International Medical Society
http://imedicalsociety.org

INTERNATIONAL ARCHIVES OF MEDICINE
SECTION: ENDOCRINOLOGY
ISSN: 1755-7682

2018
Vol. 11 No. 4
doi: 10.3823/2545

Disease Free Survival of Well Differentiated Thyroid Cancer: 20 Years Experience at a Tertiary Care Center in Lebanon

ORIGINAL

Rita Hajj Boutros[1], Asma Arabi[1], Mahmoud Shoucair[1], Jaber Abbas [2], Ibrahim Salti[1]

1 Department of Internal Medicine, Division of Endocrinology.
2 Department of Surgery American University of Beirut.

Contact information:

Ibrahim Salti.

Address: Department of Internal Medicine, Division of Endocrinology, American University of Beirut.
Tel: +9611350000.

isalti@aub.edu.lb

Abstract

Background: Thyroid cancer is the most common endocrine malignancy. Although relatively common, to date, there is no study about its prognosis in Lebanon. The objectives of this study were to determine the disease free survival, the recurrence rate and possible predictors of recurrence, as well as the rate of post thyroidectomy complications among patients with differentiated thyroid cancer who received treatment at the American University of Beirut Medical Center.

Methods and Findings: Retrospective observational study of 480 cases of differentiated thyroid cancer who underwent thyroidectomy between January 1995 and June 2014. The mean age was 42±14 years. 74.4% were females. The mean tumor size was 1.9 cm±1.4. Papillary type was predominant (91%). Males had more extra-glandular extension than females (24.8% versus 10.9% respectively, p=0.001), more lymph node involvement (69.7% versus 52.9% respectively, p=0.017) and more vascular invasion (28.1% versus 14.9%, p=0.007). Around 70% of patients had at least one follow up visit after the surgery; among those, the median follow up duration was 4 years (1 month-19 years). At last follow-up visit, 78.7% were disease free, 14.9% had residual disease and only 6.3% had recurrent disease. By multivariate analysis, age greater than 45 years was the only independent predictor of persistence or recurrence (p=0.03) whereas both age below 45 years and lack of vascular invasion were significant predictors of disease free survival (p=0.001 and p=0.019 respectively).

Conclusion: Differentiated thyroid cancer has an overall good prognosis in this cohort of Lebanese patients. Young age and lack of vascular invasion are the most important predictors of disease free survival.

Keywords
Differentiated Thyroid Cancer; Disease Free Survival; Prognostic Factors; Recurrence.

Introduction

Thyroid cancer, the most common endocrine malignancy, has recently witnessed a steady increase in its incidence [1], due not only to medical surveillance and more sensitive diagnostic studies [2], but also to increased exposure to radiation from the increased use of imaging techniques such as computed tomography (CT) and other diagnostic x-rays [3, 4]. Differentiated thyroid cancer (DTC) is the most common type and includes papillary (80%) and follicular (15%) cancers [5]. It accounts for approximately 2% of all malignancies in the US [6]. It is 2-3 fold more common in females than males. It is associated with an overall excellent prognosis and a mortality rate that has been slowly decreasing in spite of the rising incidence of thyroid cancer [1]. Overall, greater than 90% are alive at 10 years after diagnosis. This excellent prognosis results from a combination of the indolent biological behavior of most cases of DTC and effective primary treatment options.

Surgery is the primary treatment for patients with DTC. However, controversy exists as to the optimal extent of thyroidectomy because of the lack of randomized controlled trials (RCT).

Total or near-total thyroidectomy with dissection of involved lymph node basins (therapeutic lymph node dissection) is the standard treatment for DTC [7]. However, up to 80% of patients with papillary thyroid carcinoma (PTC) would have microscopic lymph node metastasis at the time of initial surgery [8, 9]. Accordingly, the American Thyroid Association (ATA) suggests that central neck dissection may be performed in patients with advanced papillary cancer (>4cm and/or extra-thyroidal extension) even in the absence of clinical evidence of nodal involvement.

