

Characteristics and Management of Papillary Thyroid Microcarcinoma in the United Arab Emirates: Experience from a Large Tertiary Hospital

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Abstract

Background: Recent guidelines in the management of papillary thyroid microcarcinoma (PTMC) recommend limiting surgery. However, trends in the characteristics and management of PTMC from the Middle East and North Africa region is lacking.

Objectives: To determine the clinical features, management strategy, and outcomes of PTMC in a large tertiary care center in the United Arab Emirates (UAE).

Patients and Methods: This retrospective study included all patients diagnosed with PTMC (i.e., size ≤ 10 mm) at Tawam Hospital, Al Ain, UAE, between 2008 and 2019. Tumor histopathology, management strategy, and outcomes were the primary analyzed variables.

Results: A total of 213 patients with PTMC met the inclusion criteria, of which 83.6% were women and 58.7% were Emiratis. The majority had the classical tumor subtype (76.1%) and tumor of size 5–10 mm (71.4%). Multifocal disease was present in 41.1% and lymph node metastasis (LNM) in 16.6% of the patients. According to the 2015 American Thyroid Association categorization, the majority (93.9%) had a low-risk disease, and all except one patient had Stage 1 disease. Total thyroidectomy was performed in 91.1% of the patients, and 47.9% received radioiodine (RAI) therapy. None of the patients were under active surveillance strategy. RAI treatment was used more often in patients with non-incidental tumors, larger tumor size, multifocal disease, positive LNM, tumors in the intermediate/high ATA category, and those who underwent total thyroidectomy or neck dissection (for all, $P < 0.05$). After a median follow-up of 32.4 months, about 73% had an excellent response to dynamic risk stratification assessment, and only one patient had disease recurrence.

Conclusions: The majority of the patients had low-risk PTMC, yet most patients underwent total thyroidectomy, and almost 50% were treated with RAI ablation. Further studies are needed to determine if these trends are also present regionally and to explore reasons for not adopting a less aggressive approach in this indolent tumor.

Keywords: Active surveillance, microcarcinoma, papillary, radioiodine, thyroid cancer, thyroidectomy

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INTRODUCTION

Papillary thyroid microcarcinoma (PTMC), defined as a tumor of size ≤ 1 cm, represents about one-third of all thyroid cancer cases.^[1,2] Its incidence has significantly increased over the past three decades.^[2] Comprehensive use of head and neck imaging and fine-needle aspiration of small thyroid nodules are key factors contributing to this increase.^[3] The accurate pathological diagnosis of PTMC is paramount, as other benign conditions such as hyperplastic nodules, follicular adenomas, and Hashimoto's thyroiditis may present some cytological features that mimic those in PTMC. Special attention to distinctive nuclear features including nuclear size, shape, chromatic pattern, and membrane irregularity as well as discussion of challenging cases in quality assurance meetings can assist in the accurate diagnosis of PTMC.

The prevalence of PTMC in autopsy studies is about 7–36%.^[4,5] However, only a small proportion is significant enough to reach clinical attention. Besides, most patients are free of disease after the initial surgery, whether lobectomy or total thyroidectomy, even when radioiodine (RAI) therapy is not administered, suggesting an indolent nature of PTMC.^[6] In one study, about 70% of PTMC patients underwent active surveillance instead of immediate surgery and had no disease progression.^[7] These findings were replicated in other parts of the world and led to a remarkable shift in PTMC management, with several professional organizations now considering active surveillance as a valid option for many patients with PTMC.^[8-11]

Most studies on PTMC characteristics and management outcomes were conducted in countries outside the Middle East and North Africa region.^[1,2,12-14] Data from our group showed that from 2008 to 2018, there was a significant decline in RAI therapy, but not in surgery, in a wider cohort of thyroid cancer in the United Arab Emirates (UAE).^[15] Scoping of the current practice in PTMC management is crucial in light of an expected rise in the number of such patients in the future, especially in the absence of regional guidelines on the management of thyroid cancer. Therefore, the current study was conducted with the objective of determining PTMC patients' characteristics, management patterns, and outcomes in a large referral center in the UAE over the past decade. We also aimed to identify clinicopathological features associated with lymph node metastasis and the use of RAI.

