

Differentiated thyroid carcinoma referred for radioiodine therapy

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ABSTRACT

Objective: The current work was conducted to study the disease status and treatment results of patients with differentiated thyroid carcinoma referred for radioactive iodine therapy.

Methods: Retrospective review of 78 patients with differentiated thyroid carcinoma referred for radioiodine therapy in the Nuclear Medicine Unit, King Abdulaziz Hospital and Oncology Center, Jeddah, Kingdom of Saudi Arabia. Analysis of the clinicopathologic characteristics, age correlation to different risk factors, treatment protocol and results were performed.

Results: Seventy seven percent were female and the female to male ratio was 3.5:1. The age of patients ranged between 13-63 years with a median age of 36 years. Cervical lymph node involvement was detected in 22 patients (25%). Papillary carcinoma was encountered in 78 patients (90%) and follicular carcinoma in 9 patients (10%). Analysis of the clinicopathologic characteristics showed no statistically significant difference between patients in the different age groups except for extrathyroid extension and lymph node involvement. Patients older

than 45 years had a statistically significant lower incidence of nodal involvement and higher incidence of extra thyroid extension ($P < 0.02$). In the current study we used a high dose method (Radioiodine-131 dose 75-100mCi) for thyroid remnant ablation after thyroidectomy (total or near total) in 67 patients. An Iodine 131 dose of 150 mCi was used in 12 patients with radioiodine-avid cervical lymph nodes and in 3 patients with gross residual tumor. In 4 patients with distant metastases an Iodine 131 dose of 200 mCi was used. For the whole study group the 5-year overall survival and disease-free survival was 96% and 88%.

Conclusion: The current study, as with many other retrospective studies, concluded that despite the fact that differentiated thyroid carcinoma is among the most curable cancers, some patients are still at high risk for recurrent disease and associated mortality.

Keywords: Thyroid cancer, thyroidectomy, radioiodine therapy.

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Although thyroid nodules are common, differentiated thyroid carcinomas are relatively rare. Clinically detectable thyroid carcinomas constitute less than 1% of all cancers. The median age at diagnosis is 45 to 50 years. Thyroid carcinomas are 2 to 4 times as frequent in women as in men.¹ In Saudi Arabia, thyroid carcinomas accounted for 5% of all newly diagnosed cancers. This cancer ranked 14th for males and 2nd for females.² Papillary and follicular thyroid carcinomas

are among the most curable cancers. However, for several decades the management of differentiated thyroid cancer has been controversial.³ For the majority of patients, standard initial management consists of thyroidectomy followed by radioiodine ablation. But there is great controversy regarding the ablative dose of iodine 131 (I131) and its indication.⁴ Other conventional modes of neoplastic treatment; chemotherapy and external beam irradiation have much poorer results and consequently are much less

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studied.⁵ The overall survival rate at 10 years for middle aged adults with thyroid carcinoma is approximately 80-95%. Five to 20% of patients have local or regional recurrences and around 10% have distant metastasis. The prognostic indicators of recurrent disease and death are the age at time of diagnosis, the histopathology subtype and extent of the tumor.⁶⁻⁹ The relationship between these factors remains incompletely defined. However, Coburn and Wanebo,¹⁰ concluded that the prognostic importance of age in thyroid cancer may be due to the greater prevalence of pathologic risk factors in older patients. The aim of the current study is to analyze retrospectively all patients referred for radioiodine therapy at our center as regards the clinico pathologic characteristics, age correlation to different risk factors as well as treatment results.

Methods. All patients with the diagnosis of thyroid carcinoma that were referred to the Nuclear Medicine Unit, Oncology Center, King Abdulaziz Hospital (KAAH), Jeddah, Kingdom of Saudi Arabia (KSA), during the period between 1993-1999 are included in the current study. At the first visit, all patients were subjected to full clinical examination, laboratory investigations (complete blood count, renal profile, serum calcium and serum thyroglobulin), thyroid scan, neck ultrasonography and chest x-ray. The details of histopathology diagnosis should include subtype histopathology, size of the tumor, presence of capsular invasion or extrathyroid extension, or both. If a patient was found to have conservative surgery, he was referred for completion near total thyroidectomy. In an attempt to identify the possible correlation between the age of the patient at presentation and other risk factors, the study group was analyzed in 3 age groups. Group A included patients younger than 30 years. Group B included those ranging between 30-45 years and Group C included patients older than 45 years. Statistical analysis was performed using the student's t-test. Significance level was set at $P < 0.05$. Six weeks after surgery, when Thyrotrophin (TSH) level > 30 iu/ml, diagnostic whole body scan was performed. Thereafter, radioiodine 131 therapeutic dose was given: 75-100 mCi for remnant ablation, 150 mCi for lymph nodes metastases or residual tumor and 200 mCi for distant metastases. During hospitalization radiation exposure rate was measured every day. Patients were discharged when exposure rates < 1.8 mR/hr at 1 meter. After radioiodine therapy, patients with gross residual disease received external beam radiotherapy (whole neck irradiation up to a total dose of 50-60 Gy over 5-6 weeks) by 2 anterior oblique fields excluding the spinal cord. All patients were put on a suppressive dose of L-thyroxine and kept under regular follow up. Three months later, the patients were seen for clinical