Adjuvant Radio-active iodine (RAI) is administered after initial surgery for DTC in cases where there exists risk of systemic spread [7, 10, 11]. The optimal dose of adjuvant RAI is also controversial. Low-dose RAI ablation with doses of 30-50 mCi is sufficient for most patients with a lower risk profile [12, 13]. Whereas higher doses ranging from 100-200 mCi should be considered in patients with incomplete resections, invasive primary tumors, tumors of intermediate differentiation, or distant metastasis.

Although the long-term survival of patients with DTC is generally excellent, the recurrence rate is significant ranging between 10%-30% [14]. Approximately 80% of recurrences are locoregional [15, 16]. Many prognostic factors have been identified that permit individualized estimation of recurrence rates and survival and help guide long term oncologic surveillance strategies. The patient's age at the time of presentation is the most important one [8]. Recurrence rates and disease-specific mortality rates are lower in younger than older patients, with a cut off of 45 years [8].

Thyroid cancer prognosis is determined by several variables, even with relatively high survival rate. The

most debatable issues are the type of thyroidectomy, the extent of lymphadenectomy as well as the dose of RAI ablation therapy post-thyroidectomy.

Differentiated thyroid cancer is very common in the Midle East region. To our knowledge, no study was done previously in Lebanon to assess the clinical outcome of less aggressive interventions in the treatment of DTC. Moreover, reaching good outcomes with less aggressive options will spare patients from the complications of extensive surgery and the adverse effects of high dose of RAI.

Objectives

The primary objective of this study was to determine the disease free survival among patients with differentiated thyroid cancer who received treatment at an academic, tertiary care center in Lebanon: the American University of Beirut Medical Center (AUBMC). Secondary objectives were to determine the recurrence rate and possible predictors of recurrence, as well as the rate of post thyroidectomy complications (transient or permanent hypoparathyroidism and vocal cord dysfunction).

Methods

Study design and data collection

This was a retrospective observational study. We conducted chart review of all cases with differentiated thyroid cancer who underwent thyroidectomy at AUBMC over the last 20 years (January 1995 – June 2014). We also included those who underwent thyroidectomy outside AUBMC but received post operative treatment (RAI) at AUBMC. The below relevant information were retrieved from the chart of the patients and included: Age at presentation, Gender, Presence of comorbidities (hypertension, Cardiac diseases, diabetes mellitus, dyslipidemia, pulmonary diseases and other malignancies), personal history of radiation exposure to the neck, family history of thyroid cancer, clinical presentation, characteristics of thyroid nodule(s) on physical exam (if palpable), Lymph node status, size of the nodule that was FNA, baseline thyroid function tests and antibodies, cytology report, date of surgery, type of surgery, dose and frequency of RAI post surgery (if given), result of whole body scan (WBS), post-operative complications (hypoparathyroidism and vocal cord dysfunction), date of last visit and final assessment. Also the pathological reports were reviewed and tumor size, type and subtype, extent, vascular and capsular invasion as well as LN status were recorded.

641cases were retrieved initially from which 161 cases were excluded because of either lack of relevant information, or the charts were not available, or had the thyroid surgery done before January 1995. This left 480 cases for analysis.

Statistical analyses

Continuous variables [age, size of the nodule that was FNA, tumor size, follow up duration] are presented as mean±SD and independent t-test was used to check for difference between groups. Chi-square or Fisher's exact-test were used to assess the correlations between categorical variables. Multivariable analyses were then performed, where using binary logistic models were built, with the disease status was entered as a dependent variable and the potential predictors were entered as independent variables.

Survival analysis were also performed and Kaplan-Meier survival plot were generated to compare the disease free survival of the patients according to some predictors such as age, gender, tumor size, capsular invasion, vascular invasion and lymph node involvement at baseline.

Data was analyzed using SPSS 20. P-value < 0.05 was considered statistically significant.

Ethical clearance

The study was approved by the Institutional Review Board of the American University of Beirut. Data was reviewed and entered for analyses anonymously.