PATIENTS AND METHODS

Study design, population, and setting

This retrospective study included all patients diagnosed with PTMC (i.e., ≤ 10 mm) at Tawam Hospital, Al Ain,

UAE, between September 2008 and December 2019. Details of the database has been reported previously.^[15] The study was approved by the local ethics committee.

Cases with incomplete histopathology data, non-papillary thyroid carcinoma, and non-invasive follicular-variant papillary thyroid carcinoma were excluded. The demographic and clinical data included age, gender, nationality, year of diagnosis, size of the tumor, location, multifocality, histopathological subtype, vascular invasion, nodal involvement, the extent of surgery, use of radioiodine ablation (RAI), and/or need for repeat surgery. The 8th edition of the American Joint Committee on Cancer TNM for staging. The 2015 American Thyroid Association (ATA) categorization was used for risk stratification.

Tawam Hospital is the largest oncology referral center in the country, and our thyroid cancer cohort represents both treatment-naïve patients and those who received initial therapy (surgery with or without RAI) in outside facilities before visiting our center.

There is no local protocol for thyroid cancer management in our center. However, there are monthly thyroid cancer multidisciplinary team (MDT) meetings, where most cases are discussed for planning RAI therapy, follow-up investigations, and decision for additional treatments (radiotherapy or targeted therapy). The MDT comprises endocrinologists, ENT specialists, general surgeons who frequently perform thyroid surgeries, pathologist, nuclear medicine physicians, and radiologists. In addition, medical and radiation oncologists attend when required. The selection of cases for presentation at the MDT is at the discretion of the treating physicians. Furthermore, the decisions from the MDT help better guide the management of the discussed cases but are not considered obligatory, and the final decision remains at the discretion of the treating physicians.

Statistical analysis

Data were extracted into Microsoft Excel and analyzed using Stata version 16.0 (StataCorp., College Station, Texas, USA). Missing data were not treated, and only complete case analysis was performed. Quantitative variables were tabulated as mean \pm standard deviation (SD) or median, minimum, and maximum, as appropriate. Qualitative variables were tabulated as frequencies and percentages (%). Chi-square or Fisher's exact tests were performed to compare RAI and lymph node metastasis (LNM) with qualitative variables, as appropriate. In contrast, unpaired *t*-tests were performed to compare RAI and LNM with quantitative variables, as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Demographics and tumor characteristics

A total of 213 patients of PTMC were included in the study [Table 1]. The mean age at diagnosis was 41.7 ± 12.0 years. The majority were female (83.57%) and UAE nationals (58.69%). The mean tumor size was 0.64 ± 0.3 cm, with the two most common histological subtypes being the classical (77.5%, 162/209) and follicular (18.2%, 38/209) variants. PTMC was an incidental finding in 65 cases (30.8%). Multifocal disease was present in 67 patients (41.1%), while only 3 (2%) and 5 (3.2%) patients had vascular invasion and extrathyroidal extension, respectively. Overall, most patients underwent total thyroidectomy (TT) ($n = 194$, 91.1%). Thyroiditis was found on histopathological examination in 69 patients (33.3%).

Overall, the vast majority of patients ($n = 199$) had low-risk classification according to the ATA guideline criteria [Table 2]. Only one patient had Stage II disease: a 36-year-old female with a 1-cm multifocal sclerosing variant of papillary thyroid cancer, positive family history of thyroid malignancy, 10 of 39 positive lymph nodes, and evidence of lung metastasis. This patient underwent total thyroidectomy and neck dissection followed by RAI therapy.

Radioiodine treatment

RAI administration did not differ significantly among PTMC by tumor subtypes: 44.4% in classic, 52.6% in follicular, and 77.8% in the other subtypes. However, the proportion of patients who received RAI was significantly lower in those with incidental tumors (30.8%) than those with non-incidental malignancy (55.9%) ($P = 0.001$).