evaluation and measurement of TSH to check for adequate TSH suppression. Then 6-12 months after radioiodine therapy, a follow-up radioiodine whole body scan was performed for each patient. If there was persistent abnormal radioiodine uptake, a 2nd dose of I131 was given. When 2 consecutive scans, one year apart, are negative and serum thyroglobulin has not increased, radioiodine scans should be repeated every 3-5 years.

Results. Clinical characteristics. The current study included 87 patients with a histopathologically confirmed diagnosis of well-differentiated thyroid carcinoma, referred for radioiodine therapy at the Nuclear Medicine Unit, Oncology Center, KAAH, Jeddah, KSA during the period between January 1993 and June 1999. Seventy seven percent were female and the female to male ratio was 3.5:1 (Table 1). The age of patients ranged between 13-63 years with a median age of 36 years. Cervical lymph node involvement was detected in 22 patients (25%). Metastases in neck nodes were detected by clinical examination, neck ultrasonography or whole body I131 scan. Distant metastasis was found on clinical, radiologic and radionuclear assessment performed at presentation in 4 patients. The lungs (2 patients) bone (1 patient) or both (1 patient) were the sites of the metastatic deposits.

Extent of surgery. In 66 patients (76%), fine needle aspiration (FNA) confirmed the diagnosis of

Table 1 - Age, sex and metastatic deposit at presentation in 87 patients with differentiated thyroid carcinoma.

Variable	No (%)
Sex	
Male	20 (23)
Female	67 (77)
Female:Male - 3.5:1	
Age in years	
Median	36
Range	13-63
<30	28 (32)
30-<45	33 (38)
≥45	26 (30)
Cervical Lymphadenopathy	
Absent	65 (75)
Present	22 (25)
Distant Meastasis	
Absent	83 (95)
Lung	2 (2)
Bone	1 (1)
Lung and bone	1 (1)

Table 2 - Extent of surgery in 87 patients with differentiated thyroid carcinoma.

Extent of surgery	No (%)
Thyroidectomy	
Subtotal	28 (32)
One-step near-total	38 (44)
Completion near-total (Re-operation)	21 (24)
Cervical lymph node dissection	
Not done	69 (79)
Unilateral	14 (16)
Bilateral	4 (5)

cancer before surgery; Subtotal thyroidectomy (28 patients) or near-total thyroidectomy (38 patients). For the other 21 patients, the diagnosis of cancer was not known before surgery due to the lack of the facility for diagnosis by FNA at the referring hospital (14 patients) or because the FNA was indeterminate (7 patients). These patients were subjected to partial thyroidectomy or lobectomy at the first operation then they underwent completion thyroidectomy (Table 2). Cervical lymph nodes dissection was performed in 18 patients [(unilateral (14) and bilateral (4)]. The primary tumor in the thyroid was very small (few millimeters) in 3 patients who presented by cervical lymphadenopathy.

Pathologic characteristics. Papillary carcinoma was encountered in 78 patients (90%) and follicular carcinoma in 9 patients (10%). Follicular variant of papillary carcinoma was found in 12 cases (14%). The primary tumor was larger than 2 cm in all but 3 patients who had very small tumor (few millimeters) and presented with cervical lymphadenopathy. Approximately half of the study group (51%) had tumor measuring less than 3 cm. Only in 9 patients (11%) the primary tumor was larger than 4cm. Capsular invasion was documented histopathologically in 27 patients (31%). During surgery, extrathyroid extension was seen in 7 patients and in 3 of them there was post-operative gross residual tumor. Microscopic extrathyroid extension was also confirmed histopathologically in 4 more patients (Table 3).

