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The Relationship of Age and Clinicopathologic Pattern to the Aggressiveness of Thyroid Cancer

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Abstract

Objective: To study the relation of age and clinicopathologic pattern to the aggressiveness of thyroid cancer cases and the treatment results of patients from western region of Saudi Arabia with differentiated thyroid carcinoma referred for treatment in King Abdulaziz Hospital and Oncology Center, Jeddah, Saudi Arabia. **Methods:** Retrospective review of 174 patients with differentiated thyroid carcinoma and analysis of the clinicopathologic characteristics, age correlation to different risk factors, treatment protocol and results were performed. **Results:** Analysis of the clinicopathologic pattern 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 a higher rate of extrathyroid extension (<0.02). In this study, we used a high dose method (Radioiodine-131 dose 75 - 100 mCi) for thyroid remnant ablation after thyroidectomy (total or near total) in 134 patients. An Iodine-131 dose of 200 mCi was used in 8 patients with distant metastases. In 24 patients with radioiodine-avid cervical lymph nodes and six patients with a gross residual tumor, an Iodine-131 dose of 150 mCi was used. For the whole study group, the 5-year overall survival and disease-free survival were 96% and 88%. **Conclusion:** Despite the fact that differentiated thyroid carcinoma is among the most curable cancer some patients are still at high risk for recurrent and increased mortality.

Keywords

Radioiodine Therapy, Thyroid Cancer, Thyroidectomy

1. Introduction

Differentiated thyroid carcinomas are relatively rare despite that thyroid nodules

are common. Thyroid carcinoma constitutes less than 1% of all cancer. The median age at diagnosis is 45 to 50 years. The incidence of thyroid carcinomas are 2.9 times more common in women than men. It is one of the fastest growing tumors [1] [2].

In Saudi Arabia, thyroid carcinomas accounted for 11% of all newly diagnosed female cancers [3].

This cancer ranked 2nd for females and 14th for males. Papillary and follicular thyroid carcinomas are among the most curable cancers. However, for several decades the management of differentiated thyroid cancer has been controversial. However, the treating doctor must weigh the risk of complications versus any potential benefit carefully since most thyroid cancers behave indolently, and complications of the disease or the treatment could be lifelong [4]. For the majority of patients, standard initial management consists of thyroidectomy followed by radioiodine ablation, but there is considerable controversy regarding the ablative dose of Iodine-131 and its indication [5] [6]. Other conventional modes of neoplastic treatment: chemotherapy and external beam radiation have much weaker results and consequently are much less studied [7] [8].

The overall survival rate at 10 years and 15 years for middle-aged adults with thyroid carcinoma is approximately 97% and 95% respectively. About 5% - 20% of patients have local or regional recurrence, and around 10% have distant metastasis. The prognostic indicators of recurrent disease and death are the old age, the histopathology subtype and the distant metastasis [9]. The relationship between these factors remains incompletely defined. However, Coburn and Wanebo concluded that the prognostic importance of age in thyroid cancer might be due to the higher prevalence of pathologic risk factors in older patients [10] [11]. In our research, we study all patients referred for surgery and radioiodine therapy at our oncology center as regards the age, the clinicopathologic characteristics correlation to different risk factors as well as treatment results.

2. Methods

In this research, we studied 174 patients with the diagnosis of thyroid carcinoma referred for treatment in Oncology Center, King Abdulaziz Hospital (KAAH), Jeddah, Kingdom of Saudi Arabia, during the period between 1997-2012. To identify the possible relation between the age of the patient at presentation, the clinicopathological pattern and the distant metastasis, all patients with thyroid cancer referred for surgery had been admitted in this study. The study group was divided 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.

In the outpatient clinic, all patients had been subjected to full clinical examination, laboratory investigations (complete blood count, thyroid function tests, serum thyroglobulin, renal profile, serum calcium), neck ultrasonography, chest x-ray and thyroid scan. The details of histopathology should include the

size of the tumor, tumor subtype, presence of capsular invasion or extrathyroid extension or both.

Diagnostic whole body scan was performed six weeks after surgery, when thyrotrophin (TSH) level > 30 iu/ml, after that, Radioiodine-131 therapeutic dose was given: 75 - 100 mCi for remnant ablation, 150 mCi for lymph nodes metastasis or residual tumor and 200 mCi for distant metastasis. Radiation exposure was measured every day during hospitalization. Patients usually discharged when exposure rate < 1.8 mR/hr at 1 meter. Patient with the gross residual disease after radioiodine therapy, received external beam radiotherapy (whole neck irradiation up to a total dose of 50 - 60 Gy over 5 - 6 weeks) by two anterior oblique fields excluding the spinal cord. A suppressive dose of L-thyroxin was given for all patients and kept under regular follow up. Clinical evaluation of all patients and measurement of TSH to check for adequate TSH suppression three months later. A follow-up radioiodine whole body scan was performed for each patient 6 - 12 months after radioiodine therapy. If there was persistent, abnormal radioiodine uptake, the second dose of I131 was given. When two consecutive scans, one year apart, are normal and serum thyroglobulin has not increased, radioiodine scans should be repeated every 3 - 5 years.