Results

General characteristics of the study population

The general characteristics of the study population are shown in **Table 1**. Female represented around 75% of the population. The mean age was 42±14 [range 6-84] without difference between genders. 10.8% had family history of thyroid cancer and 2.1% had personal history of radiation exposure to the neck, without difference between genders. The most common presentation in both genders was a neck mass (42.3%). Males had more suspected lymph node involvement compared to females by physical examination and by ultrasound (p<0.001). Among those who had TSH record at baseline (n=289), the majority were euthyroid (87.5%), whereas 7.6% were hyperthyroid and 4.8% were hypothyroid without difference between genders. Record for baseline antibody status (anti-thyroglobulin or anti-thyroid peroxidase Ab) was available in 81 cases only, and around one third (28.4%) had at least one anti-thyroid antibody positive. Concerning the type of surgery, 52.5% had underwent total thyroidectomy and 44.8% underwent total thyroidectomy with neck dissection. Males had more neck dissection then females (56.9% versus 40.6%, p=0.006).

Cytological findings by FNA before surgery

Cytology report before thyroidectomy were not available in 123 cases (FNA was not performed in 93 cases, and in 30 cases it was done however the result was not available in their charts), therefore only 357 cases had cytology report prior to surgery. Among those, 13.4% had initially benign cytology report and found on pathology to have DTC (to note that surgery was performed in this group due to compressive symptoms in the majority or for cosmetic reasons), 25.5% had initially suspicious cytology, 44.3% had papillary thyroid cancer

Table 1. General Characteristics of the whole study population and by gender*#.

	Overall (N=480)#		Men N=123#		Women N= 357#		P value**
Age (years): Mean±SD	42±14		42±15		42±13		NS
Range	6-84		9-81		6-84		
	n	%	n	%	n	%	
Family history of thyroid cancer	50/462	10.8	10/121	8.26	40/341	11.7	NS
Personal history of radiation exposure	10/468	2.1	4/121	3.3	6/347	1.7	
Clinical presentation							
Compressive symptoms	50/468	10.6	9/122	73	41/346	11.8	NS
Incidentally	131/468	27.9	32/122	26.2	99/346	28.6	
Neck Mass	198/468	42.3	61/122	50	137/346	39.5	
Others	63/468	13.4	12/122	9.8	51/346	14.7	
Neck mass and compressive symptoms	26/468	5.5	8/122	6.5	18/346	5.2	
Lymph Node suspicious by physical exam	63/402	15.7	30/106	28.3	33/296	11.1	<0.001
Lymph Node suspicious by ultrasound	75/368	20.4	37/100	37	38/268	14.2	<0.001
Baseline thyroid status							
Hyperthyroid TSH<0.27	22/289	7.6	5/70	7.1	17/219	7.8	1
Euthyroid 0.27 ≤TSH ≤ 4.2	253/289	87.5	62/70	88.6	191/219	87.2	
Hypothyroid TSH>4.2	14/289	4.8	3/70	4.3	11/219	5	
Antithyroid antibody status							
At least one antibody positive	23/81	28.4	1/12	8.3	22/69	31.9	0.16
Negative	58/81	71.6	11/12	91.7	47/69	68.1	

*: Data is presented as mean±SD and/or N (%) as appropriate.
**: p-value for difference between gender by independent test for continuous variables (age), and by chi-square or Fisher's exact test for categorical variables.
#: The total number of cases for each variable is different depending on the number of available data for each variable (after excluding the missing information).

on cytology, 9.5% had follicular lesion of uncertain significance, 5.6% had follicular neoplasm and the exam was unsatisfactory in 1.7% of cases **(Table 2)**.

Pathological characteristics of DTC

Table 3 showed the characteristics of thyroid tumor on pathology. The mean tumor size was 1.9 cm [0.1-7cm] with no difference between genders. Papillary type was the predominant type in both genders. Males had more extra-glandular extension of the tumor, more lymph node involvement than females and more vascular invasion than females **(Table 3)**. However, capsular invasion was present in only 22.6% of cases without difference between genders.

RAI treatment post surgery

The majority of patients (83.7%) received radioactive iodine after the surgery. The mean dose was 85milliCurie (mCi) [range from 10-200]. Almost 80% of patients had evidence of residual disease after the surgery manifested by increase uptake in the thyroid bed and in the neck area on whole body scan.

