Association between prognostic factors and clinical outcome of well-differentiated thyroid carcinoma: A retrospective 10-year follow-up study

SHANGTONG LEI[1], ZIHAI DING[2], JUNNA GE[1] and DONGHUI ZHAO[1]

[1]Department of General Surgery, Nanfang Hospital; [2]Anatomical Institute of Minimally Invasive Surgery, Southern Medical University, Guangzhou, Guangdong 510515, P.R. China

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Abstract. Differentiated thyroid carcinoma (DTC) is one of the most common metabolic disorders and accounts for 98% of all cases of thyroid cancer. Previously, a number of studies have investigated the prognostic factors associated with well-differentiated thyroid carcinoma (WDTC); however, these studies yielded conflicting results. The current study used a retrospective study design to collect data from WDTC patients who had received the same treatment regimen from the same institute, with a minimum follow-up of 10 years. The De Groot staging system was used to classify WDTC in a total of 320 patients (240 females and 80 males). Among the subjects, the pathological subtypes identified were as follows: Papillary carcinoma (240 cases, 75%), follicular carcinoma (67 cases, 21%) and Hürthle cell carcinoma (13 cases, 4%). Prognostic factors that significantly affected the clinical outcome of the disease were advanced age (P=0.001), tumor size (P=0.03), presence of thyroglobulin (P=0.001) and De Groot stage (P=0.005). The 10-year follow-up study revealed that WDTC is associated with a high survival rate of 96% (307/320 patients survived) and a low mortality rate (4%).

Introduction

Differentiated thyroid carcinoma (DTC) is among the most common metabolic disorders, and accounts for 98% of all cases of thyroid cancer. Annually, 20,000 new cases of DTC are diagnosed in USA, and 200,000 patients undergo monitoring for recurrence or progression of the disease (1,2). There are three main types of thyroid carcinoma: Well-differentiated thyroid carcinoma (WDTC), poorly differentiated thyroid carcinoma (PDTC) and undifferentiated thyroid carcinoma (UDTC). WDTC has a better prognosis and decreased mortality and morbidity rates compared with PDTC and UDTC. WDTC neoplasms may arise from follicular cells [papillary (PTC), follicular (FTC) or Hürthle cell (HTC) carcinomas] or from parafollicular cells (medullary thyroid carcinoma) (3,4). Although WDTC accounts for <1% of all cancers, it results in >70% of mortalities from thyroid carcinomas (5).

A number of studies have attempted to determine the prognostic factors associated with WDTC. However, these studies yielded conflicting results (6-8), which may be due variations in the study settings and in the participants enrolled in each study. Furthermore, the use of different pathological classifications of WDTC and of different treatment approaches may have contributed to the heterogeneity among the studies. In order to overcome these limitations, the present study used a sample of WDTC patients undergoing the same treatment, to test the prognostic significance of clinical and pathological factors of WDTC. The identification of clinicopathological factors in cancer is crucial to improve the accuracy of recurrence rate estimates, and to facilitate the calculation of patient-specific disease mortality rates. Furthermore, it aids in the selection of therapeutic modalities and in determining the frequency of follow-up examinations (9).

Materials and methods

Subjects. The current study utilized a retrospective study design to collect medical documentation of patients suffering from WDTC, who were treated at the same institute with a minimum follow-up period of 10 years. A single center was used for data collection to avoid variation in treatment modalities and facilitation of follow-up. A number of classification systems may be used to classify WDTC: De Groot (stage 1, intrathyroidal; stage 2, cervical node metastases; stage 3, extrathyroidal system; stage 4, distant metastases) (10); AMES (age, metastases, extra thyroidal invasion, size of tumor) (11); or TNM (tumor size, nodal status, metastases) (12). For the current study, the De Groot classification system was selected, as it utilizes the combination of clinical, surgical and pathological data (13,14).

Correspondence to: Dr Shangtong Lei, Department of General Surgery, Nanfang Hospital, Southern Medical University, 1838 Guangzhou Avenue North, Guangzhou, Guangdong 510515, P.R. China
E-mail: drshangtonlei@yahoo.com

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Inclusion criteria. Patients with a complete medical record of ≥10 years with the selected treatment regimen were included. The study was approved by the ethical review board of Nanfang Hospital (Guangzhou, China; reference no. HG/2012/6776891).

