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Original

The prevalence, clinical and histopathological features of patients with papillary thyroid carcinoma in Semnan, 2014-2020

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Abstract

Introduction: Thyroid cancer is a rare malignancy and accounts for less than one percent of malignant neoplasms, however, it is the most common type of endocrine malignancy and accounts for most deaths caused by all of the endocrine tumors combined. Differentiated thyroid cancer, including papillary and follicular types, accounts for 95% of all thyroid cancers.

Objectives: Studying the characteristics of thyroid cancer is useful in identifying at-risk populations and early diagnosis. In this study, the demographic, clinical and histopathological features of patients with papillary thyroid cancer were investigated.

Patients and Methods: In a retrospective and descriptive study, patients with papillary thyroid cancer who referred to endocrinology clinics in Semnan province between 21 March 2014 to 20 March 2020 were enrolled. Demographic, clinical, histopathological and laboratory data were extracted from patients' medical files and recorded in the checklist. Data were analyzed at 95% confidence intervals and significance level less than 0.05.

Results: A total of 43 patients were diagnosed with papillary thyroid cancer. The mean age (± SD) was 39.07±13.9 years (14-75), 39 patients (90.7%) were female. The mean tumor size was 24.20±12.6 mm. Papillary thyroid tumor was multifocal in 13 patients (30.2%). Tumor variant in 8 patients (18.6%) was micro-papillary. The result of needle aspiration was reported to be malignant in 81.4% of cases. Tumor spread was more lymphatic and vascular (11.6%) and distant metastasis was seen in only one case (2.3%) since, cervical lymph node metastasis was seen in 10 patients (23.3%). The prevalence of recurrence was 34.8% and the most type was nodal. Nodal recurrence was seen at younger ages and local recurrence was seen at older ages ($P=0.024$). This study showed a significant inverse correlation between age and anti- thyroglobulin levels ($P=0.005$).

Conclusion: The results of our study showed that papillary thyroid cancer with a prevalence of 1.1 per 100000 is more common in young females, with a recurrence rate of 35%, which indicates a relatively low prevalence but high recurrence and more incidence in the younger population. Due to the high recurrence rate, follow-up of patients after thyroidectomy and complementary therapies is very important.

Keywords: Papillary thyroid cancer, Needle aspiration, Thyroidectomy

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Introduction

Thyroid cancer is a rare malignancy which constitutes about 1% of all malignant tumors. It is the most common malignancy in the endocrine system and is responsible for most deaths from endocrine cancers. Differentiated thyroid cancer accounts for 95% of all thyroid cancers, which can be classified into two major groups, namely papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Other types of thyroid cancers originate from para-follicular cells (1). The most common type of thyroid malignancy is papillary cancer with an incidence rate of 70%-90% (2). Other types of papillary thyroid cancer include follicular, diffuse sclerosis, long cells, cylindrical cells, hobnails, and several very rare types. According to the WHO definition, PTC is defined as a diameter of 1 cm or less in papillary thyroid micro-carcinoma (PTMC) (3).

Various factors play a role in the prognosis, including histological pattern, tumor stage, age at diagnosis, gender, and delay in primary surgery of more than one year after diagnosis of a nodule. PTC is more common in women in the age group of 30-50 years (4). Radiation, genetic factors, underlying thyroid disease, hormonal and nutritional factors, especially iodine, play an important role in the pathogenesis of thyroid cancer. PTC is more common in areas with adequate iodine intake, but slightly higher in areas with iodine deficiency and endemic goiter (4). One of the important factors involved in thyroid papillary cancer is exposure to ionizing radiation (radioactive

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Implication for health policy/practice/research/ medical education

There have been few studies on the prevalence of thyroid cancer in Iran, but studies on the prevalence of papillary thyroid cancer and, more importantly, treatment, the results of treatment and its recurrence are much less. Assessment of some characteristics including demographic data, clinical data, type of treatment, complications of thyroidectomy, histopathological information, type of recurrence and laboratory results can help us to identify high-risk groups and lead to early diagnosis.

radiation therapy), therefore 85% of ionizing radiation tumors are thyroid papillary cancer. The prevalence of PTC following ionizing radiation in studies varies from 2.8% to 13%. Pathologically, PTC is often multifocal and encapsulation is rare.

