original article

High rate of persistent/recurrent disease among patients with differentiated thyroid cancer in Saudi Arabia: factors affecting non-remission

Hussein Raef,[a] Eman Alfadhli,[a] Alya Al-Hajjaj,[a] Usman H. Malabu,[a] Saif Al-Sobhi,[b] Ayman Rifai,[c] Abdulrahman Al-Nuaim[a]

From the Departments of [a]Medicine, [b]Surgery and [c]Radiology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Correspondence and reprints: Hussein Raef, MD, FACP, FACE · Section of Endocrinology, Department of Medicine, King Faisal Specialist Hospital and Research Centre MBC 46, PO Box 3354, Riyadh 11211, Saudi Arabia · T: +966-1-464-7272 x. 32119 F: +966-1-442-7499 · hraef@kfshrc.edu.sa · Accepted for publication May 2008

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BACKGROUND AND OBJECTIVES: A fairly high number of patients with differentiated thyroid cancer (DTC) in our center had locally advanced disease at presentation and/or persistent disease after standard treatment. Therefore, we conducted a retrospective study to find the rate of successful ablation and remission and the factors affecting these outcomes.

METHODS: The study included 100 consecutively treated patients (20 males, 80 females; median age 36 years) diagnosed with DTC. Univariate and multivariate logistic regression was used to evaluate the effect of risk factors on the persistence or recurrence of thyroid cancer. All patients underwent total thyroidectomy and had cervical lymph node dissection when indicated. All patients received sodium iodide I 131 ablation once or twice post surgery. Patients were followed clinically by neck ultrasound, ^{123}I whole body scan and by thyroglobulin measurements and other diagnostic tests as needed.

RESULTS: Over a median follow-up of 7.6 years (range 7-10 years), ablation occurred in 93%, remission in 50%, disease persisted without remission in 41%, and 9% had recurrence after at least 1 year of remission. Papillary thyroid cancer was found in 76%, the follicular variant in 14%, other variants (tall cell and sclerosing types) in 2%, Hurthle cell carcinoma in 4%, and pure follicular thyroid cancer in 4%. Compared with patients in remission, patients with persistent/recurrent disease were older (mean 41 versus 31 years, *P*=.003), had higher postoperative thyroglobulin (193 versus 29 ng/mL, *P*=.04) and more advanced TNM staging (*P*=.005). Risk factors significant for non-remission were age >40 years (odds ratio 4.1, 95% CI 1.5-10.9 years, *P*=.003) and TNM stage other than 1 (odds ratio 5.5, 95% CI 1.9-16.3, *P*=.001). Only TNM Stage 1 was significant for remission in the multivariate analysis.

CONCLUSION: The low remission rate in our DTC patients is probably due to more advanced disease at time of presentation. Early detection may, therefore, be essential in improving outcome.

At King Faisal Specialist Hospital and Research Centre (KFSH&RC), a national referral cancer center, thyroid cancer ranked second only to breast cancer among females, eleventh among males and second in the general cancer population.[1] Differentiated thyroid cancer (DTC) represents 85% to 90% of all thyroid malignancies, and usually has an excellent prognosis; complete remission is usually the rule after treatment.[2,3] Remission rates for DTC patients were reported to range from 75% in the series of DeGroot et al (average follow-up, 12 years), 80% in Samaan et al (average follow-up, 11 years), and 80% in Mazzaferri et al (average follow-up, 10 years).[4-7] Several studies have shown that age, gender, tumor size, histological type, grade of tumor, and distant metastases are significant prognostic factors for achieving complete ablation or remission.[8] The therapeutic strategy at KFSH&RC for patients with DTC who have a tumor equal to or greater than 1 centimeter in diameter includes total or near total thyroidectomy, ablation of any thyroid remnant using sodium iodide I 131 (^{131}I), and lifelong thyroxin as suppressive/replacement therapy. It was observed

that there were a fairly high number of patients with DTC in our center who had locally advanced disease at presentation and or persistent disease after adequate standard treatment. We therefore conducted a retrospective study to find the rate of successful ablation (negative follow-up ^{123}I scan) and remission (negative follow-up ^{123}I scan, undetectable thyroglobulin [Tg], and no other clinical or radiological evidence of disease) and the factors affecting these outcomes among DTC patients at KFSH&RC.