Table 1: Demographic and clinical characteristics of the study population (N = 213)

Variables	n (%)
Year of diagnosis	
Before 2009	14 (6.6)
2009-2015	97 (45.5)
2016-2019	102 (47.9)
Age (years)	41.7 ± 12.0
Gender	
Female	178 (83.6)
Male	35 (16.4)
Nationality	
UAE national	125 (58.7)
Expatriates	88 (41.3)
Family history of thyroid cancer*	
No	196 (96.5)
Yes	7 (3.5)

*Family history was available for only 203 patients. UAE – United Arab Emirates

The average tumor size was larger in patients receiving RAI compared with those not receiving RAI (0.71 ± 0.3 vs. 0.58 ± 0.3 ; $P = 0.006$). The rate of RAI treatment was 45.0% (89/198) in low-risk patients but increased in intermediate (91.0%, 10/11) or high-risk (100%, 2/2) category patients. Likewise, significantly high proportion of patients with multifocal tumors (67.2%), positive LNM (75.9%), and neck dissection (72.7%) received RAI compared with unifocal (34.4%), node-negative (40.0%), and no neck dissection patients (41.0%) [Table 3]. One patient initially underwent hemithyroidectomy and then completion surgery for a small nodule on the other lobe, which revealed a small focus of PTMC (0.3 cm) and was treated with RAI therapy.

Lymph node metastasis

Thirty-five of 211 patients with available data (16.6%) had a nodal disease. Compared with those without LNM, patients with LNM were younger (35.3 ± 10.6 years vs. 42.9 ± 11.9 years, respectively, $P < 0.001$) and had a larger tumor size (0.75 ± 0.2 vs. 0.62 ± 0.3 , respectively; $P = 0.025$). The proportion of LNM was significantly ($P < 0.001$ each) higher in patients with intermediate/higher ATA risk (69.2%) and neck dissection (48.5%) than those with low ATA risk (13.2%) and without neck dissection (9.38%), respectively [Table 3].

Follow up and recurrence risk

After 32.4 months, most patients had an excellent response on the dynamic risk stratification at last visit. About a quarter of the patients had an indeterminate response ($n = 45$). Only one patient (0.5%) developed recurrence in the other lobe 10 years after lobectomy but had an excellent response on dynamic risk assessment at the last visit 7 months later.

DISCUSSION

The present study is the second-largest account of the characteristics of patients with PTMC in the Gulf region. The majority (77.5%) of our cohort had classical tumor subtype, which is slightly lower than studies from KSA (81.3%) and Philippines (90.3%).^[12,16] The median tumor size in this study was 0.6 cm, which is higher than reported in France but similar to other centers from the US (0.7 cm) and Italy (0.7 cm).^[1,2,17] Furthermore, the multifocal disease was present in about 41% of our patients, which is slightly higher than the reported rates in other studies (20.6 to 38%).^[2,13,14] Like other studies, most of our patients had a low-risk ATA classification.^[1,13]

In the present study, LNM was reported in 16.6% of the patients, which lies within the 5–38% prevalence documented

Table 2: Characteristics of study thyroid cancer, management details, and outcomes

Variables (n*)	n (%)
Subtype (209)	
Classical	162 (77.5)
Follicular	38 (18.2)
Others [†]	9 (4.3)
Incidental (211)	
Yes	65 (30.8)
No	146 (69.2)
Type of surgery (213)	
Total	194 (91.1)
Hemithyroidectomy	19 (8.9)
Stage (213)	
Stage 1	212 (99.5)
Stage 2	1 (0.5)
RAI therapy (212)	
Used	102 (48.1)
Dosage (85)	79.0 ± 37.2 mCi
Tumor size (cm) (182)	
<0.5	52 (28.6)
>0.5	130 (71.4)
Mean±SD	0.6 ± 0.3
Thyroiditis (207)	
Yes	69 (33.3)
No	138 (66.7)
ATA risk stratification (212)	
Low	199 (93.9)
Indeterminate	11 (5.2)
High	2 (0.9)
Dynamic risk stratification (166)	
Indeterminate response	45 (27.1)
Excellent response	121 (72.9)
Duration of follow-up (months) (213)	32.3 (0.4-1378.0)
Lateralization (166)	
Bilateral	44 (26.5)
Isthmus	6 (3.6)
Left	49 (29.5)
Right	67 (40.4)
Focality (163)	
Multifocal	67 (41.1)
Unifocal	96 (58.9)
Presence of local and distant spread	
Vascular invasion (154)	3 (2.0)
Extrathyroidal extension (155)	5 (3.2)
Nodal involvement (211)	35 (16.6)
Distant metastasis (197)	1 (0.5)
Neck dissection (194)	33 (17.0)
Repeat surgery (204)	
Yes	14 (6.9)
No	190 (93.1)