Most nodules size is 1-4 cm and are bilateral in 20%-80% of cases. PTC tends to spread through lymphatic system to both thyroid and parathyroid tissue and neck lymph nodes. At the same time, metastasis to the lungs and bones are found in the PTC. Among the various diagnostic methods, fine needle aspiration (FNA) with 90% accuracy and false negative value of 4-10% has been widely accepted as a simple, safe and accurate method in the evaluation of thyroid nodules (5).

The treatment of PTC is total thyroidectomy (treatment of multifocal cases, reduction in local and distant recurrence and reduction in risk of anaplastic changes in saved thyroid tissue, facilitation of radioactive iodine administration and possibility of measuring thyroglobulin as tumor marker for the prevention). The extent of surgery varies depending on the type and stage of tumor. Thyroidectomy can be associated with complications such as permanent or transient hypoparathyroidism and laryngeal recurrent nerve damage. After thyroidectomy, for preventing of distant metastasis and long-term recurrence, radioactive iodine is prescribed which destroys any remaining thyroid tissue or cancer cells that were not removed during surgery (6). For detecting of neoplastic tissue, whole body scan is performed by injection of 2-5 mCi of iodine 131, three to seven days following radioactive iodine therapy (7). In general, iodine therapy is recommended in high-risk cases, patients with incomplete thyroid resection and in children and infants due to the possibility of extensive lymph node involvement, at thyroglobulin levels higher than 5-10 ng/mL, and presence of residual tissue or lymph nodes involvement based on ultrasound assessment. Neck and mediastinal radiotherapy are performed in patients over 45 years of age with advanced PTC in whom, tumor tissue cannot be removed. Administration of levothyroxine by inhibiting thyroid stimulating hormone (TSH) restricted the growth of tumor cells, which increases survival and reduces recurrence (8).

Mortality and recurrence are two possible events for thyroid cancer. Many people with this cancer are well-treated, because the cancer is usually diagnosed and treated at early stages. The risk of recurrence in PTC is 15%-25% and mortality rate are less than 5%. Three forms of recurrence may occur in PTC which include postoperative nodal metastases, local recurrence and distant postoperative metastasis (6). Local recurrence occurs in 5% to 20% of patients with PTC and FTC. Small lymph node metastases may be treated by radioactive iodine, but if persist after two or three courses, may be need to surgery. Distant metastases are rare in PTC (1%-7% of cases) and have a poor prognosis (5- and 10-year survival rates are 65% and 75%, respectively). Lung metastasis is more common in young patients with PTC and bone metastasis in older patients. Other less common organs for metastasis include the brain, liver, and skin (8).

Several factors associated with recurrence include histological features, tumor size, tumor spread beyond the thyroid capsule, lymph node metastasis, distant metastasis, the presence of residual tissue due to incomplete resection by surgery, and whether the tumor is monoclonal or multifocal. The encapsulated follicular type is associated with a low risk of recurrence. On the other hand, invasive histology, necrosis, high mitotic activity and vascular invasion are associated with a higher rate of recurrence. The risk of recurrence in multifocal tumors is 4% and in monofocal tumors is 2%. The risk of recurrence increased with the number and size of lymph nodes involved. Lymph node involvement with more than three metastasis has a significant predictive effect on recurrence and increases the risk of recurrence by up to 40%. The risk of recurrence is related to genetic status and BRAF mutation is associated with an increased risk of recurrence (8).

Thyroglobulin (TG) is a protein synthesized only by the thyroid follicular cells, both normal and neoplastic tissue and is a valuable biochemical marker to assess the presence of residual, recurrent and metastasis. Serum TG levels should not be measurable in patients who have undergone total ablation. There is an association between tumor size and TG level during levothyroxine intake and after TSH stimulation and is used as a prognostic indicator. In case of non-measurable TG after TSH stimulation, recurrence is less than 2%. In contrast, high TG indicates lymph node involvement and distant metastasis or recurrence (7).

It is noteworthy that in cases where a patient has anti-thyroglobulin antibody, thyroglobulin loses its function as a tumor marker and TG measurement is not accurate enough and leads to false negative results (9). In patients with complete recovery after total ablation, anti-TG antibodies gradually decline to low or non-measurable levels over an average of three years. Their persistence or recurrence during the follow-up period should be considered as a persistent disease or recurrence (7).

