced in these patients as per recommended by experts.[21]

Neck Ultrasound: This audit shows under-utilization of ultrasound neck at initial and 1 year follow-up for detection of residual disease at thyroid bed and nodal metastasis as per recent guidelines (recommendation rating B).[19]

DWBIS and TWBIS: DWBIS having low accuracy and risk of inducing stunning has been relatively over-used at 1 year follow up and this could be explained by under-utilization by ultrasound (recommendation rating F).[19] TWBIS which has better sensitivity for lesion detection has been exploited in an efficient manner as per guidelines (recommendation rating B).[19]

Follow-Up at 1st Year: Major goals long term follow-up are accurate surveillance for possible recurrence in patients thought to be free of disease and to monitor thyroxin suppression or replacement therapy, to avoid under replacement or overly aggressive therapy.[22] There has been a significantly high lost to follow up rate noticed in this audit and this needs to be addressed properly.

Conclusions

This audit regarding the management of DTC at KIRAN reveals adequacy of extent of surgery, use of I-^{131} ablation, TWBIS and measurement of clinical markers are in good agreement with recommended guidelines. However, this audit shows over utilization DWBIS, under-utilization of neck ultrasound and dismal follow-up at 1 year and these need to be addressed properly.

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