3. Results

Clinical characteristics: 174 patients with a confirmed diagnosis of well-differentiated thyroid carcinoma. Twenty-four percent were male, and the male to female ratio was 1:3.2 (Table 1). The age of patients ranged between 15 - 70 years with a median age of 42 years. Cervical lymph node involvement had been detected in 45 patients (26%) by ultrasonography or whole body I131 scan. Eight patients were found to have distant metastasis by a clinical, radiologic and radionuclear assessment performed at presentation, bone (2 patients), lungs (4 patients) or both (2 patients).

The extent of surgery: Fine needle aspiration (FNA) confirmed the diagnosis of cancer before surgery in 134 patients (77%). Those patients underwentnear total thyroidectomy (104 patients) and subtotal thyroidectomy (29 patients). For the other 41 patients, the diagnosis of cancer was not known before surgery due to lack of the facility for determination by the FNA at the referring hospital. These patients underwent completion thyroidectomy (Table 1). Cervical lymph nodes dissection was performed in 38 patients (bilateral 9 patients & unilateral 29 patients). In eight patients who presented with cervical lymphadenopathy the primary tumor in the thyroid was very small.

Pathologic pattern: Papillary carcinoma was found in 155 patients (89%) and follicular carcinoma in 19 patients (11%). In 145 patients, the primary tumor was larger than 2 cm and less than 4 cm, whileonly in 21 patients (12%), it was larger than 4 cm. Capsular invasion was documented histopathologically in 54 patients (31%). An extrathyroid extension was seen in 14 patient intraoperatively, and in 8 of them, there was gross residual tumor postoperatively. A microscopic

Table 1. Patients & tumor characteristics.

Variable	No	%
Sex		
Male	42	24
Female	132	76
Age		
Median	42	
Range	15 - 70	
<30	56	32.2
30 - 45	66	37.9
>45	52	29.9
Cervical Lymphadenopathy		
Absent	129	74
Present	45	26
Distant Metastasis		
Absent	166	95.4
Lung	4	2.3
Bone	2	1.15
Lung and bone	2	1.15
Extent of surgery Thyroidectomy		
Subtotal	29	17
One step near-total	104	60
Completion near total (Re operation)	41	23
Cervical lymph node dissection		
Not done	136	78
Unilateral	29	17
Bilateral	9	5

extrathyroid extension was also confirmed histopathologically in 8 more patients (Table 2).

Risk factors: In this study three groups were identified depending on the correlation between the age of the patient at presentation with other risk factors such as sex, tumor size, nodal status, extra thyroid extension, distant metastasis, operative procedure, and histopathological pattern. Group A patients younger than 30 years, included 56 patients, group B patients ranging between 30 and 45 years comprised 66 patients, and group C included 52 patients older than 45 years. Analysis of the clinicopathologic pattern showed no significant difference between patients in the three groups except for lymph node involvement and extrathyroid extension. Patients older than 45 years had statistically significant lower incidence nodal involvement and a higher incidence of extrathyroid extension (Table 3).

Table 2. Pathologic characteristics.

Pathological characteristics	No	%
Histopathologic subtype		
Follicular	19	11
Papillary	155	89
Size of the tumor		
Range (cm)	2 - 7	
Median (cm)	2.6	
<2 cm	8	5
2 - 3 cm*	92	53
3 - 4 cm	53	30
>4 cm	21	12
Capsular invasion		
Absent	120	69
Present	54	31
Extra thyroid soft tissue invasion		
Absent	152	87
Microscopic	8	5
Macroscopic**	14	8

*Eight patients had small primary tumor with metastatic cervical lymphadenopathy. **Gross residual disease was left behind after surgery in eight cases.

Table 3. Clinicopathological pattern in relation to different age groups.