Post operative complications

35.8% developed hypocalcemia post surgery, defined as total calcium level below 8mg/dl; and this was more evident in females than in males (39.1% versus 26.1%, p=0.013) and it was transient in the majority of cases. Only 5% developed transient vocal cord dysfunction after the surgery, without difference between genders

Follow up post surgery

70.4% of patients had at least one follow up visit after the surgery; among those, the median follow up duration was 4 years (range 1 month-19years). Disease free at last visit was defined as no evidence of disease clinically (negative physical exam), biochemically (stimulated thyroglobulin less than 2ng/dl or unstimulated thyroglobulin less than 0.1ng/dl) and radiologically (normal neck ultrasound and/or scan). Residual disease was defined as biochemical and/or radiological evidence of disease after the initial surgery, whereas recurrent disease is defined as biochemical, radiological and/or clinical evidence of disease after a disease free state.

78.7% were disease free at last follow up visit, 14.9% had residual disease and only 6.3% had recurrent disease.

Table 2. Cytological findings by Fine Needle Aspirate (FNA) before surgery.

Cytology diagnosis	Number	%*
Benign	48	13.4
Suspicious for malignancy	91	25.5
Malignant (Papillary Thyroid Cancer)	158	44.3
Follicular lesion of uncertain significance	34	9.5
Follicular neoplasm	20	5.6
Unsatisfactory	6	1.7
Total	357	100

*: Calculated based on a total of 357 cases in whom FNA results were available.

Table 3. Characteristics of DTC on pathology*#.

	Overall (N=480)#		Men N=123#		Women N= 357#		P value**
Tumor size (cm)	1.91		2.08		1.85		0.15
Tumor extent	n	%	n	%	n	%	
Intraglandular	352	85.4	82	75.2	270	89.1	0.001
Extraglandular	60	14.6	27	24.8	33	10.9	
Lymph node involvement							
N0	103	41.9	23	30.3	80	47.1	0.017
N1	143	58.1	53	69.7	90	52.9	
Type of cancer							
Papillary	433	91	113	91.9	321	90.7	0.48
Follicular	41	8.6	9	7.3	32	9	
Both	2	0.4	1	0.8	1	0.3	
Vascular invasion							
Yes	64	18.3	64	71.9	222	85.1	0.007
No	286	81.7	25	28.1	39	14.9	
Capsular invasion							
Yes	76	22.6	17	21	59	23.1	0.76
No	260	77.4	64	79	196	76.9	

* Data is mean±SD or N(%) as appropriate. **: P-value for difference between gender by independent t-test for continuous variables (age), and by chi-square or Fisher's exact test for categorical variables. #: Percentage was calculated based on the total number of patients in whom information was available.

Table 4. Comparison of potential predictors of disease recurrence/persistence between those who were disease free and those who had recurrent/residual disease at last visit*.

	Disease free	Recurrent or residual disease	P value**
Age at presentation (years)	41±13.1	46±17.4	0.02
Tumor size (cm)	1.8±1.3	2.3±1.7	0.05
Folow up duration (years)	4.8±4.0	4.5±4.6	0.57
Type of surgery			
Lobectomy	1.5	2.7	0.10
Total thyroidectomy	48.5	36.5	
Total thyroidectomy with neck dissection	50	60.8	
LN status on pathology			
N0	44	25.6	0.03
N1	56	74.4	
Vascular invasion			
N0	83.2	68.7	0.02
N1	16.8	31.3	
Capsular invasion			
N0	78.7	60	0.01
N1	21.3	40	
RAI post surgery			
Yes	85.2	90.3	0.33
No	14.8	9.7	
Family history of thyroid cancer			
Yes	10.8	11.3	1
No	89.2	88.7	
Personal history of radiation exposure			
Yes	1.8	4.1	0.37
No	98.2	95.9	
Anti-thyroid antibodies			
Negative	66.7	100	0.09
Positive (at least one)	33.3	0	

*: Data are Mean±SD and/or percentage as appropriate. **: P value for difference between disease free and recurrent/residual disease by independent t-test for continuous variables, and by Chi-aquare or Fisher's exact test for categorical variables.

