Well-Differentiated Thyroid Cancer: The Philippine General Hospital Experience

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Background: Well-differentiated thyroid cancer (WDTC) is the most common form of thyroid malignancy. While it is typically associated with good prognosis, it may exhibit higher recurrence and mortality rates in selected groups, particularly Filipinos. This paper aims to describe the experience of a Philippine Hospital in managing patients with differentiated thyroid cancer.

Methods: We performed a retrospective cohort study of 723 patients with WDTC (649 papillary and 79 follicular), evaluating the clinicopathologic profiles, ultrasound features, management received, tumor recurrence, and eventual outcome over a mean follow-up period of 5 years.

Results: The mean age at diagnosis was 44±13 years (range, 18 to 82), with a majority of cases occurring in the younger age group (<45 years). Most tumors were between 2 and 4 cm in size. The majority of papillary thyroid cancers (PTCs, 63.2%) and follicular thyroid cancers (FTCs, 54.4%) initially presented as stage 1, with a greater proportion of FTC cases (12.7% vs. 3.7%) presenting with distant metastases. Nodal metastases at presentation were more frequent among patients with PTC (29.9% vs. 7.6%). A majority of cases were treated by complete thyroidectomy, followed by radioactive iodine therapy and thyroid stimulating hormone suppression, resulting in a disease-free state. Excluding patients with distant metastases at presentation, the recurrence rates for papillary and FTC were 30.1% and 18.8%, respectively.

Conclusion: Overall, PTC among Filipinos was associated with a more aggressive and recurrent behavior. FTC among Filipinos appeared to behave similarly with other racial groups.

Keywords: Thyroid neoplasms; Thyroid cancer, papillary; Thyroid cancer, follicular

INTRODUCTION

Thyroid cancer accounts for only 1% of all malignancies yet is the most common form of endocrine tumor. Over the past two decades, the incidence of thyroid cancer has increased fourfold in females and threefold in males [1]. Well-differentiated thyroid cancer (WDTC), particularly papillary thyroid cancer (PTC), is the most common thyroid malignancy, comprising ~90% of new cases in iodine-sufficient areas of the world [2]. Asian women in particular were observed to have the highest incidence of WDTC, among which PTC was the most common form [3]. The prognosis of WDTC is generally excellent, with 10-year overall survival rates exceeding 90% [4]; however, higher rates of recurrence and mortality have been observed in select groups of patients [5].

Despite its clinical impact, differentiated thyroid cancer re-

mains a difficult topic for evidence-based decision making, with most management strategies largely empirical. Due to its slow rate of progression, very large cohorts of patients followed over several decades are required to confirm significant differences in prognostic factors and treatment efficacy [6]. During the last decade, there has been a dramatic change in our understanding of the natural history of the disease resulting from the continuous evolution of diagnostic modalities and advancement in therapeutic options [7]. Over this time, follow-up paradigms have progressed considerably, and the standard of care is now focused on achieving a balance between curative therapies and minimizing overtreatment [8].

Because of the longer survival of thyroid cancer patients, description of their clinical profile and understanding of their natural history and clinical outcome are of great importance. Asian populations have been shown to exhibit higher incidence rates, further strengthening the need for location-specific data among Asian populations [3]. Filipinos in particular have consistently been reported as the ethnic group with the highest incidence of thyroid cancer in studies conducted in Hawaii [9,10] and Los Angeles, California [11]. A recent survey on the cancer incidence trends among Asian American populations in the United States revealed Filipino females to have the highest increase of thyroid malignancy [12]. Thyroid cancer among Filipinos was also observed to be more aggressive and recurrent in nature [13], with the risk of malignancy in Filipinos with thyroid nodules significantly higher than that of other racial ethnicities [14].