Mortality rate for differentiated tumors, including PTC, is 2% in the first five years, 4% in the first ten years, and 5% in the first twenty years. 20% of deaths are in the first year and 80% in the first ten years. The mortality rate of thyroid cancer can be determined based on some variables

including metastasis, age, complete tumor resection and invasion (8).

Objectives

Early and proper diagnosis and treatment are very important in the prognosis. In addition, reviewing various treatment methods, complications and identifying the factors affecting relapse can help to identify appropriate treatment algorithms, behavior and recurrence rate and increase patients' life expectancy, reduce treatment-related problems, costs and unnecessary procedures. Due to the increasing incidence and recurrence of papillary thyroid cancer in the past few decades, this study was designed and conducted to investigate the prevalence and incidence of papillary thyroid cancer and clinical and histopathological features of patients in Semnan province.

Patients and Methods

Study design

In a descriptive cross-sectional study, all patients with thyroid cancer referred to the endocrine clinics in Semnan from 21 March 2014 to 20 March 2020 were assessed and patients with papillary thyroid cancer who met the inclusion criteria and did not meet the exclusion criteria enrolled in study. Incomplete files were excluded from the study. In this study, all patients with papillary thyroid cancer in a 7-year period were studied and due to the small population of Semnan, the number of samples was 43.

Demographic data including age, gender and clinical information, type of treatment, family history, tumor size and consistency, thyroidectomy complications, radioactive iodine intake, and histopathologic data, type of recurrence, tumor echogenicity, multifocal or monofocal, micropapillary type, needle aspiration results, tumor spread, distant and cervical lymph node metastasis as well as laboratory results such as TSH, thyroxine (T4) and TG level were extracted from the clinical records of patients.

Statistical analysis

Numerical variables including laboratory results were presented as mean and standard deviation. Qualitative variables were presented as frequency distribution tables (number and percentage). Parametric and non-parametric tests were used to compare the subgroups, based on appropriateness and statistical hypotheses. Data were analyzed at 95% confidence interval and significance level less than 0.05 in SPSS software, version 23.

Results

Among 43 patients with papillary thyroid cancer who referred to endocrine clinics in Semnan province (Semnan University of Medical Sciences), 39 (90%) were females. The mean (±SD) age of patients was 39.07 ± 13.9 years (14-75 years). Five patients had a family history. The mean tumor size was 24.20 ± 12.6 mm. Four patients had two masses and one patient had three masses (Table 1).

In the most cases the echogenicity of tumor was mostly iso- or hypoechoic. Papillary thyroid tumor in 13 patients (30.2%) was multifocal and in 8 patients (18.6%) was micropapillary type. The result of needle aspiration was reported to be malignant in 81.4% of cases. The most common pattern of tumor spread was lymphocytic and vascular (11.6%) and 31 patients did not have tumor spread. Neck lymph node metastasis was present in 10 patients (23.3%) and only one patient had distant metastasis. Treatment's methods were thyroidectomy or thyroidectomy accompanied with radioactive iodine. Most patients in this study received combination therapy. The dose of radioactive iodine was 125.14 ± 44.01 (range 30-300 mCi; Table 1).

Thyroidectomy complications were seen in 5 patients, which were transient hypoparathyroidism and laryngeal

Table 1. Frequency distribution of patients based on demographic and clinical characteristics

Parameters		No	%
Gender	Male	4	9.3
	Female	39	90.7
Age (y)	≤ 20	3	7.0
	21-40	25	58.1
	41-60	10	23.3
	> 60	5	11.6
Family history	+	5	11.6
	-	38	88.4
Tumor echogenicity	Isoecho	16	37.2
	Hypoecho	16	37.2
	Hyper & Isoecho	1	2.3
	Hyper & Hypoecho	1	2.3
	Hypo & Isoecho	5	11.6
	Hyperm hypo & Isoecho	4	9.3
FNA finding	Benign	1	2.3
	Malignant	35	81.4
	Suspicious	7	16.3
Cervical lymph nodes metastasis	+	10	23.3
	-	33	76.7
Invasion pattern	Lymphatic	1	2.3
	Vascular	2	4.7
	Capsular	3	7.0
	Lymphatic & vascular	5	11.6
	Vascular & capsular	1	2.3
	None	31	72.1
Focality	Unifocal	13	30.2
	Multifocal	30	69.8
Complications	Transient hypothyroidism	2	4.7
	RLN Injury	3	7.0
	None	38	88.4
Recurrence type	Local	1	2.3
	Nodal	13	30.2
	Local & nodal	1	2.3
	None	28	65.1
Distance metastasis	+	1	2.3
	-	42	97.7
Treatment	Thyroidectomy	7	16.3
	Thyroidectomy & iodine	36	83.7