Predictors of disease persistence/ recurrence

Male gender was a predictor of recurrent and/or residual disease (71%) of men versus 81.4% of women were disease free at the last follow up visit, p<0.05). Other predictors are shown in **Table 4**. Age was a significant predictor of disease persistence/recurrence: the mean age was 41±13years for disease free group compared to a mean age of 46±17 years for recurrent/persistence disease (p=0.02). Tumor size was also a significant predictor of disease persistence and/or recurrence with a larger tumor size for the recurrent/residual disease group compared to disease free group (Mean tumor size 2.3±1.7cm vs 1.8±1.3cm; P=0.05). Furthermore, lymph node involvement, vascular and capsular invasion were also found to be predictors of disease persistence/recurrence (p<0.05 for all comparisons).

After adjustment for age, gender, tumor size, capsular invasion, lymph node involvement and vascular invasion: only age remains a significant predictor of persistence or recurrence of disease (beta estimate 0.03 and p-value 0.03). **(Table 4)**

Predictors of disease free survival

Age was a significant predictor of disease free survival (DFS): The median DFS for those who are younger than 45 years at baseline was 18 years whereas the median DFS for those 45 years or older was 13 years, and the difference was statistically significant (p=0.01) **(Figure 1)**

Furthermore, vascular invasion was also found to be a significant predictor of DFS with a median DFS of 12 years for those with vascular invasion com-

Figure 1: Disease free survival by age.

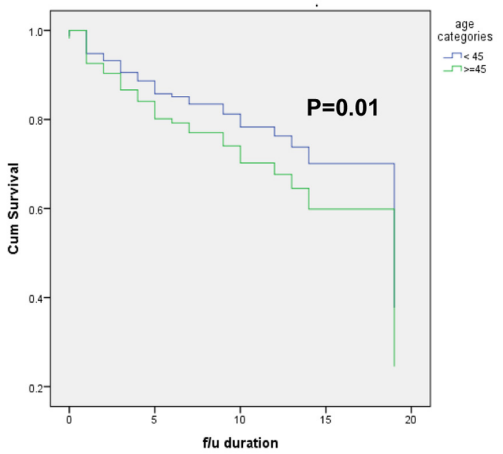


Figure 2: Disease free survival by gender.

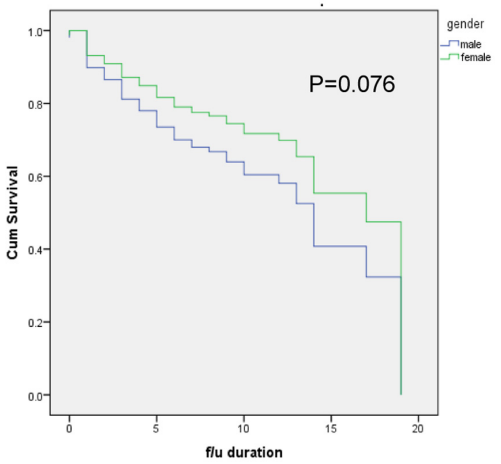


Figure 3: Disease free survival by tumor size.

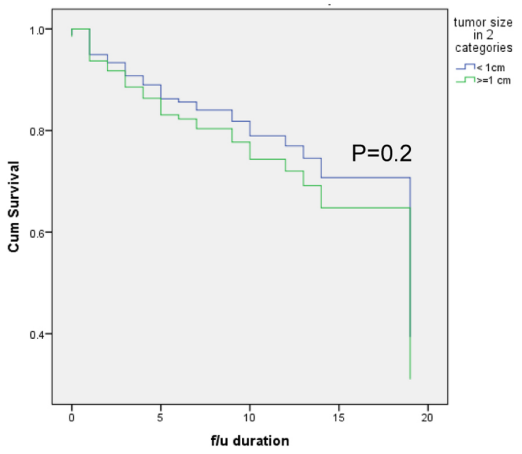
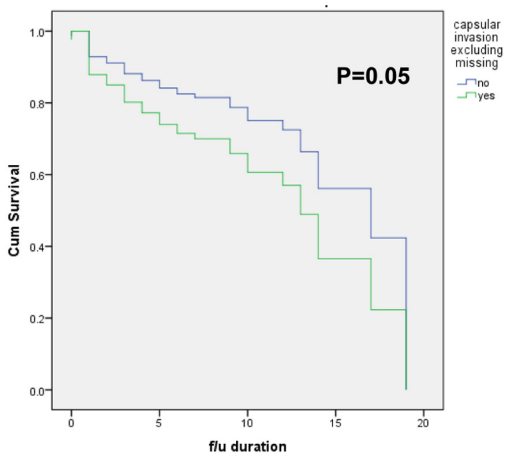