Despite the strong association between Filipinos and thyroid cancers, only a handful of case studies have been reported from the Philippines. Similarly, the most recent retrospective study of thyroid cancer in Filipino patients by De La Pena [15] in 1988 only described the incidence, diagnostic modalities, and therapeutic treatments used for these patients, with no details regarding the clinical and histologic profiles or long-term outcomes associated with WDTC in this population. Here, we performed a retrospective analysis of patients presenting with WDTC at a tertiary care hospital center in the Philippines (Philippine General Hospital).

METHODS

Study design

We performed a retrospective cohort study consisting of 765 patients diagnosed with thyroid cancer seen at the thyroid outpatient clinic of the Philippine General Hospital, Manila, Philippines, between January 1990 and June 2014.

Inclusion criteria

Adult patients >18 years of age diagnosed with WDTC (papillary or follicular) by final histopathological biopsy at Philippine General Hospital after thyroid surgery, regardless of completion, were included in this study.

Exclusion criteria

A total of 37 cases were excluded from this study due to the following reasons: follicular adenoma (eight cases), poorly differentiated thyroid cancer (five cases), thyroid lymphoma (three cases), metastatic cancer (one case), hurtle cell carcinoma (two cases), insular thyroid carcinoma (three cases), and anaplastic thyroid cancer (15 cases).

Chart retrieval

Outpatient charts of 728 included patients were retrieved using their hospital case numbers via the Philippine General Hospital medical record section. Once retrieved, all charts were then carefully assessed and documented.

Data collection

Clinical profiles, presentation at diagnosis, ultrasound features, management received, cancer staging, clinical course, tumor recurrence, and eventual outcome were all documented and described. Patients with incomplete data or diagnostic tests were still included in the study and reported accordingly. All data were then tabulated and recorded using a descriptive statistical analysis (mean, median, mode, and standard deviation).

Tumor recurrence was assessed only after thyroidectomy and expressed in terms of the number of months post-thyroidectomy. It was considered and reported if one of the following was present: (1) elevated stimulated (>1 µg/L) or unstimulated (>2 µg/L) serum thyroglobulin after thyroidectomy and radioactive ablation; (2) recurrent or new-onset lymphadenopathies proven to be thyroid cancer by biopsy or radioiodine scan; and (3) recurrent or new-onset distant metastases proven to be thyroid cancer by biopsy or radioiodine scan.

RESULTS

A total of 728 patients diagnosed with WDTC by final histopathologic biopsy were included in this study. The vast majority of cases (89%) were diagnosed as PTC, with only 79 cases (11%) of follicular thyroid cancer (FTC). Females were disproportionately affected (84.9%) in both groups. The mean age at diagnosis was 44±13 years (range, 18 to 82), with a majority

of cases occurring in the younger age group (<45). Thyroid cancer incidence was distributed normally across age groups, with the highest incidence seen among 41- to 50-year olds. Most patients presented with a slowly enlarging goiter, with an average duration of 6 years. These cases tended to be sporadic in nature, with only a few cases with family members with similar malignancies. None of our patients had a history of neck irradiation prior to diagnosis. Palpable lymphadenopathies at presentation were observed more often among cases of PTC, while distant metastases at presentation were more common in patients with FTC. Lungs appeared to be the most common site of distant metastasis in PTC, while bones and scalp were predominant in FTC. Concomitant lymphocytic thyroiditis and hyperthyroidism were reported in some cases of PTC, but rarely seen in FTC. Breast cancer appeared to be the most common concomitant malignancy reported (Table 1).

Fine needle aspiration biopsy (FNAB), as an initial histolog-ic test for malignancy, exhibited low sensitivity, as 44% of PTC and 68% of FTC were initially deemed benign cases. Given the low sensitivity of this test, only 32% of FTC cases were assessed by FNAB, with the majority of patients considered to have a Bethesda score of 4, indicative of follicular neoplasm or suspicious for follicular neoplasm. Average tumor size at presentation was larger in FTC cases, while lymph node metastases, multifocality, and bilateral involvement were more common in patients with PTC. Micropapillary (18%) and follicular (15.6%) variants were among the most commonly observed PTC histologic variants (Table 2).