Age of the patient and other risk factors. In an attempt to identify the correlation of the age of the patient at presentation and other risk factors, the study group was divided in 3 age groups. Group A included 28 patients younger than 30 years, group B included 33 patients ranging between 30 and 45 years and group C included 26 patients older than 45 years. Analysis of the clinicopathologic characteristics showed no statistically significant difference between patients in the 3 groups except for extrathyroid

extension and lymph node involvement. Patients older than 45 years had a statistically significant lower incidence of nodal involvement and a higher incidence of extra thyroid extension ($P < 0.02$) (Table 4).

Radioiodine therapy. The I-131 uptake in the neck, post-operatively, was not available in the files of all the patients included in the current retrospective study. High dose method (Radioiodine-131 dose 75-100mCi) for thyroid remnant ablation was given to 67 patients. Iodine 131 dose of 150 mCi was used in 12 patients with radioiodine-avid cervical lymph nodes and in 3 patients with gross residual tumor. In 4 patients with distant metastases I131 dose of 200 mCi was used (Table 5). One patient had no thyroid remnants or abnormal tracer uptake in the radiiodine whole body scans so that he did not receive radioiodine therapy. Follow up serum thyroglobulin measured in this patient 3 months later was low (1.2 ng/ml). Radioiodine therapy was tolerated well in all patients. However, acute and subacute treatment related morbidity occurred in some e.g. nausea and gastric upset in 30 (34%), vomiting in 4 patients (4.5%), pain and swelling due to sialoadenitis in 7 patients (8%).

Table 3 - Pathologic characteristics of 87 patients with differentiated thyroid carcinoma.

Pathological characteristics	No (%)
Histopathologic subtype	
Follicular	9 (10)
Papillary	78 (90)
-Follicular variant	12 (14)
-Tall-cell variant	2 (2)
-Diffuse sclerosis variant	1 (1)
Size of the tumor	
-Range (cm)	2-7
-Median (cm)	2.8
*2-<3 cm	45 (51)
3-<4 cm	33 (38)
≥4cm	9 (11)
Capsular invasion	
Absent	60 (69)
Present	27 (31)
Extrathyroid soft tissue invasion	
Absent	76 (87)
Microscopic	4 (5)
Macroscopic**	7 (8)
*Three patients had small primary tumor with metastatic cervical lymphadenopathy. **Gross residual disease was left behind after surgery in 3 cases.	

Table 4 - Clinicopathologic characteristics in different age groups of 87 patients with differentiated thyroid carcinoma.

Clinicopathological characteristics	Group (A) <30 years No=28 (%)	Group (B) 30=45 years No=33 (%)	Group (C) ≥45 years No=26 (%)
Sex			
Female:Male	3.7:1	3.7:1	3.3:1
Cervical lymph node involvement	10 (35)*	8 (24)	4 (15)*
Distant metastases	1 (3.5)	2 (6)	1 (4)
Surgery			
Subtotal thyroidectomy	9 (32)	12 (36)	7 (27)
Near-total thyroidectomy	19 (68)	21 (64)	19 (73)
Lymph node dissection	7 (25)	7 (21)	4 (15)
Size of the tumor in cm Median	2.6	2.9	3.1
Histopathologic subtype			
Papillary	26 (93)	29 (88)	23 (88)
Follicular	2 (7)	4 (12)	3 (12)
Capsular invasion	6 (21)	10 (30)	11 (42)
Extrathyroid soft tissue invasion	1 (4)*	3 (9)	7 (27)*
*P<0.02			

Patients were hospitalized for an average period of 3 days (range 2-7 days) and discharged when radiation exposure rate <1.8 mR/hr at 1 meter. Follow up radioiodine whole body scan performed 6-12 months later showed persistent tracer uptake in 4 patients with thyroid remnants (successful ablation in 94%), in 2 patients with cervical lymph nodes metastases, in one patient with residual tumor and in 2 patients with distant metastases (bone deposits). A 2nd dose of radioiodine 131 was given to these patients with good response as documented by follow-up serum thyroglobulin and radioiodine scans. During the period of follow up no late effects attributed to radioiodine therapy were observed.

External beam radiotherapy. Following radioiodine therapy, the 3 patients with gross residual extrathyroid disease in the neck received external beam radiotherapy, (whole neck irradiation up to 50-60 Gy over 5-6 weeks). Two of them showed local tumor progression, treatment was well tolerated. External beam radiotherapy was also given for 2 more patients older than 45 years with histopathologic evidence of microscopic positive surgical margins. Both remained clinically free during the study period.