Figure 4: Disease free survival by capsular invasion.



pared to a median of 17 years for those without (p=0.009). **(Figure 5)**

Similarly, those with capsular invasion had shorter disease free survival (median DFS is 13y) compared to those without capsular invasion (median 14y), p=0.05. **(Figure 4)**

Whereas gender, tumor size and lymph node status were not found to be significant predictors of DFS **(Figure 2, 3** & **6)**.

After adjusting for age, vascular invasion, tumor size and capsular invasion, both age and vascular invasion remained statistically significant as predictors of DFS (p=0.001 and p=0.019 respectively).

Figure 5: Disease free survival by vascular invasion.

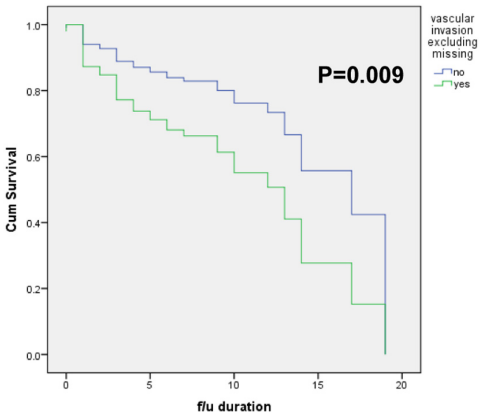
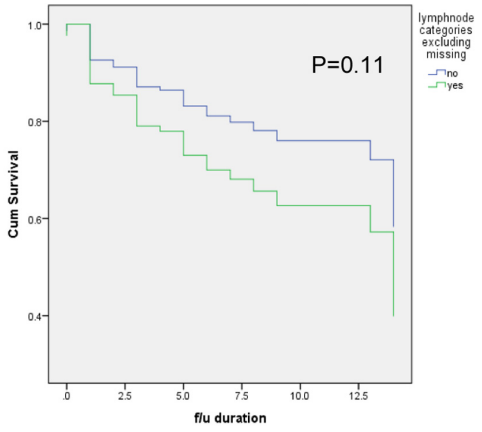


Figure 6: Disease free survival by LN status.



Discussion

This retrospective chart review study showed that two third of cases of differentiated thyroid cancer are women with a mean age of 42 years at presentation. The majority are papillary cancers with 11% of cases having family history of thyroid cancer. Age was the only independent predictor of disease persistence or recurrence after adjustment for other predictors whereas both age and vascular invasion were significant predictors of disease free survival.

Our findings are in accordance with the reports from other populations, in which differentiated thyroid cancer was shown to be more common in women than in men with a ratio of 3:1 [17]. The mean age at diagnosis is 42 years in both men and women, younger than the mean age in other populations of 50 years [17]. DTC is not usually hereditary, although some studies have demonstrated a 3%-10% risk in first-degree relatives of patients with DTC [18, 19]. In our study, 10.8% of cases had family history of thyroid cancer. However this was only based on self-reporting and possibly underestimating the true prevalence.

Papillary thyroid cancer is the predominant type accounting for 91% of all cases of DTC in our study, results similar to reports from other populations. Men had significantly more aggressive features than women on pathology including extra-glandular extension, lymph node involvement and vascular invasion. Lebastchi *et al.* reported that the significance of gender in predicting thyroid cancer prognosis is not completely clear [17]. Men typically present at an older age than women do. The peak age at the time of cancer diagnosis is 10-20 years later in men than in women. Men have more than twice the frequency of distant metastases and approximately 30% more regional metastases at the time of diagnosis. These differences have been largely attributed to how men and women access the healthcare systems, with men presenting at a later age and with more advanced stage tumors. So, male gender when corrected for age may not be an independent predictor of outcome for patients with PTC [17].