Calcifications, hypoechogenicity, and solid predominance were the most common sonographic findings, and most cases were multinodular and bilateral in nature. Lymph node involvement was detected by ultrasound less frequently; similarly, reported tumor size was discordant with the final histologic biopsy in most cases (Table 3).

Table 1. Clinical Profile of Patients with Differentiated Thyroid Cancer

Variable	Differentiated thyroid cancer (n=728)	Papillary thyroid cancer (n=649)	Follicular thyroid cancer (n=79)
Sex			
Female	625 (85.9)	553 (85.2)	72 (91.1)
Male	103 (14.1)	96 (14.8)	7 (8.9)
Age at diagnosis, yr	44±13	43±13	44±13
<45	395 (54.3)	355 (54.7)	40 (50.6)
>45	333 (45.7)	294 (45.3)	39 (49.4)
18–30	136 (18.7)	124 (19.1)	12 (15.2)
31–40	176 (24.2)	158 (24.3)	18 (22.8)
41–50	192 (26.4)	170 (26.2)	22 (27.8)
51–60	162 (22.2)	145 (22.3)	17 (21.5)
61–70	54 (7.4)	46 (7.1)	8 (10.1)
>70	8 (1.1)	6 (0.9)	2 (2.5)
Duration of goiter, mo	71±78	65±76	77±89
Family history of thyroid cancer	11 (1.5)	8 (1.2)	2 (2.5)
Prior neck irradiation	0	0	0
Palpable lymph nodes at presentation	131 (18.0)	122 (18.8)	9 (8.9)
Distant metastases at presentation	36 (4.9)	26 (4.0)	10 (12.7)
Lungs	21 (2.9)	16 (2.5)	5 (6.3)
Bone	21 (2.9)	13 (2.0)	8 (10.1)
Spine	1 (0.1)	1 (0.2)	0
Scalp	0	0	1 (1.3)
Associated comorbidities			
Diabetes	60 (8.2)	56 (8.5)	4 (5.1)
Hypertension	187 (25.7)	167 (25.7)	20 (25.3)
Lymphocytic thyroiditis	41 (5.6)	40 (6.2)	1 (1.3)
Graves disease/hyperthyroidism	44 (6.0)	41 (6.3)	3 (3.8)
Other malignancies	21 (2.9)	20 (3.1)	1 (1.3)
Breast cancer	7 (1.0)	7 (1.1)	0

Values are expressed as number (%).

Although a majority of both PTC (63.2%) and FTC (54.4%) presented initially as stage 1, a greater proportion (12.7%) of FTC cases presented with distant metastases. Alternatively, nodal metastases were observed more frequently among cases of PTC. Based on TNM classification scores, most tumors were between 2 and 4 cm in size. Only a small percentage of cases had a worsening of the initial cancer staging due to recurrence or persistence of the disease (Table 4).

Surgery was the treatment of choice for all patients in this study, with total thyroidectomy the most common initial surgical procedure. Nodal dissection was only performed for cases with suspected lymph node involvement. A second surgical procedure (completion thyroidectomy) was more frequent in

Table 2. Histologic Profile of Patients with Well-Differentiated Thyroid Cancer

Variable	Papillary thyroid cancer	Follicular thyroid cancer
Fine needle aspiration biopsy	627	75
Benign	276 (44.0)	51 (68.0)
Malignant	351 (56.0)	24 (32.0)
Bethesda score		
1	0	0
2	274 (43.7)	51 (68.0)
3	2 (0.3)	0
4	10 (1.6)	16 (21.3)
5	64 (10.2)	3 (4.0)
6	277 (44.2)	5 (6.7)
Final surgical histopathologic features	649	79
Tumor size, cm	2.9±2.0	3.5±1.9
Lymph node metastasis	212 (32.7)	6 (7.6)
Multifocality	152 (23.4)	6 (7.6)
Bilateral involvement	114 (17.6)	5 (6.3)
Micropapillary cancer	117 (18.0)	-
Follicular variant	101 (15.6)	-
Tall cell variant	5 (0.8)	-
Oncocytic variant	1 (0.2)	-

Values are expressed as number (%) or mean±SD.