Exclusion criteria. Patients with incomplete medical records, with a follow-up period of <10 years, or who succumbed to medical conditions other than thyroid carcinoma were excluded from the study.

Treatment. All patients were given I^{131} treatment 34 days following thyroidectomy. The dosage of I^{131} used varied depending on the clinical condition of the patients. Following whole body scan, the presence of serum thyroglobulin was considered a 'positive result', and an absence was considered a 'negative result'. Thyroglobulin levels were measured using RIA kits (#KR6270; Kronus, Inc., Star, ID, USA) that were able to detect <1μg/l, while a radioimmunoassay was used to detect anti-thyroglobulin antibodies. Follow-up examinations were conducted every three months for the first two years, and biannually thereafter, and clinical factors were recorded for each patient. Unfavorable clinical factors included the presence or persistence of increased thyroglobulin levels, recurrence or mortality due to thyroid carcinoma. The following were considered to be favorable clinical outcomes, indicating effectiveness of the treatment regimen: Undetectable serum thyroglobulin, very low level of serum thyroglobulin or complete absence of thyroglobulin (negative result at follow-up scan). A brief overview of the methodology adopted for the current study is shown in Fig. 1.

All subjects underwent the following treatment: i) After performing radical surgery (i.e. thyroidectomy) all patients underwent a radioiodine scan and evaluation of serum thyroglobulin level; ii) all subjects with hypothyroidism were treated with radioactive iodine I^{131} thyroid ablation (dose, 25-30 mCi) 34 days after the first surgery; iii) subjects with traceable amounts of serum thyroglobulin without the presence of anti-thyroglobulin antibodies were treated with an increased dose of I^{131} (100-150 mCi) to achieve normal thyroglobulin levels; iv) all subjects were treated with thyroid stimulating hormone suppressive therapy.

Statistical analysis. Continuous data are presented as the mean ± standard deviation, while categorical data are presented by numbers or frequencies. All the data was analyzed using SPSS software, version 20.0 (IBM SPSS, Armonk, NY, USA). Univariate and multivariate analyses were conducted in stepwise manner to evaluate prognostic factors associated with WDTC. P<0.05 was considered to indicate a statistically significant difference.

Results

In total, 320 patients with WDTC were selected to participate in current study. The demographic profile of the subjects is summarized in Table I.

The mean age of the participants was calculated to be 45.3±17.9 years. The mean follow-up period was 87.9 months. Of the 320 patients, 253 (79%) had undergone a single thyroidectomy, while the remaining 67 (21%) had undergone a second surgery 14 days after the initial surgery (i.e. partial resection). The following pathological subtypes of WDTC were identified among the participants: 240 (75%) PTCs, 67 (21%) FTCs and 13 (4%) HTCs. At the end of follow-up, the following unfavorable outcomes were observed: 109 (34%) patients presented with persistent or recurrent carcinoma and 13 (4%) patients succumbed to carcinoma. Table II summarizes the prognostic factors along with their statistical significance as determined by multivariate analysis.

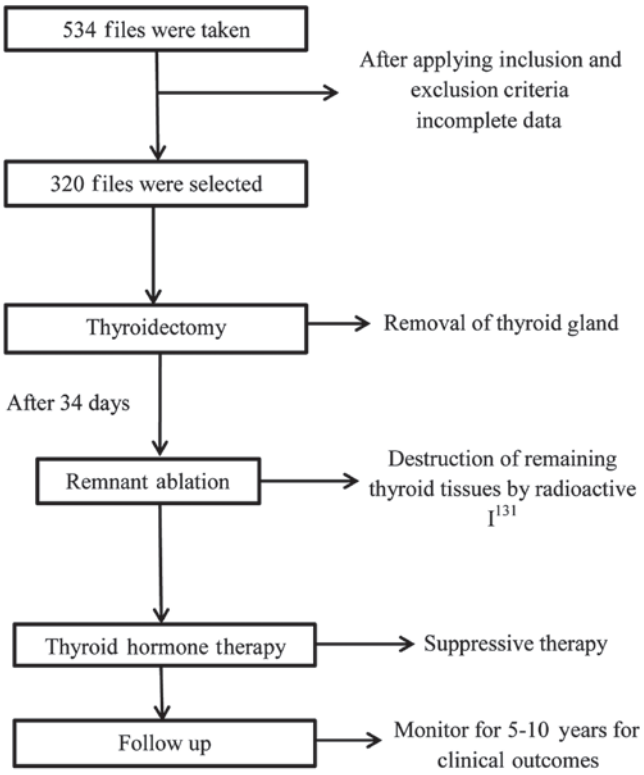

Figure 1. Flow chart showing methodology.