*Only those with available data in each variable were included, [†]Other subtypes were as follows: Oncocytic variant, n=3; sclerosing, 2; tall cell, 1; poorly differentiated, 1; combination of oncocytic and hobnail, 1; and oncocytic and follicular, 1. RAI – Radioiodine; SD – Standard deviation; ATA – American Thyroid Association

in the literature.^[1,2,14] This wide range of nodal involvement could be attributed to the heterogeneity of the studied cohorts and the indication and extent of surgery. We found that younger age, tumor size (>0.5 cm), ATA intermediate or high-risk category, and the extent of surgery were independent predictors of LNM. Similarly, in a large meta-analysis of 8345 patients with PTMC, central LNM was more common in men, young patients, and those with larger tumor size or multifocal disease.^[18] Recently, Luo *et al.*^[19] showed that not

only male gender, age <40 years, and multifocality, but also tumors in the lower part of the thyroid lobe and the added size of all tumor foci are predictors of central LNM. Moreover, Kaliszewski *et al.* found higher rate of multifocal and bilateral disease in patients with LNM and suggested adopting a more aggressive approach in such patients.^[20] Nonetheless, the long-term outcomes remain favorable in those with bilateral multifocal than unifocal disease, with a similar recurrence risk after a median follow-up of 60 months.^[21]

Distant metastasis is rare in PTMC with a prevalence of 0.1–2.7%.^[1,2,14,17] Only one patient in our cohort had distant metastasis at diagnosis. This patient had multiple risk factors: larger tumor size, extensive cervical lymphadenopathy, and a positive family history of thyroid malignancy.

Management of papillary thyroid carcinoma in general, and PTMC with low-risk features specifically, has evolved to a less aggressive approach over the past two decades.^[3] Most of our patients underwent total thyroidectomy, which is similar to another study from KSA.^[16] This rate is much higher than those reported in studies from Canada, China, and France, where total thyroidectomy was performed in 48%, 79%, and 80% of the patients, respectively [Table 4].^[2,14] This discrepancy may relate to multiple factors such as tumor characteristics, patient and/or physician preferences, the initial indication for surgery, and the ease of follow up. In a Canadian survey where 113 physicians (55.8% endocrinologists, 44.2% ENT surgeons) were asked to select their therapy of choice in a hypothetical case of a young female with 0.8-cm biopsy-proven papillary thyroid carcinoma, hemithyroidectomy was selected by 47% of the participants compared with 43% for TT, with a minority opting for non-operative or more aggressive surgical intervention.^[22] More participants selected TT as the treatment option when additional risks were added to the case, such as the history of radiation exposure and family history of cancer as well as with a different gender.^[22] This is not surprising, as physicians try to optimize their patients' surgical treatment, especially those with risk factors for aggressive disease, knowing that TT has better outcomes in reducing long-term recurrence risk than lobectomy.^[23] Furthermore, the recommendation to limit surgery's extent has received more attention in the latest 2015 ATA guidelines than the prior version from 2009.^[24]

Several studies have shown that RAI use is not associated with reduced recurrence (locoregional or distance) or mortality in patients with PTMC.^[25,26] Conversely, a recent large meta-analysis of 22 studies of 8724 patients suggested a lower risk of locoregional disease recurrence in those who

Table 3: Patient and disease characteristics by use of radioiodine therapy and presence of lymph node metastasis