Clinicopathological characteristics	Group (A) <30 years No.	Group (B) 30 - 45 years No.	Group (C) >45 years No.
Sex			
Female:Male	3.6:1	3.5:1	3.4:1
Cervical lymph node involvement	20	17	8
Distant Metastasis	2	4	2
Capsular invasion	13	21	20
Extra thyroid soft tissue invasion	2	6	14
Surgery			
Subtotal thyroidectomy	11	13	5
Near-total thyroidectomy	35	43	26
Lymph node dissection	13	15	10
Size of the tumor in cm (Median)	2.65	2.95	3.15
Histopathologic subtype			
Papillary	43	61	51
Follicular	4	7	8

$P < 0.02$.

Radioiodine therapy: High dose method (Radioiodine-131 dose 75 - 100 mCi) for thyroid remnant ablation was given to 134 patients. Iodine dose of 150 mCi was used in 24 patients with radioiodine-avid cervical lymph node and to 6 patients with a gross residual tumor. In 8 patients with a distant Metastasis-131 dose of 200 mCi was used (Table 4). Two patients had no thyroid remnant or abnormal tracer uptake in the radioiodine whole body scan so that they did not receive radioiodine therapy, their serum level of thyroglobulin was low (1.2 ng/ml) after three months of follow up. Despite that all patients tolerated the radioiodine therapy, few acute and sub-acute treatment-related morbidity occurred in some, e.g., vomiting in 8 patients, pain, swelling due to sialoadenitis in 14 patients and nausea and gastric upset in 60 patients. Patients were hospitalized for an average mean of 3.5 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 successful ablation in 154 patients and persistent tracer uptake in 8 patients with thyroid remnants (5%), in 4 patients with cervical lymph node metastasis (2%), in two patients with residual tumor (1%) and in four patients with distant metastasis (bone deposits) (2%). A second dose of Radioiodine-131 was given to these patients with a 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. Following radioiodine therapy, the six 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). Four of them showed local tumor regression, and treatment was well tolerated. External beam radiotherapy was also given for four more patients older than 45 years with histopathologic evidence of microscopic positive surgical margin.

Survival and relapse rates: Out of the 174 patients included in the current study 148 were evaluable for treatment results with a median follow up of 46 months (range 26 - 62 months), 15 patients showed treatment failure (9%). 26 patients did not come for follow up because they transfered to another city or they felt that they were well and no need for follow up. During follow up, 2 patients showed elevated levels of thyroglobulin. Clinical examinations and imaging investigations (neck ultrasound, I131 whole body scan, chest computer

Table 4. Radioiodine (I131) therapy.

Indication	No. of patients	Dose of I131	Persistent I131 uptake in follow-up radio iodine scan after 6 - 12 months
Thyroid remnant ablation	134	75 - 100 mCi	8
Cervical lymph nodes	24	150 mCi	4
Residual tumor	6	150 mCi	2
Distant metastasis	8	200 mCi	4

*Two cases had no significant I131 uptake at the thyroid bed or other areas so that they did not receive radioiodine therapy.

tomography and whole body thallium scan) could not identify the site of recurrence. These two patients received an I131 dose of 100 mCi; post therapeutic radioiodine scan was unremarkable. The measurement of thyroglobulin level four months later dropped from 32 ng/ml to 12 ng/ml. Surgical excision followed by radioiodine therapy treated all patients with recurrence. Similarly, the patient with distant metastasis received radioiodine therapy. For the whole study group, the 5-year overall survival and disease-free survival was 96% and 88%.

4. Discussion

The most crucial role in the treatment of thyroid cancer is the extensive resection to perform and how to weigh the outcome as well as operative morbidity. The degree of surgery for locally aggressive tumors has been the source of considerable controversy [12] [13] [14]. Ernest *et al.*, 2001 and Mazzaferri EL *et al.*, 1995 through substantial retrospective analysis they found that a conservative operation was shown by multi-variant analysis to be an independent variable associated with both a higher recurrence rate and a higher overall death rate [14] [15].

In this research, patients were treated by total thyroidectomy with postoperative radioiodine ablation, and the thyroglobulin levels used as a tumor marker for follow-up [16]. Therefore, the 42 patients who were subjected to conservative surgery were sent later for completion total thyroidectomy. The improvement of the diagnostic value of FNA cytology and its accuracy has significantly reduced the number of nodules that are surgically excised and that turn out to be malignant [17].