Survival and relapse rates. Out of the 87 patients included in the current study 74 were evaluable for treatment results with a median follow-up of 38 months (range 15-76 months), 7 patients showed

Table 5 - Radioiodine therapy in 87* patients with differentiated thyroid carcinoma.

Indication	No of patients	Dose of I 131	Persistent I131 uptake in follow-up radio iodine scan after 6-12 months
Thyroid remnant ablation	67	75-100 mci	4
Cervical lymph nodes	12	150 mci	2
Residual tumor	3	150 mci	1
Distant metastasis	4	200 mci	2
*One patient had no significant I 131 uptake at the thyroid bed or other areas so that he did not receive radioiodine therapy I131 - Iodine 131			

Table 6 - Clinicopathologic characteristics of 7 patients with differentiated thyroid carcinoma showing treatment failure (locoregional recurrence and distant metastasis or both).

No	Age (yrs)	Sex	Extent of surgery	Size of the tumor (cm)	Histopathology	Lymph node involvement	Capsular invasion	Extrathyroid extension	Disease free interval (yrs)	Site of treatment failure
1	58	F	Subtotal thyroidectomy	3.5	Papillary (follicular variant)	Absent	Present	Absent	5	Local recurrence
2	49	M	Near-total thyroidectomy (completion)	4	Follicular	Absent	Present	Present	3.5	Local recurrence
3	45	F	Subtotal thyroidectomy & LN dissection	2.8	Papillary	Present	Absent	Absent	3	Cervical lymph nodes
4	55	F	Near-total thyroidectomy	5	Papillary	Absent	Present	Present	3	Local recurrence
5	25	F	Subtotal thyroidectomy	3.2	Papillary	Absent	Absent	Absent	2	Cervical lymph nodes
6	61	M	Near-total thyroidectomy (completion)	2.5	Follicular	Absent	Present	Absent	1.5	Lung & bone metastases
7	52	M	Near-total thyroidectomy	3	Papillary	Absent	Absent	Absent	4	Increased serum thyroglobulin

LN - Lymph node; yrs-years

treatment failure (9%). The clinico pathologic characteristics of these patients are illustrated in Table 6. During follow-up, patient number 7 showed elevated levels of serum thyroglobulin. Clinical examination and imaging investigations (including: I131 whole body scan, neck ultrasound, chest CT and whole body thallium scan) could not identify the site of recurrence. However, an I131 dose of 100 mCi was given. Post-therapeutic radioiodine scan was unremarkable. But follow-up serum thyroglobulin measured 4 months later dropped from 32ng/ml to 12 ng/ml. Patients with disease relapse were treated by surgical excision for loco-regional recurrence followed by radioiodine therapy. Similarly the patient with distant metastases received radioiodine therapy. All these patients are still under treatment and follow-up. For the whole study group the 5-year overall survival and disease free survival was 96% and 88%.

Discussion. The key decision in the surgical management of thyroid cancer is how extensive a resection to perform and how the choice relates to outcome as well as operative morbidity. In Mazzaferri's¹¹ and De Grout¹² large retrospective analysis, conservative operation was shown by multivariate analysis to be an independent variable associated with both a higher recurrence rate and a higher overall death rate. In the current study we

favour total thyroidectomy as it eradicates multicentric disease, facilitates post-operative radioiodine ablation and allows thyroglobulin levels to be used as a tumor marker for follow-up.¹³ Therefore, the 21 patients who were subjected to conservative surgery were sent later for completion of near-total thyroidectomy. The development of FNA cytology and its proven accuracy has significantly reduced the proportion of nodules that are surgically excised and that turn out to be cancer.⁵ In the current study, FNA confirmed the diagnosis of thyroid carcinoma in 76% of our patients, so that they were subjected directly to subtotal or near-total thyroidectomy. Although lymph node metastases from differentiated thyroid carcinoma correlates with increased local recurrence, they do not carry a poorer prognosis per se as seen in several series.¹⁴⁻¹⁶ Other investigators have noted a positive correlation between lymph node metastases and outcome.^{17,18} Therefore, the surgical management of lymph node deposits is somewhat controversial. In the current study, 18 patients were subjected to neck-node dissection (unilateral or bilateral). We do not recommend formal modified radical dissection as the prognostic significance of nodal involvement is not well established and also because small lymph nodes with good I131 uptake can be eradicated by radioiodine therapy. In the current study, 4 patients with iodine-avid small cervical lymph nodes were treated by radioiodine without undergoing lymph