RLN, Recurrent laryngeal nerve.

recurrent nerve damage. Of the 43 patients, 15 patients had recurrences, of which one was local recurrence, one was local recurrence with nodal and 13 were nodal recurrence (Table 1).

Thyroxine levels were lower than normal in 2 patients (4.7%), normal in 4 patients (9.3%) and higher than normal in 37 patients (86.0%). TSH levels were lower than normal in 13 patients (30.2%), normal in 8 patients (18.6%) and higher than normal in 22 patients (52.2%). TG level was higher than normal in 33 patients (76.7%) and higher than normal in 10 patients (23.3%). The level of anti-TG level was higher than normal in 11 patients (25.6%) and higher than normal in 32 patients (74.4%) (Table 2).

Frequency of thyroidectomy complications were not significantly different between age groups ($P=0.801$), male and female ($P>0.999$), in patients with different treatments ($P>0.999$), in patients with and without family history ($P=0.255$), with and without multifocal tumors ($P=0.058$), with different results of needle aspiration ($P=0.196$), with and without distant metastasis ($P<0.999$) and in patients with and without cervical lymph node metastasis ($P=0.745$; Table 3).

There was no significant difference between the mean age, tumor size and the amount of iodine received between patients with and without complications of thyroidectomy. The mean age of patients with nodal recurrence was lower than other types of recurrence ($P=0.024$). There was no significant difference between the mean tumor size and the received dose of iodine in patients with different types of recurrence (Table 4).

There was no significant difference in mean levels of biochemical and serological parameters between age groups, male and female, patients with different types of treatment, with and without family history, with and without focal tumor, with papillary and micropapillary tumors, with different results of needle aspiration, with different patterns of tumor spread, with and without distant metastases, and patients with and without metastases to cervical lymph nodes (Table 5).

There was a significant inverse correlation between age and levels of anti-TG ($P=0.005$), TG and anti-TG ($P=0.011$), TSH and T4 ($P<0.001$). There was no significant correlation between the other parameters (Table 6).

Table 2. Mean (±SD) of biochemical and serological parameters in patients with papillary thyroid cancer

Markers	Normal Range	Mean	SD	Min.	Max.	<Normal		Normal		>Normal	
						No.	%	No.	%	No.	%
T4	0.8-2.8 MIU/L	24.26	45.1	0.30	190.00	2	4.7	4	9.3	37	86.0
TSH	0.4-4.0 MIU/L	20.17	26.5	0.01	100.00	13	30.2	8	18.6	22	51.2
Thyroglobulin	≥ 33 ng/mL	24.17	39.7	0.00	162.00	0	0	33	76.7	10	23.3
Anti-thyroglobulin	< 4 IU/mL	34.52	71.9	0.40	457.00	0	0	11	25.6	32	74.4

Table 3. Frequency distribution of thyroidectomy complications adjusted by demographic and clinical characteristics

		Complications						χ^2	*P* value[a]
		None		Transient Hypothyroidism		RLN Injury			
		No.	%	No.	%	No.	%		
Age (y)	≤ 20	3	7.0	0	0	0	0	3.490	0.801
	21-40	21	48.8	1	2.3	3	7.0		
	41-60	9	20.9	1	2.3	0	0		
	> 60	5	11.6	0	0	0	0		
Gender	Male	4	9.3	0	0	0	0	0.629	>0.999
	Female	24	79.0	2	4.7	3	7.0		
Treatment	Thyroidectomy	7	16.3	0	0	0	0	3.051	>0.999
	Thyroidectomy & Iodine	31	72.0	2	4.7	3	7.0		
Family history	+	4	9.3	1	2.3	0	0	2.894	0.255
	-	34	79.1	1	2.3	3	7.0		
Focality	Multifocal	10	23.0	2	4.6	0	0	4.822	0.058
	Unifocal	28	65.1	0	0	3	7.0		
FNA findings	Benign	1	2.3	0	0	0	0	7.178	0.196
	Malignant	32	74.4	2	4.7	1	2.3		
	Suspicious	5	11.6	0	0	2	4.7		
Distance metastasis	+	1	2.3	0	0	0	0	2.473	>0.999
	-	37	86.0	2	4.7	3	7.0		
Lymph nodes metastasis	+	10	23.3	0	0	0	0	0.903	0.745
	-	28	65.1	2	4.7	3	7.0		

RLN, Recurrent laryngeal nerve. [a] Fisher's exact test.