Gender. The rate of unfavorable clinical outcomes did not differ significantly between males and females; unfavorable clinical outcomes were observed in 62 (51%) females versus 60 (49%) males at the end of study (P=0.435).

Age. In the present study, 48 years was observed to be the age above which the majority (66%; 81 individuals) of the unfavorable outcome population were. By contrast, only 73 (37%) disease-free subjects were above this age (P<0.001). Additionally, the presence of distal metastases during the follow-up period was more common among the subjects >48 years of age, compared with the younger subjects (P<0.001). Young age (<20 years) was associated with better clinical outcome than the older age group (>48 years) (71.7% vs. 28.3%; P<0.001, respectively). The association between age and unfavorable clinical outcomes is shown in Fig. 2.

Pathological subtype of carcinoma. Histological examination at the time of diagnosis, revealed that PTC was observed in the greatest number of subjects (240 cases; 75%), followed by FTC (67 cases; 21%) and HTC (13 cases; 4%) (Fig. 3). During diagnosis and follow-up, PTC was associated with the

Table I. Demographic and clinical profile of study participants.

Demographic factor	Cases, n (%)
Gender	
Male	80 (25%)
Female	240 (75%)
Age, years (mean ± SD)	45.3±17.9
Follow-up, months (mean)	87.9
Pathological type	
Papillary carcinoma	240 (75%)
Follicular carcinoma	67 (21%)
Hurtle cell carcinoma	13 (4%)
Clinical outcome	
Favorable	198 (62%)
Unfavorable	122 (38%)

SD, standard deviation.

Table II. Prognostic factors associated with well-differentiated thyroid carcinoma at the end of the follow-up period.

Prognostic factors	P-value
Gender	0.435
Advanced age (>48 years)	0.001
Type of carcinoma	0.325
Tumor size	0.03
Lymph node involvement	0.126
Thyroglobulin	0.001
De Groot staging	0.005
Tumor extension	0.387
Multi-focality	0.425

highest rate of lymph node involvement (P=0.002 vs. 0.004) compared with FTC and HTC. In subjects with unfavorable clinical outcomes, HTC was observed in the highest number of subjects (69 cases; 57%) and was associated with poorer clinical outcomes (P=0.005) on univariate analysis. However, multivariate analysis demonstrated no significant difference (P=0.325).

Tumor size. Examination of tumor size revealed that FTCs had the greatest diameter (mean ± SD, 44.7±16.8 mm] followed by HTC (mean ± SD, 29.8±9.8 mm). The mean diameter of PTC was the smallest (mean ± SD, 26.3±15 mm). The size of the tumor was strongly correlated with clinical outcome (Fig. 4); regardless of tumor type, a tumor size of >50 mm was significantly associated (P=0.03) with unfavorable clinical outcomes, including recurrence of disease or mortality.

Involvement of nodes. The involvement of nodes, at the time of surgery or follow-up examination, was not significantly associated with clinical outcomes. At the time of surgery, 121 (38%) subjects had involvement of nodes; 47 (39%) of these subjects showed unfavorable clinical outcome at end of the follow-up

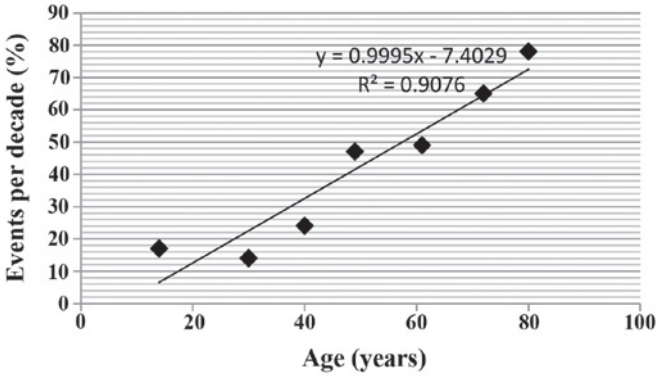

Figure 2. Association between patient age and unfavorable clinical outcome (death or recurrence).