Variable	RAI therapy			LNM		
	Yes	No	P	Yes	No	P
Years						
Before 2009	8 (57.1)	6 (42.9)	0.372	1 (7.69)	12 (92.3)	0.474
2009-2015	50 (52.1)	46 (47.9)		14 (14.4)	83 (85.6)	
2016-2019	44 (43.1)	58 (56.9)		20 (19.8)	81 (80.2)	
Age	41.6±12.2	41.8±12.0	0.940	35.34±10.6	42.9±12.0	<0.001
Sex						
Female	84 (47.5)	93 (52.5)	0.667	29 (16.4)	148 (83.6)	0.458
Male	18 (51.4)	17 (48.6)		6 (17.7)	28 (82.4)	
Ethnicity						
UAE national	53 (42.7)	71 (57.3)	0.063	25 (20.3)	98 (79.7)	0.084
Expatriates	49 (55.7)	39 (44.3)		10 (11.4)	78 (88.6)	
Family history of thyroid cancer						
No	92 (46.9)	104 (53.1)	0.262	31 (16.0)	163 (84.0)	0.323
Yes	5 (71.4)	2 (28.6)		2 (28.6)	5 (71.4)	
Subtype						
Classical	72 (44.4)	90 (55.6)	0.116	25 (15.6)	135 (84.4)	0.080
Follicular	20 (52.6)	18 (47.4)		5 (13.2)	33 (86.8)	
Other	7 (77.8)	2 (22.2)		4 (44.4)	4 (55.6)	
Incidental						
No	81 (55.9)	64 (44.1)	0.001	27 (18.6)	118 (81.4)	0.320
Yes	20 (30.8)	45 (69.2)		8 (12.5)	56 (87.5)	
Type of surgery						
Total thyroidectomy	101 (52.3)	92 (47.7)	<0.001	35 (18.2)	157 (81.8)	0.048
Hemithyroidectomy	0	18 (94.7)*		0	19 (100.0)	
Tumor size (mm)						
Mean±SD	0.7±0.3	0.6±0.3	0.006	0.7±0.2	0.6±0.3	0.025
<0.5	19 (36.5)	33 (63.5)	0.044	2 (3.8)	50 (96.2)	0.001
>0.5	69 (53.1)	61 (46.9)		30 (23.1)	100 (76.9)	
Evidence of thyroiditis						
No	67 (48.6)	71 (51.5)	0.689	19 (13.9)	118 (86.1)	0.164
Yes	31 (45.6)	37 (54.4)		15 (22.1)	53 (77.9)	
American thyroid association risk level						
Indeterminate/high	12 (92.3)	1 (7.7)	0.001	9 (69.2)	4 (30.8)	<0.001
Low	89 (45.0)	109 (55.1)		26 (13.2)	171 (86.8)	
Lateralization, locality, and side						
Bilateral	27 (61.4)	17 (38.6)	0.056	7 (15.9)	37 (84.1)	0.971
Isthmus	1 (16.7)	5 (83.3)	<0.001	1 (16.7)	5 (83.3)	1.000
Left	23 (47.0)	26 (53.1)		7 (14.3)	42 (85.7)	
Right	26 (38.8)	41 (61.2)		12 (17.9)	55 (82.1)	
Multifocal	45 (67.2)	22 (32.8)		11 (16.7)	55 (83.3)	
Unifocal	33 (34.4)	63 (65.6)		16 (16.7)	80 (83.3)	
LNM						
No	78 (44.6)	97 (55.4)	0.048	-	-	-
Yes	22 (62.9)	13 (37.1)		-	-	-
Neck dissection						
No	66 (41.0)	95 (59.0)	0.001	15 (9.4)	145 (90.6)	<0.001
Yes	24 (72.7)	9 (27.3)		16 (48.5)	17 (51.5)	

*One patient had completion thyroidectomy and received RAI. RAI – Radioiodine; SD – Standard deviation; UAE – United Arab Emirates; LNM – Lymph node metastasis

received RAI (1.9 vs. 7.4%; $P = 0.08$).^[27] In our study, almost half of the patients received RAI ablation. This rate is higher than those reported from the USA and France (15% and 21% respectively).^[1,2] As the number of patients classified with intermediate/high-risk by ATA criteria and those with nodal or distant metastasis is small in our study, RAI therapy is over-prescribed in our cohort. Nonetheless, there was a similar RAI usage rate in the studies from KSA, Philippines, and China.^[13,14,16] In addition, in a recent study from Chile, about 88% of PTMC patients who underwent total thyroidectomy received RAI ablation.^[28] The absence

of high-quality data on RAI's role in this population might considerably affect its use across different studies.