There are no prospective randomized studies evaluating the appropriate extent of thyroidectomy for DTC. Most recommendations are based on expert opinion or large patient cohorts that have been treated in a nonrandomized fashion. The 2009 ATA guidelines have endorsed total thyroidectomy as the primary initial surgical treatment option for nearly all DTC greater than 1cm with or without evidence of loco-regional or distant metastasis. This was based on retrospective data suggesting that total thyroidectomy would improve survival, decrease recurrence rates, allow for routine use of RAI remnant ablation and facilitate detection of recurrent/persistent disease during follow up. However recent data have demonstrated that in properly selected patients, clinical outcomes are very similar following lobectomy or total thyroidectomy and encourage lobectomy for specific situations [20]. In our retrospective chart review, the majority of patients had undergone a total thyroidectomy with or without lymph node dissection (97.3%) whereas only a minority had undergone lobectomy (2.7%).

The American Thyroid Association has recommended that follow-up treatment varies according to a patient's risk for recurrence [21], yet management including the extent of surgery, necessity of post-operative ablative radioiodine, and degree of thyroid hormone suppression, has been controversial and practices are not uniform among clinicians. Our study have shown that 21.2% had persistence/recurrence of their disease after initial treatment (thyroid surgery with or without radioactive iodine) after a median follow up duration of 4 years. This is similar to what was observed in a similar cohort assessed over 30 years by Mazzaferri and Jhiang [22]. In our study, age, tumor size, male gender, lymph node involvement, vascular and capsular invasion were all found to be associated with disease persistence/recurrence in univariate analyses. This is in line with other reports. Palme *et al.* reported

that male sex, advanced initial stage, and presence of extra-thyroidal spread were independent predictors of multiple recurrences of DTC [23]. In a retrospective review of papillary micro-carcinoma (≤1cm), Mercante *et al.* found that capsular invasion, extra-thyroidal tumor extension, and neck lymph node metastasis at presentation were the only independent risk factors for the persistence or recurrence of disease [24].

DTC is among the most curable cancers. The prognosis is related to several factors, which remain controversial. These controversies may be due to the populations studied, treatment modalities, or patient-related factors. In our study, age and vascular invasion were significant predictors of disease free survival after adjustment for other covariates. Several studies indicate that age is an important factor for prognosis of DTC. Among a sample of DTC patients, 80% of deaths occurred in patients >40 years old [25]. In a study by Ronga *et al.* [26], multivariate analysis revealed that age at diagnosis was the most important factor in conditioning the time to death. The influence of cervical lymph node metastases on disease free survival of DTC patients remains as a controversial topic. Several studies indicate that cervical lymph node involvement at the time of initial surgery has no adverse effect on outcome [25, 27]. In our study we failed to show a significant effect of lymph node involvement on disease free survival, a finding that is similar to other studies. This issue may be due to the fact that, in the presence of lymph node metastases, aggressive initial surgery and post-operative radioiodine ablation therapy is the therapy of choice, which may lead to an improvement in the outcome in these patients.

There has been a significant reduction in the incidence of complications in thyroid surgery since the beginning of the 20th century. The rates of postoperative complications reported in literature are variable (7.4% to 53%) and the incidence of symptomatic postoperative hypocalcemia ranges from 4% to 42% [28]. In our series, we observed postoperative hypocalcemia in 35.8% of the cases, most of whom were transient. Moreover, 5% developed vocal cord dysfunction, mostly transient, a rate that is similar to that reported in the literature (0 to 5%) [28].

Our study has some limitations. Like any other retrospective chart review, missing information is a major drawback. But this was somewhat overcome by the large sample size. Although a long term follow up (19 years) should be considered as a strength, it could also be a limitation since the approach to patients with differentiated thyroid cancer has changed over the years, which would affect the disease free survival of patients across the years. In summary, this retrospective descriptive study shed light on the overall good prognosis of Lebanese patients with DTC. A prospective study at a national level is needed for better evaluation of the management approach in order to optimize further the outcome of patients with DTC.