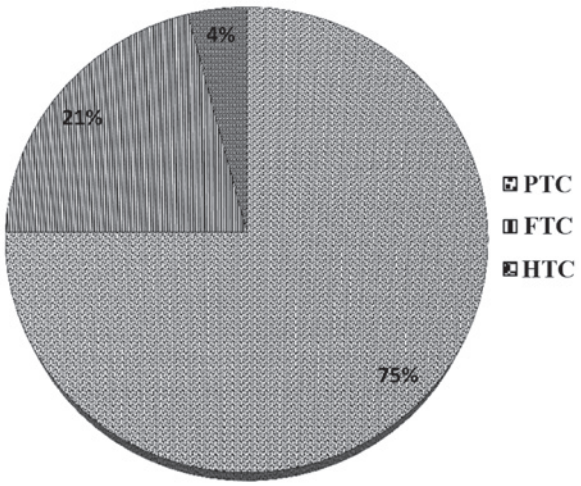

Figure 3. Prevalence of different types of well-differentiated thyroid carcinoma at the time of diagnosis. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HTC, Hürthle cell thyroid carcinoma.

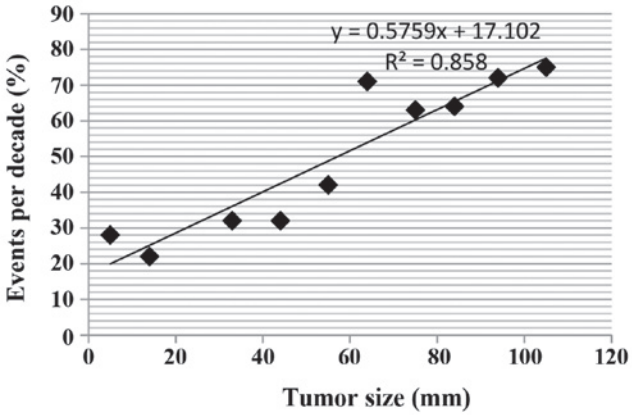

Figure 4. Correlation between tumor size and unfavorable clinical outcome (death or recurrence).

period (P=0.126). During follow-up, 80 patients (25%) exhibited nodal involvement, and 12 (15%) had unfavorable outcomes (P=0.354; Fig. 5).

Thyroglobulin. At 6 months following thyroid surgery, 259 (80%) subjects had detectable serum thyroglobulin

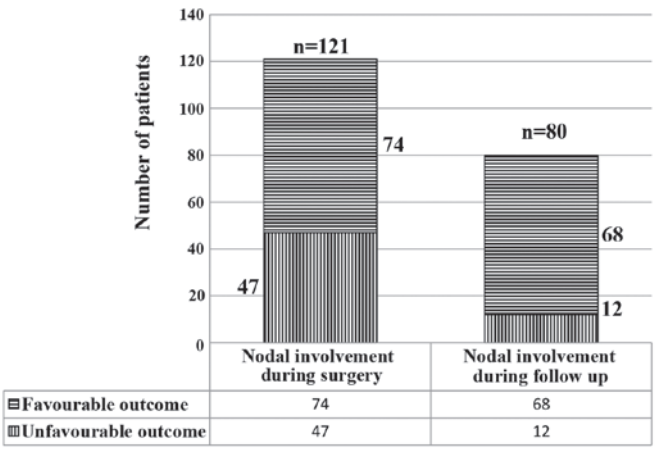

Figure 5. Association between nodal involvement and clinical outcome.

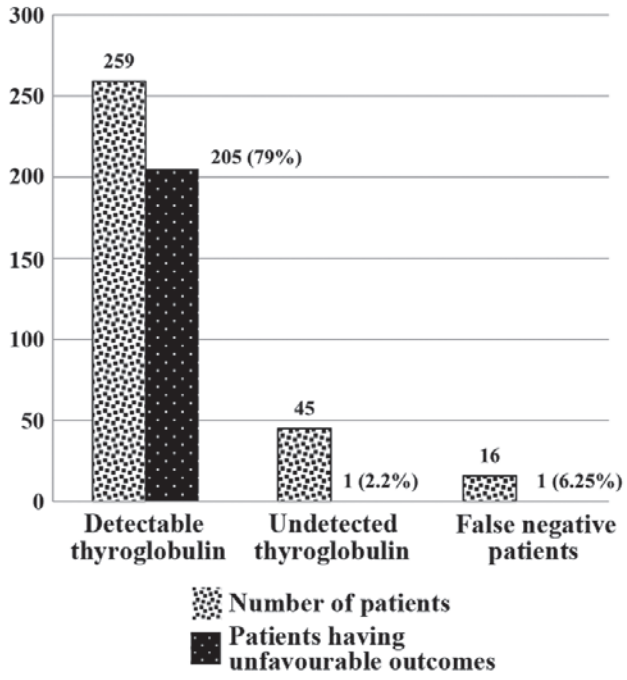

Figure 6. Association between serum thyroglobulin level and unfavorable clinical outcomes.