Table 3. Ultrasonographic Features of Well-Differentiated Thyroid Cancer

Variable	Papillary thyroid cancer ($n=610$)	Follicular thyroid cancer ($n=74$)
Calcifications	142 (23.3)	15 (20.3)
Hypoechogenicity	466 (76.4)	57 (77.0)
Solid predominance	503 (82.5)	61 (82.4)
Multinodularity	484 (79.3)	58 (78.4)
Bilateral involvement	381 (62.5)	40 (54.1)
Lymph node involvement	140 (23.0)	5 (6.8)
Largest tumor size, cm	3.3±2.1	3.3±2.1

Values are expressed as number (%) or mean±SD.

Table 4. Staging of Patients with Well-Differentiated Thyroid Cancer

Stage	Papillary thyroid cancer ($n=649$)		Follicular thyroid cancer ($n=79$)	
	Initial staging	Final staging	Initial staging	Final staging
Revised cancer stage	100 (15.4)		11 (13.9)	
I	410 (63.2)	387 (59.6)	43 (54.4)	38 (48.1)
II	74 (11.4)	78 (12.0)	16 (20.3)	18 (22.8)
III	97 (14.9)	88 (13.6)	9 (11.4)	7 (8.9)
IV-A	50 (7.7)	64 (9.9)	1 (1.3)	1 (1.3)
IV-B	5 (0.8)	3 (0.5)	0	0
IV-C	13 (2.0)	29 (4.5)	10 (12.7)	15 (19.0)
TNM classification and staging				
T1	230 (35.4)	228 (35.1)	18 (22.8)	18 (22.8)
T2	268 (41.3)	257 (39.6)	36 (45.6)	33 (41.8)
T3	105 (16.2)	103 (15.9)	21 (26.6)	20 (25.3)
T4a	40 (6.3)	54 (8.3)	4 (5.1)	8 (10.1)
T4b	6 (0.9)	7 (1.1)	0	0
N0	455 (70.1)	398 (61.3)	73 (92.4)	65 (82.3)
N1a	150 (23.1)	173 (26.7)	5 (6.3)	8 (10.1)
N1b	44 (6.8)	78 (12.0)	1 (1.3)	6 (7.6)
M0	625 (96.3)	595 (91.7)	69 (87.3)	61 (77.2)
M1	24 (3.7)	54 (8.3)	10 (12.7)	18 (22.8)

Values are expressed as number (%).

FTC cases. Post-surgical hypoparathyroidism was seen in only a small percentage of both PTC and FTC cases. Post-surgical radioactive iodine (RAI) therapy was performed in ~75% of cases with a 6-month interval for PTC and a 12-month interval for FTC. Thyroid stimulating hormone (TSH) suppression to <0.1 mIU/L was achieved in the majority of cases. External beam radiotherapy and chemotherapy were used rarely and only offered in cases unresponsive to RAI therapy (Table 5).

The mean follow-up duration of patients with PTC was 5 years, ranging from 5 months to 10 years; similar follow-up durations were seen with FTC patients, with a mean of 6 years, and a range of 5 months to 12 years. The majority of patients achieved a disease-free state following complete thyroidectomy, subsequent RAI therapy, and TSH suppressive therapy. Structural and biochemical recurrence rates for PTC and FTC were 32.7% and 29.1%, respectively. Excluding patients with distant metastases at presentation, recurrence rates for PTC and FTC were 30.1% and 18.8%, respectively. Structural or biochemical recurrence of PTC generally occurred within 30 months of the initial surgery and within 15 months of the initial post-surgical RAI therapy. Similarly, structural or biochemical recurrence of FTC frequently occurred within 49 months of the initial surgery and within 16 months of the initial post-surgical

RAI therapy. Structural recurrences due to nodal metastases were commonly seen in PTC, while recurrences due to distant metastases prevailed in FTC. A majority of recurrent cases underwent repeated RAI therapy. Finally, FTC patients had a higher mortality rate (2.5%), compared with only 0.3% in PTC patients (Table 6).