Conclusion

Differentiated thyroid cancer has an overall good prognosis in Lebanon with age and vascular invasion being the most important predictors of disease recurrence and disease free survival.

Acknowledgment

None.

Financial disclosure

Nothing to disclose.

References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *J Am Med Assoc* 2006; 295(18):2164–2167.
2. Udelsman R, Zhang Y. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. *Thyroid* 2014; 24(3):472-479.

3. Leitzmann MF, Brenner A, Moore SC, et al. Prospective study of body mass index, physical activity and thyroid cancer. *Int J Cancer*. 2010; 126:2947-2956.
4. Zhao G, Wang Z, Zhou H, Zhao Q. Burdens of PBBs, PBDEs, and PCBs in tissues of the cancer patients in the E-waste disassembly sites in Zhejiang, China. *Sci Total Environ*. 2009; 407:4831-4837.
5. Carling T, Udelsman R. Thyroid cancer. *Annu Rev Med* 2014; 65:125-137.
6. Eheman C, Henley SJ, Ballard-Barbash R, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer*. 2012; 118: 2338-2366.
7. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19(11):1167-1214.
8. Sanders LE, Cady B. Differentiated thyroid cancer: reexamination of risk groups and outcome of treatment. *Arch Surg* 1998; 133(4):419-425.
9. Rossi RL, Cady B, Silverman ML, et al. Current results of conservative surgery for differentiated thyroid carcinoma. *World J Surg* 1986; 10(4):612-622.
10. Sawka AM, Thephamongkhol K, Brouwers M, et al. Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab* 2004; 89(8):3668-3676.
11. Taylor T, Specker B, Robbins J, et al. Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Ann Intern Med* 1998; 129(8):622-627.
12. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N EnglJ Med* 2012; 366(18):1674-1685.
13. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012; 366(18):1663-1673.
14. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; 97(5):418-428.
15. Dinneen SF, Valimaki MJ, Bergstralh EJ, et al. Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. *J Clin Endocrinol Metab* 1995; 80(7):2041-2045.
16. Samaan NA, Schultz PN, Haynie TP, et al. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. *J Clin Endocrinol Metab* 1985; 60(2):376-380.
17. A.H. Lebastchi, G.G. Callender. *Thyroid cancer.* Current problems in cancer, 2014.
18. Loh KC.Familial non-medullary thyroid carcinoma: a meta-review of case series. *Thyroid* 1997.
19. Goldgar DE, EastonDF,Cannon-AlbrightLA, et al. Systematic population-based assessment of cancer risk in first-degree relatives ofcancer probands. *J Natl Cancer Inst* 1994.
20. 2015 ATA management guidelines for adult patients with thyroid nodules and DTC.
21. Cooper DS, Doherty GM, Haugen BR, et al:Revised American Thyroid Association management guidelines for patients with thyroid nodules and differenciated thyroid cancer. *Thyroid 2009*, 19:1167.
22. Mazzaferri EL, Jhiang SM: Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994, 97:418.
23. Palme CE, Waseem Z, Raza SN, et al. Management and outcome of recurrent well-differenciated thyroid carcinoma. *Arch Otolaryngol Head neck Surg* 2004, 130:819.
24. Mercante G, Frasoldati A, Pedroni C, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* 2009, 19:707.
25. Krausz Y, Uziely B, Karger H, et al: Recurrence-associated mortality in patients with differenciated thyroid carcinoma. *J Surg Oncol* 1993; 52: 164-168.
26. Ronga G, Filesi M, Montesano T, et al.: Death from differenciated thyroid carcinoma: Retrospective study of a 40-year investigation. *Cancer Biother Radiopharm* 2002; 17:507-514.
27. Ward LS, Souza SL, Assumpcao LV: The impact of nodal metastases on prognosis of well-differenciated thyroid cancer suggests the practice of prophylactic neck dissection. *Arch Otolaryngol Head Neck Surg* 2003; 129:495-496.
28. Filho JG, Kowalski LP. Postoperative Complications of Thyroidectomy for Differenciated Thyroid Carcinoma. *American Journal of Otolaryngology*, 2004.