METHODS

This retrospective study included 100 patients (20 males, 80 females) diagnosed consecutively with DTC. Patients were excluded from the study if they were <15 years of age, or diagnosed as having anaplastic or medullary thyroid carcinoma. Patients were treated by total thyroidectomy with cervical lymph node dissection on the basis of known lymph node involvement prior to surgery or an abnormal finding at the time of surgery. Histological examination was conducted and patients were staged according to the pathologic tumor-node-metastasis (pTNM) classification.[9] Other histopathologic characteristics recorded were tumor size, multifocality, extrathyroidal extension and vascular invasion.

Shortly after surgery, levothyroxine (LT4) was withdrawn, and triiodothyronine (LT3) was given for 2 to 3 weeks and then withdrawn for 2 weeks. Serum thyroid-stimulating hormone (TSH) was then measured and exceeded 30 mIU/L in all patients. The serum Tg levels were measured. Diagnostic ^{123}I scanning was done using 370-555 MBq. The scanning was performed 24 hours after oral ingestion of ^{123}I as previously described.[10] Following the diagnostic scan, 100-150 mCi (3.7×10^3 to 5.6×10^3 MBq) of ^{131}I was administered. A whole body scan (WBS) was performed 4 days after the administration of ^{131}I. T4 treatment was then initiated with the aim of decreasing serum TSH to low levels (<0.1 mIU/L) without inducing clinical thyrotoxicosis. Repeated ^{123}I WBS was done 6 to 12 months after initial treatment using the same protocol. A second ablative dose of ^{131}I was then given to those with continuous positive uptake on WBS.

During the follow-up period, a clinical examination and neck ultrasound were carried out every 6 to 12 months. In the first few years of follow-up, diagnostic ^{123}I WBS and measurement of Tg levels when not taking LT4 were carried out every 1 to 2 years. Afterward, determinations were done at longer intervals. The Tg level was measured by double antibody radioimmune assay before September 1997 and by chemiluminescent immunometric assay after that date. When off-LT4 Tg levels were detected but ^{123}I WBS was negative, other radiological methods such as CT, magnetic resonance imaging, and positron emission tomography were used to determine the localization of tumor.

Median follow-up was 7.6 years (range, 7-10 years). Patients with evidence of persistent or recurrent disease would be subjected to repeat surgery, ^{131}I treatment, or external radiation as indicated. When no disease could be located, patients were closely observed with repeated imaging or a dose of ^{131}I treatment was given empirically.

We defined a successful ablation as a negative ^{123}I WBS scan, or <0.1% uptake. A cut-off Tg value of 2 ng/mL was used in this study, according to the current recommendation[3], to define remission. It is noteworthy however, that a higher Tg level (8 ng/mL) was used in our hospital practice but not for the purpose of this study, with the older less specific assay as a cut off for remission. Remission of the disease was defined as a negative clinical examination, negative ^{123}I WBS uptake, a Tg level below 2 ng/mL off L-thyroxine, and no other clinical or radiological evidence of the disease. Persistence was defined as absence of remission as defined above. Recurrence was defined as evidence of disease after at least one year of remission.

Univariate analyses were done to estimate the odds ratios (OR), their confidence intervals (CI) and the *P* values to assess significance. A *P* value less than 5% was deemed significant. Analyses were performed using the SAS software version 9.1.3. Multivariate logistic regression was used to evaluate the joint effect of the risk factors. The t test or the chi-square test was used as appropriate to examine differences in clinical or biochemical characteristics.