DISCUSSION

PTC accounted for the vast majority of WDTC cases, consistent with previous reports [3]. The mean age at presentation of 44 years and female predominance were also consistent with findings from different international studies [16-18]. In contrast, the mean duration of the goiter before initial consult of 6 years and larger mean tumor size reflect the limited access to medical care typical of most patients seen at our institution. Despite the larger mean tumor size observed here, most PTC and FTC cases were classified as stage 1 (63% and 54%, respectively), similar to the findings of other studies, which observed stage 1 tumors in 44% to 74% of patients [17,19-21]. This apparent discrepancy is likely due to the younger age at presentation (<45 years) seen in most cases of thyroid malignancies in our institution.

Table 5. Treatment Modalities Received by Patients with Well-Differentiated Thyroid Cancer

Variable	Papillary thyroid cancer (n=649)	Follicular thyroid cancer (n=79)
Initial surgery		
Total thyroidectomy	525 (80.9)	54 (68.4)
Near total thyroidectomy	21 (3.2)	1 (1.3)
Subtotal thyroidectomy	54 (8.3)	15 (19.0)
Lobectomy	49 (7.6)	9 (11.4)
Nodal dissection	168 (25.9)	6 (7.6)
2nd Surgery (completion)	86 (13.3)	17 (21.5)
Interval from 1st surgery, mo	18±43	7±9
Postsurgical hypoparathyroidism	46 (7.1)	5 (6.3)
Radioactive iodine therapy	465 (71.6)	58 (73.4)
Interval from total/completion surgery, mo	6±9	12±26
TSH suppression therapy, <0.1 mIU/L	465 (71.6)	60 (75.9)
External beam radiotherapy	9 (1.4)	6 (7.6)
Chemotherapy	1 (0.2)	1 (1.3)

Values are expressed as number (%) or mean±SD.
TSH, thyroid stimulating hormone.

Table 6. Recurrence and Clinical Outcome of Patients with Well-Differentiated Thyroid Cancer

Variable	Papillary thyroid cancer (n=649)	Follicular thyroid cancer (n=79)
Total follow-up duration, mo	61±56	74±69
Overall recurrence	212 (32.7)	23 (29.1)
Interval from surgery, mo	30±43	49±57
Interval from RAI therapy, mo	15±22	16±18
Elevated serum Tg[a]	84 (39.6)	9 (39.1)
Nodal metastasis after 1st surgery	161 (75.9)	10 (43.5)
Distant metastasis after 1st surgery	47 (22.2)	17 (73.9)
Lungs	35 (16.5)	5 (21.7)
Bones	14 (6.6)	5 (21.7)
Repeated surgery	47 (22.2)	6 (26.1)
Repeated RAI therapy	142 (67.0)	12 (69.6)
Recurrence excluding M1 patients	188/625 (30.1)	13/69 (18.8)
Mortality	2 (0.3)	2 (2.5)

Values are expressed as mean±SD or number (%).
RAI, radioactive iodine; Tg, thyroglobulin.
[a]>1 ng/mL for suppressed Tg, >10 ng/mL for stimulated Tg.

Prior neck irradiation was not seen observed in our study, since neck irradiation as a form of therapy has yet to be widely adopted in the Philippines. As expected, nodal involvement was more common in PTC cases, since it usually spreads via lymphatic drainage, as opposed to FTC which spreads hematogenously, resulting in more distant metastases at presentation [22]. Breast cancer was the most common secondary malignancy associated with thyroid cancer, consistent with the observations of Sandeep et al. [23].