node dissection. In one of these patients, more than one dose of I131 was required to eradicate the involved lymph nodes. On the other hand only one patient with positive lymph nodes at presentation showed local recurrence after 3 years of diagnosis in spite of being subjected to unilateral cervical lymph nodes dissection before radioiodine therapy. This finding may draw attention to the importance of external beam irradiation in such cases. Farahati et al¹⁹ concluded that adjuvant external beam radiotherapy might have a role in improving the recurrence-free survival in patients older than 40 years with invasive papillary thyroid carcinoma and lymph node involvement. However, Lerch et al.²⁰ showed that total thyroidectomy followed by high dose radioiodine therapy and early surgical intervention in cases of locoregional recurrence, yielded a high survival rate even without adjuvant external irradiation. In the current study, external beam radiotherapy was given to 5 patients with extrathyroid extension (ETE), 3 with gross residual disease and 2 patients > 45 years with microscopic positive surgical margin. Out of the 7 patients with relapse, 2 had ETE in spite of the relatively low incidence of ETE among the study group (13%). This demonstrates the poor prognostic significance of the presence of ETE at presentation regardless of the treatment modality. Several investigators^{21,22} showed that patients with ETE are more likely to die of their disease and to fail at all sites. Also, it was found that survival in older patients was not affected by incomplete excision while it was in younger patients. Prognostic factors associated with differentiated thyroid cancer include the patient's age at the time of diagnosis, tumor size, extrathyroid extension, nodal status, distant metastasis, operative procedures, sex and histopathology. Multivariate analysis showed that distant metastases, ETE age and tumor size were the most significant prognostic factors.²³ However, Coburn and Wanebo¹⁰ suggested that the prognostic importance of age in thyroid cancer may be due to the greater prevalence of pathologic risk factors in older patients. In the current study, we tried to correlate age with other risk factors. We found statistically significant association between older age and ETE. Higher incidence of lymph node involvement was encountered in younger patients. This finding was previously observed by many investigators.²⁴ The post-operative treatment of patients with well-differentiated thyroid cancer, particularly relating to radioiodine therapy is controversial. The dose of I131 for ablation is not standardized. Some recommend low-dose ablation with less than 30 mCi given as an outpatient with the successful ablation rate ranging between 27% to 83%. But with this method repeated doses are usually required for ablation.^{25,26} Higher ablative doses

ranging from 100 to 150 mCi should be used for older high risk patients particularly those known to have an incomplete resection of the primary tumor, an invasive primary tumor or metastases with a successful ablative rate of 87%.²⁷ Doses may be calculated using one of several dosimetric approaches or a standard fixed dose may be used for all patients.⁵ In the current study, we achieved complete ablation with the use of high dose (75 mCi-100mCi) of I131 in 94% of patients after one dose. This high ablative dose was well tolerated by all patients without serious morbidity. Patients were hospitalized on average for 3 days and discharged from the hospital when radiation exposure rate was < 1.8 mR/hr at 1 meter. The policy of hospital discharges depending on exposure rate measurement enabled us to accommodate all patients within the same available space limitations. This observation was reported previously by Mohammadi et al.²⁸ Serum thyroglobulin has a pivotal role in the post-operative surveillance of patients with a differentiated thyroid carcinoma. After the elimination of thyroid tissue by total thyroidectomy or by combined surgical treatment and radioiodine therapy, increased thyroglobulin levels may be a useful indicators of the presence of metastatic differentiated thyroid carcinoma. Pineda et al²⁹ treated elevated serum thyroglobulin in 17 patients with papillary thyroid cancer in whom diagnostic whole body scans were negative by radioiodine 131 (150-300 mCi). Reduction of the serum thyroglobulin level was observed. They concluded that this therapeutic approach might be effective in improving prognosis and survival of such patients. In the current study we used the same therapeutic approach in one patient who presented while on follow-up by increased serum thyroglobulin with negative radioiodine scan. Following radioiodine therapy there was a response by decreasing level of serum thyroglobulin.

The current study, as many others, concluded that although little doubt exists regarding the pivotal role of FNA biopsy in the pre-operative diagnosis of thyroid cancer, each step in the subsequent management gives rise to controversy. Part of the controversy results from the lack of prospective controlled therapeutic trials and the continuing reliance on novel therapies that are often compared with inappropriate controls. As cancer-related deaths are mediated through biologically significant recurrent events at local or distant sites, a better understanding of independently important prognostic variables may result in improved patient care and treatment.³⁰ Considerable debate continues, particularly with regard to the extent of primary surgical resection, the need for extensive regional lymph node dissection and the role of external irradiation and radioiodine therapy.

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