levels, while 45 (14%) had no detectable serum thyroglobulin; 16 (6%) had positive thyroglobulin antibodies with no detectable serum thyroglobulin (false negative patients). At the end of the 10-year follow-up period, unfavorable outcomes were observed in 205 (79%) patients with detectable thyroglobulin levels six months following thyroid ablation (P=0.001), while unfavorable outcomes were observed in only 1 (2.2%) patient without detectable serum thyroglobulin levels and 1 (6.25%) false negative patient (Fig. 6).

De Groot staging system. The De Groot classification system was used to categorize subjects into stages according to their level of risk. At the time of diagnosis, subjects were categorized as follows: Stage 1, 166 (52%); stage 2, 77 (24%); stage 3, 61 (19.2%); and stage 4, 16 (5%; Table III). At the end of the follow-up period, the highest percentage of unfavorable clinical outcomes was observed in subjects categorized as stage 4 (12 cases; 77%) while the lowest was identified in stage 1 (16 cases; 31%). These results indicated that the De Groot classification system is significantly associated with clinical outcome (P=0.005).

Table III. Association between De Groot staging and clinical outcome.

De Groot stage	Cases at time of diagnosis, n (%)	Unfavorable outcome at end of follow-up, n (%)	P-value
Stage 1	166 (52%)	16 (31%)	
Stage 2	77 (24%)	26 (34%)	
Stage 3	61 (19.2%)	27 (44%)	
Stage 4	16 (5%)	12 (77%)	
			0.005

The P-value indicates the association between the De Groot stage and unfavourable outcome.

Table IV. Prevalence of extrathyroidal tumor extension in different types of WDTC.

Type of WDTC	Extrathyroidal tumor extension, n (%)
Papillary thyroid carcinoma	47 (74%)
Follicular thyroid carcinoma	12 (19%)
Hurtle cell thyroid carcinoma	5 (7%)

WDTC, well-differentiated thyroid carcinoma.

Tumor extension. Extrathyroidal tumor extension was observed in 64 (20%) patients at the time of diagnosis. Table IV shows the prevalence of tumor extension with respect to type of WDTC. This was independent of patient age and tumor size (P=0.561 and P=0.328, respectively). At the end of follow-up, 25 (39%) patients with extra-thyroidal extension showed favorable clinical outcomes (i.e. disease-free status). The results clearly showed that extension of tumors to recurrent sites is not a statistically significant prognostic factor of WDTC (P=0.387).

Tumor focality. At the time of diagnosis, multiple tumor foci in one or both lobes of the thyroid, were present in 70 (22%) study subjects. The prevalence of multifocality in different pathological types of WDTC is shown in Fig. 7; no statistically significant association was observed (P=0.234).

At the end of follow-up, 43 (61%) of the 70 patients that had exhibited multifocality showed favorable clinical outcomes (P=0.425). The prevalence of multifocality associated risk factors among patients at the time of surgery was also assessed (Fig. 8), demonstrating that multifocality is significantly associated with the risk of node development during follow-up (P=0.003).

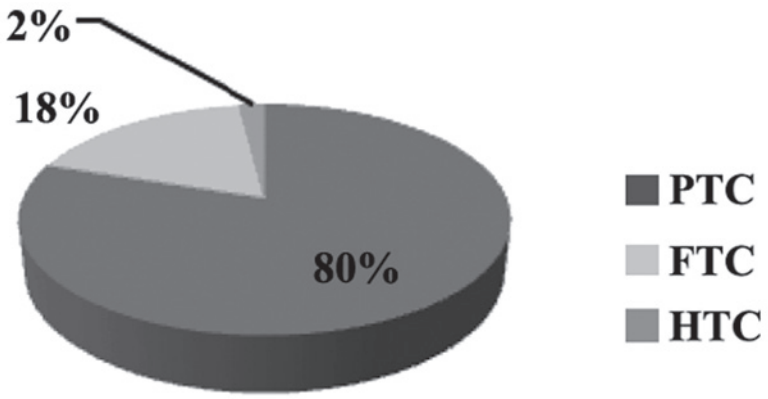

Figure 7. Prevalence of multifocality in different types of well-differentiated thyroid carcinoma. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HTC, Hürthle cell thyroid carcinoma.