Intriguingly, none of our patients underwent active surveillance for PTMC, despite the recent guidelines suggesting it as an alternative option instead of immediate surgery.^[10,11] However, it is essential to note that the concept of active surveillance was first introduced in Japan in 1993, and it was not until about 20 years later that it gained popularity in the same center,^[7] and was only been introduced as a viable option in Japanese guidelines in 2010.^[29] Since

Table 4: Comparison of papillary thyroid microcarcinoma characteristics in the present (United Arab Emirates) and previously published series

Variables	UAE	France	USA	China	Philippine	Saudi Arabia	Latin America
Publication year	Present study	2019	2008	2019	2014	2012	2018
Number of cases	213	966	900	246	75	326	209
Females (%)	83.6	84.6	69.6	73.1	86.6	83.1	90
Incidental (%)	30.8		13	NA	49.6	-	-
Multifocal (%)	41.1	20.6	23?	36.3	28	38.3	-
Lymph node metastasis (%)	16.6	5.5	30	44.3	-	12.9	16.7
Distal metastasis (%)	Nil	0	0.3		2.7	1.65	-
ATA risk stratification at diagnosis*	Low: 93.9% Intermediate: 5.2%	NA	NA	Low: 178 Grade 1: 98%	NA	-	Low: 78.5%
Lobectomy (%)	8.9	20	14	20.7	1.2	8.3	-
Total/subtotal (%)	91.1	80	86	79.3	98.8	91.7	100
RAI Rx (%)	51.6	20.6	15	64.2	44	31.1	88
Excellent response at last follow-up	72.9	NA	NA	83.3	94.7	-	-
Comments				CND 89.5%, LND 10.3% Classic 97.6 Medical follow up 18/12			Lobectomy cases excluded

*ATA risk stratification. CND – Central neck dissection; LND – Lateral neck dissection; NA – Not applicable; RAI – Radioiodine; ATA – American thyroid association; UAE – United Arab Emirates

then, few centers worldwide (Korea and the USA) reported their experience with active surveillance.^[8,9] In the USA, the vast majority of patients with PTMC were treated surgically, with a slight increase in the rate of non-operative management in 2015 compared to 2006 (0.6 vs. 0.9%; $P = <0.001$).^[30] Furthermore, the acceptance for the active surveillance approach was low in recent single-center studies from Argentina (25%) and Italy (50%).^[31,32] Therefore, active surveillance is not yet widely adopted, and only well informed and carefully selected low-risk PTMC patients who can follow up regularly in thyroid cancer clinics might be offered this option.

The majority of our patients had an excellent response to therapy at their last follow-up assessment, with tumor recurrence occurring only in 0.5% of the cohort. This rate is much lower compared to other studies.^[1-4] This could be related to the shorter follow-up period in the present study. In addition, it is unclear if the extent of surgery and the higher use of RAI has impacted our results. As expected, none of our patients died because of PTMC, confirming the indolent nature of this tumor, in line with the published data.^[1,2]

Our study has some limitations. First, it is a retrospective study and data on indications for performing thyroid ultrasound, patients' selection for FNA, outcomes of FNA, and reasons behind type of surgery as well as radioiodine dose were not consistently available. Further, the findings are an experience from a single tertiary referral center and may not necessarily reflect the practice in other centers. In addition, we have no established thyroid cancer treatment and follow-up protocol, and the data may reflect the practice of physicians from different schools of training.

CONCLUSIONS

Most patients in this study had low-risk PTMC, with rare occurrence of distant metastasis or tumor recurrence on follow-up, yet most underwent total thyroidectomy, and about half received the RAI therapy. Additional studies are needed to determine if these trends are also present regionally and to explore factors behind the high use of total thyroidectomy and RAI ablation rather than active surveillance in patients with the indolent PTMC.

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Ethical considerations

The Al Ain Medical District Human Research Ethics Committee approved the study (Ref no.: THREC-562; dated: February 21, 2018). As this is a retrospective study, patient consent was not specifically sought from patients for this study; however, all patients at the hospital provide a general consent for anonymous use of their data for education, research, and quality assurance. The study adhered to the principles of the Declaration of Helsinki, 2013.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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