RESULTS

For the 100 patients in the study, the successful ablation rate was 93% and the remission rate was 50%, with a median follow up of 7.6 years. The remaining patients continued to have persistent disease without achieving remission in 41% of cases, whereas 9% had recurrence after at least one year of remission. The female-to-male ratio was 4:1, and the median age was 36 years (Table 1). Patients in the non-remission group were significantly older, had higher post-surgery Tg values and were more likely to have more advanced TNM staging. Ninety-one percent of patients presented with a thyroid mass, with 19% having compressive symptoms, 8% presented with cervical lymph node (LN) metastasis and 5% with distant metastasis. Papillary thyroid carcinoma (PTC) was seen in 76% of cases, the follicular variant of PTC in 14%, and other PTC variants (tall cell and sclerosing)

in 4%. Follicular thyroid carcinoma (FTC) was found in 4% and Hurthle cell carcinoma in 2%. The mean tumor size was 3.8 centimeters in diameter. Twenty-five percent of tumors were multifocal, 32% had metastasis to the cervical lymph nodes (found during surgery) and 47% had capsular or soft tissue invasion. Seventy-six percent of patients were TNM stage 1, 7% stage 2, 14% stage 3 and 3% were stage 4. The mean and standard deviation for time from onset of symptoms to seeking medical advice was 48.5±6.7 months. All patients received ^{131}I therapy once (mean dose of 137 mCi, mode 150 mCi with a range of 29-204 mCi) and 26% received a second dose (mean dose of 178 mCi, mode 200 mCi with range of 100-212). Table 2 shows the results of the multivariate logistic regression analysis, comparing the effect of risk factors between the remission and non-remission patients. Age greater than 40 years, and TNM Stage 1 and 3 predicted non-remission. However, only TNM Stage 1 was significant for remission using the multivariate step-wise logistic regression.

Table 1. Characteristics of patients in remission and non-remission.

	Remission (n=50)	Non-remission (n=50)	*P* value
Male (%)	20	20	NS
Female (%)	80	80	NS
Age <40 years (%)	82	54	
Age >40 years (%)	18	46	
Mean age (years)	31	41	.003
Thyroid mass (%)	90	92	NS
Duration to seek medical help (months)	44.0	54.1	NS
Dose of ^{131}I (mCi)	136	140	NS
Thyroglobulin post surgery (ng/mL)	29	193	.04
Pathology			
Papillary thyroid carcinoma (%)	76	76	NS
Follicular variant of papillary thyroid carcinoma (%)	14	14	NS
Other papillary thyroid carcinoma (%)	2	6	NS
Hurthle cell carcinoma (%)	4	0	NS
Follicular thyroid carcinoma (%)	4	4	NS
Tumor size (cm)	3.6±2.3	4.0±3.0	NS
Cervical lymph node metastasis (%)	32	32	NS
Multifocality (%)	26	24	NS
TMN Staging			.005
I (%)	90	62	NS
II (%)	10	4	
III (%)	0	28	
IV (%)	0	6	

NS: non-significant

DISCUSSION

We studied 100 patients diagnosed consecutively with DTC and treated with total or near-total thyroidectomy followed by high-dose thyroid ablation once or twice and followed for a median of 7.6 years. Using current criteria for remission, including a non-suppressed Tg level of less than 2 ng/mL, we found a low remission rate of 50% in our population. This is much lower than the 75% to 85% remission reported by DeGroot et al, Samaan et al, and Mazzaferri et al in 10 to 12 years of follow-up of patients with DTC.[4-7] Most of the non-remission cases were those with persistent disease (41 of 100 patients). Prognostic factors in DTC have been previously reported.[8,11,12] We were interested in finding factors that would predict non-remission in our patients.