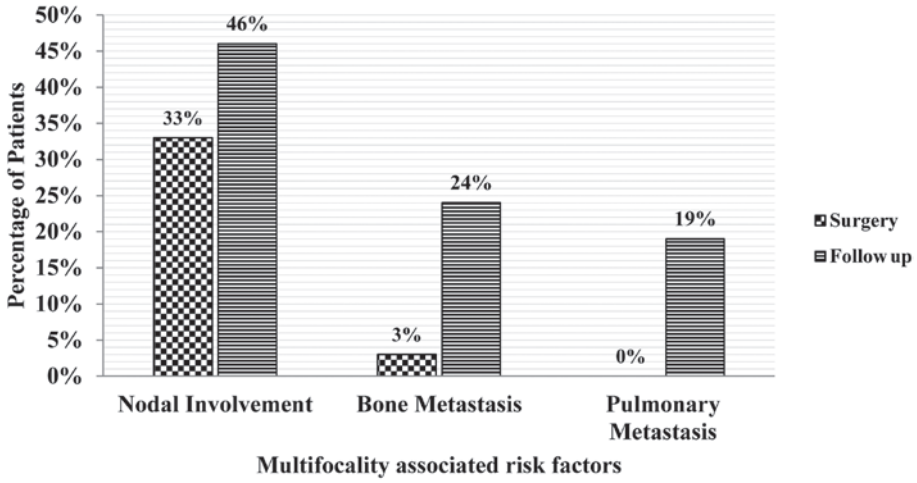

Figure 8. Prevalence of multifocality associated risk factors among patients at the time of surgery and follow up.

Discussion

Although WDTC is the most common type of thyroid carcinoma, it is the only type of this carcinoma with a low mortality rate (15-17) and increased survival rate; the current study found a rate of mortality of 4% for this condition. However, a number of studies have reported a mortality rate of ≤10% (5,18). This difference may be attributable to variability in the use of treatment approaches and classification systems between studies. Despite the low mortality rate observed in the current study, the rate of recurrence is high. Therefore, the rate of persistence or recurrence of WDTC may be a better indicator of the mortality rate associated with this disease. The main limitation associated with the current study is its retrospective nature, with participants recruited from a single centre. The current study can serve as a basis for future prospective studies. Future studies should be conducted prospectively with a large number of patients from different centres, to enable effective generalization.

A number of studies have observed that males have poorer clinical outcomes than females, however, the current study found no significant difference between genders with regard to clinical outcome or prognosis (6,18-20). At the beginning of the study, involvement of nodes was more common among males compared with females (0.045), however, this difference was not significant based on multivariate analysis. Patient age was observed to be significantly associated with outcome in WDTC. As age increases, particularly after 48 years, the likelihood of unfavorable outcome increases. Similarly, young age was associated with favorable prognosis, consistent with a number of other studies (16,18,21). Previous studies demonstrated that patients with HTC or FTC were more likely to show unfavorable clinical outcomes compared with those suffering from PTC (22-24). Consistently, the present study found that patients suffering from HTC or FTC upon diagnosis were more susceptible to bone metastases. However, multivariate analysis showed that tumor size, and not tumor type, is a predictor of unfavorable clinical outcomes (P=0.03). Other factors associated with prognosis were the presence of thyroglobulin and De Groot stage. Thyroglobulin is a well-established marker of WDTC, and may be used to detect persistence or recurrence of the disease. The present study observed the highest rate of unfavorable outcomes in patients who had detectable serum thyroglobulin six months following thyroid ablation. The De Groot staging system, which classifies thyroid carcinomas

based on extent of disease, was also found to be associated with prognosis.

The present 10-year follow-up study, conducted among patients undergoing same treatment, confirmed previous findings that WDTC is associated with a high survival rate and a low mortality rate. Unfavorable clinical outcomes were significantly associated with advanced age, tumor size, presence of thyroglobulin and extent of disease as classified by De Groot staging system.

Acknowledgements

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