In our study, 78% of our patients, were subjected directly to near-total thyroidectomy depending on FNA confirmed the diagnosis of thyroid carcinoma. Increased local recurrence correlates with lymph node metastasis from differentiated thyroid carcinoma, and they don't carry a lousy prognosis as seen in several series [18] [19]. Other investigators have noted a healthy relationship between lymph node metastasis and outcome of thyroid cancer [20] [21]. Therefore, the surgical excision of cervical lymph node deposits is somewhat controversial. About 36 patients underwent neck dissection (bilateral or unilateral). In our center we didn't recommend radical neck dissection as the prognostic significance of nodal involvement is not well established and also because the radioiodine therapy can eradicate small lymph nodes with a good I131 uptake. Radioiodine therapy treated eight patients with iodine-avid small cervical lymph nodes without undergoing lymph node dissection. In two of these patients, more than one dose of I131 was required to eradicate the involved lymph nodes. On the other hand, only two patients with lymph node metastasis at presentation showed local recurrence after four years of diagnosis in spite of being subjected to cervical nodes dissection and radioiodine therapy. Because of that, the use of external beam irradiation is essential in such cases, and that adjuvant radiotherapy might have a role in preventing the recurrence of thyroid cancer in patients with invasive papillary thyroid carcinoma and lymph node

involvement [22] [23]. However, Lerch *et al.*, 1997, showed that early surgical intervention in cases of locoregional recurrences which were treated previously by total thyroidectomy followed by high dose radioiodine therapy yielded a high survival rate even without adjuvant radiotherapy [24].

In our study, external beam radiotherapy was given to ten patients with extrathyroid extension (ETE), four patients with positive surgical margin and their ages more than forty-five years and six patients with the gross residual disease. Four patients had extra thyroid extension out of the fourteen patients with relapse. The presence of ETE at presentation leads to poor prognosis regardless of the management modality [25] [26].

Also, it was found that survival in older patients was not affected by incomplete excision while it was in younger patients. The patient sex, age at the time of diagnosis, tumor size, nodal status, extra thyroid extension, distant metastasis, operative procedure, and histopathological pattern, are prognostic factors associated with differentiated thyroid cancer. Many researchers showed that age, tumor size, ETE and distant metastasis, were the most significant prognostic factors [27] [28].

In our research we found that there is a statistically significant association between older age and extra thyroid extension. However, Coburn and Wanebo; 1995, suggested that the prognostic importance of age in thyroid cancer may be due to the higher prevalence of pathologic risk factors in older patients [26] [29]. Also, we found that the incidence of lymph node involvement was high in younger patients. Many investigators previously observed this finding [21] [30] [31].

The dose of radioiodine therapy for post operative patients with well-differentiated thyroid cancer is controversial. Some recommended low-dose of I131 ablation (30, 50 or 75 mCi of I131) But we need to give repeated doses for ablation, the cumulative ablation rate was 99% [32]. Higher ablative treatments ranging from 100 - 150 mCi should be used for older high-risk patients particularly those known to have an incomplete resection of the primary tumor, and invasive primary tumor or metastasis with a success rate of 84% [33].

With the use of high dose (75 mCi - 100 mCi) of I131, we achieved complete ablation in 154 patients after one dose. All patients well tolerated this dose without severe morbidity. Patients were hospitalized on average of 2.5 days and discharged from the hospital when radiation exposure rate was <1.8 Mr/hr at 1 meter [34]. Serum thyroglobulin level has a significant role in the post-operative follow up for patients with differentiated thyroid carcinoma. After total thyroidectomy or by combined total thyroidectomy and radioiodine therapy, increased thyroglobulin levels may be useful indicators of the presence of metastatic thyroid carcinoma. Pineda *et al.*, 1995 treated elevated serum thyroglobulin in 34 patients with papillary thyroid cancer by high dose of Radioiodine-131 (150 - 300 mCi) in spite of negative diagnostic whole-body radioiodine scan, they found that there was a reduction in thyroglobulin level, they concluded that this approach might improve disease-free survival and

overall survival [35]. We used the same therapeutic approach in two patients who presented with increased serum thyroglobulin with negative radioiodine whole body scan. We found that the thyroglobulin level was decreased as a result of radioiodine therapy.

5. Conclusion

Analysis of the clinicopathologic pattern showed no significant difference regarding patient age but patients older than 45 years had statistically significant lower incidence of nodal involvement and a higher incidence of extrathyroid extension. The papillary thyroid cancer is the most common thyroid cancer and it has better prognosis. For patients with differentiated thyroid carcinoma a better understanding of critical prognostic factors will lead to improvement of patient care and treatment. The use of selective preoperative investigation and the planning of the extension of surgery, the postoperative management modality and the close follow up will improve the disease free survival and the overall survival for those patients and also lead to improvement of outcome. Considerable debate continues, particularly with regards to the extent of primary surgical resection, the need for extensive regional lymph node dissection and the role of external beam radiation and radioiodine therapy.

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Conflicts of Interest

The author declares that there is no conflict of interest.

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