Mean and standard deviation for age at presentation in our patients was 36 years, which is similar to a previous report from our center,[13] but different from others, where an average age of 45 years was reported.[5,11] Although Toubeau and colleagues did not find age to be of prognostic value,[14] our data demonstrated that age greater than 40 years at the time of diagnosis correlated with non-remission (Table 2), which is consistent with other reports.[5,8,11]

At presentation, the majority of our patients had, as expected, a detectable thyroid abnormality upon physical examination, often noticed by the patient. An asymptomatic solitary nodule was the most common physical finding, as previously reported.[12] However, patients with obstructive goiter were found to have higher persistent or recurrent disease, although this correlation did not reach statistical significance (Table 2). The obstructive thyroid mass might indicate a delay in diagnosis, leading to an adverse outcome, as suggested by others.[5]

The value of a postoperative Tg value in predicting remission has been emphasized.[14,15] In our study, there was a large and significant difference in the value of postoperative Tg between the remission and non-remission groups (Table 1), but when a cut-off postoperative Tg value of 10 ng/mL was used to predict remission this

Table 2. Comparison of categorical risk factors between the remission and non-remission groups.

Risk Factor	Remission Group (50)	Non-Remission Group (50)	OR (95% CI)	*P* value
Age >40	9	23	4.1 (1.5-10.9)	.003
Symptoms of neck compression	6	13	2.6 (0.9-7.4)	.07
Post surgery Tg >10 ng/mL	20	27	1.8 (0.8-3.9)	.16
Duration ≥36 month	15	19	1.4 (0.6-3.3)	.3
Stage 1	45	31	5.5 (1.9-16.3)	.001
Stage 3	0	14	>999.9 (<0.001->999.9)	.0001

OR: odd ratio, CI: confidence interval.

was not significant (Table 2).

Duration from onset of symptoms (usually notice of a lump) to the time of seeking medical help was longer in the non-remission group, but this did not reach statistical significance, in contrast to other reports.[16] This is probably explained by the long duration between onset of symptoms to time of seeking help in many of our patients in both the remission (average, 44 months) and non-remission groups (average, 54.1 months). There were 34 patients who waited 3 or more years from the time a lump was noticed before seeking medical help. This observation might have a significant implication on the outcome of our patients and would argue for the need for routine neck examination by physicians.

Despite the female to male ratio of 4 to 1, which was similar to that reported in the literature for DTC, gender did not appear as a significant prognostic variable in our patients. This differs from previous findings.[6,12,16,17] Similarly, tumor size at the time of diagnosis did not correlate significantly with outcome in our analysis, in contrast with most studies,[5,7] but in line with the report by Eichhorn et al.[18] The classification we used (pTMN) had the most important bearing on recurrence and persistence in our study, as documented in other studies.[7,17,19] Stage 1 disease was the only independent risk factor that correlated with remission using the multivariate step-wise logistic regression. The difference between the successful ablation rate of 93% and the remission rate of 50% represented a group of DTC patients with negative iodine whole body scan and evidence of disease clinically, radiologically, or as only an elevated Tg value. The latter group of elevated Tg and negative whole body scan often presented a challenge in finding a clinical and radiological evidence of the disease and in the attempt to eradicate the disease. Results of treatment in this group were often disappointing as reported previously from our center.[20] It is important to stress, however, that 42% of our patients in non-remission (21% of the total patients) had only a mildly elevated Tg level (2-8 ng/mL) with no other evidence of disease either clinically or radiologically over the follow-up period. Those patients may represent a category of patients with clinically unapparent or minimal stable disease, or even patients in remission, considering the lower specificity of the older Tg assay used (RIA). One could argue that our lower rates of remission present a bias in referral to our center. Although this is a logical argument, we believe that the referral from the surrounding areas for surgical and radioactive iodine treatment of DTC was done systematically regardless of the severity of the cases and therefore might be representative of the real spectrum of thyroid cancer in the country. On the other hand it is possible that the diagnosis of DTC in Saudi Arabia is skewed towards more advanced cases. Nevertheless the findings of the study are still valid and helpful in identifying factors that might be contributing to more advanced and difficult to cure thyroid cancer.

We conclude that the patients in the non-remission group represented a more locally advanced disease as evident by more advanced TNM staging, compressive goiter, and high Tg after surgery. The time from onset of symptoms to seeking medical advice was long in our patients and this may have contributed to the higher non-remission rate. There is a clear need to educate and promote awareness among physicians and patients on the importance of early diagnosis and treatment.

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