The lower reliability of FNAB in establishing malignancy may be attributed to the poor sampling method, since most procedures are performed blindly. This observation is in stark contrast to that seen in other studies, in which FNAB appeared to be an excellent diagnostic tool in the initial management of thyroid nodules. However, this success was achieved only when the biopsy technique was ultrasound-guided [24], indicating that ultrasound-guided biopsy of suspected malignant nodules may be necessary to enhance its reliability as a screening test. Here, in the majority of FTC cases, a diagnosis was able to be made only after the initial surgery, with most patients undergoing a second procedure (completion thyroidectomy) due to an initial misdiagnosis by FNAB. This finding is similar to the study by Eilers et al. [25], in which there was a greater difficulty in establishing a clear diagnosis by FNAB in cases of FTC.

Ultrasound of the neck appeared to be a very useful imaging modality for most cases, providing preoperative insight of tumor size, lymph node involvement, and thyroid lobe involvement. However, sonographic features alone were not highly reliable for establishing malignancy in most cases [26]. Discordance between thyroid nodule sizes measured by ultrasound and the final biopsy result was similar to the findings of Deveci et al. [27]. Sub-centimeter nodules were also observed to have

higher discordance rates compared with larger nodules on ultrasound [27].

PTC is most commonly seen in younger adults, particularly those 40 to 50 years of age, with a very high female to male ratio. The larger mean tumor size observed in this study in likely attributed to a delay in medical care, as most of our patients reported a longer duration of the goiter prior to consult. Although our data showed lower extra-thyroidal extension and comparable nodal metastases at presentation, we observed a higher degree of distant metastases at presentation and higher recurrence rate in comparison with other studies. Although this finding is consistent with data previously observed in Filipinos abroad, in whom thyroid malignancies appeared to be more recurrent and aggressive (Table 7) [13,28,29], local factors likely delayed the initiation of medical treatment, as evidenced by the longer duration of the goiter. This difference may have contributed to the higher incidence of recurrence and metastasis seen in our institution. Timely diagnosis and treatment of thyroid cancer are therefore of the utmost importance to reduce recurrence rates. Further genetic studies might be warranted to further understand the innate aggressiveness of thyroid cancer in Filipinos.

In comparison with other international studies, Filipinos with FTC present at a younger age, with a higher female to male ratio, similar to that seen among Koreans. Larger tumor size at presentation was seen across different groups, with distant metastasis more common than nodal metastases at presentation. Higher recurrence rates were still observed among our population. Unlike PTC, patients with FTC did not significantly differ from those of other studies in terms of aggressiveness, presentation, or recurrence (Table 8) [30,31].

In conclusion, PTC among Filipinos presents at a younger age, with a larger tumor size, higher degree of distant metasta-

Table 7. Comparison of Papillary Thyroid Cancers across Different International Studies

Variable	Philippines (n=649)	Korea (n=189)	Japan (n=5,768)
Age at presentation	43	45	49
Female sex, %	85.2	79.9	89.4
Tumor size, cm	2.9	1.8	1.5
Extrathyroidal extension, %	7.1	47.6	13
Nodal metastases, %	29.9	31.2	20
Distant metastases, %	3.7	0.5	2
Recurrence rate, %	30.1	17.5	9.6

Data from Baek et al. [28] and Ito et al. [29].

Table 8. Comparison of Follicular Thyroid Cancers across Different International Studies

Variable	Philippines (n=79)	Korea (n=483)	Austria (n=207)
Age at presentation	44	43	57.8
Female sex, %	91.1	84.5	71.5
Tumor size, cm	3.5	3.5	3.9
Extrathyroidal extension, %	5.1	10	8.2
Nodal metastases, %	7.6	3	7.7
Distant metastases, %	12.7	8	18.4
Recurrence rate, %	18.8	3	11.1

Data from Kim et al. [30] and Asari et al. [31].

ses at presentation, and higher recurrence rate, suggesting a more aggressive and recurrent behavior for this type of thyroid malignancy. FTC among Filipinos also presents at a young age, with high recurrence rates, but appears to behave similarly to that in other racial groups. The overall prognosis and survival rates remained excellent among Filipinos with WDTC, although a higher degree of morbidity due to disease recurrence was common.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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