Table 4. Comparison of the mean (SD) age, tumor size and received iodine adjusted by complications of thyroidectomy and type of recurrence

		Parameters					
		Iodine received		Tumor size		Tumor size	
		Mean	SD	Mean	SD	Mean	SD
Complications	None	127.58	16.3	24.49	11.9	39.32	14.7
	Transient hypothyroidism	100.00	0.00	7.50	3.5	43.00	4.2
	RLN Injury	116.67	28.8	31.67	17.5	33.33	1.1
P value		0.664		0.100		0.722	
Recurrence type	Local	100.00	--	25.00	--	62.00	--
	Nodal	147.73	57.5	26.62	11.2	33.15	8.6
	Local & Nodal	150.00	--	15.00	--	38.00	--
P value		0.733		0.618		0.024	

Table 5. Mean (SD) of biochemical and serological parameters adjusted by demographic and clinical characteristics

		Parameters							
		Anti-TG		TG		TSH		T4	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age groups (y)	≤20	20.10	26.0	45.05	51.9	13.19	22.35	28.99	32.1
	21-40	45.48	90.9	17.33	31.5	22.93	31.5	26.27	46.51
	41-60	21.08	31.6	19.57	29.2	15.00	17.9	26.02	57.7
	>60	9.24	0.4	55.04	73.8	20.92	17.8	7.86	3.7
P value		0.684		0.194		0.846		0.896	
Gender	Male	9.80	10.0	18.35	24.2	12.57	16.5	9.27	2.6
	Female	37.05	75.1	24.76	41.1	20.65	27.4	25.80	47.1
P value		0.477		0.762		0.554		0.492	
Treatment	Thyroidectomy	29.62	13.5	6.66	7.9	5.83	6.9	35.01	68.3
	Iodine	18.00	--	9.00	--	40.00	--	3.00	--
	Combined	35.97	79.6	28.10	43.0	22.47	28.3	22.72	40.6
P value		0.954		0.406		0.244		0.729	
Family History	Yes	24.02	25.3	21.63	39.6	0.87	1.1	64.80	76.9
	No	36.40	77.0	25.16	40.5	23.32	27.3	18.92	37.7
P value		0.726		0.856		0.077		0.031	
Focality	Multifocal	63.24	130.4	22.82	33.8	18.52	27.4	41.46	62.9
	Unifocal	22.58	23.1	26.38	43.2	22.20	27.0	17.60	35.1
P value		0.108		0.801		0.696		0.121	
FNA Findings	Benign	19.00	--	20.20	--	0.04	--	12.50	--
	Malignant	35.38	78.3	25.04	41.7	17.69	26.3	28.45	49.15
	Suspicious	32.44	37.7	20.35	33.8	35.47	25.3	4.99	2.7
P value		0.973		0.957		0.205		0.450	
Distance Metastasis	Yes	23.00	--	0.20	--	5.60	--	11.50	--
	No	34.79	72.8	24.74	40.0	20.52	26.7	24.56	45.6
P value		0.874		0.548		0.585		0.779	
Cervical Lymph Nodes Metastasis	Yes	15.91	12.7	22.25	38.9	26.66	32.0	52.27	67.2
	No	40.16	81.3	24.74	40.5	18.20	24.9	15.77	32..8
P value		0.357		0.866		0.385		0.023	

Discussion

Thyroid cancer is the most common worldwide endocrine malignancy and despite its low risk, its prevalence is increasing. In recent decades, its prevalence has more than doubled, especially in developed countries. 40%-80% of thyroid cancers are papillary, 10%-40% follicular, 1%-10% medullary and 2%-14% are anaplastic (9).

In our study, most of the patients were female. In general, prevalence of thyroid cancer has more in women than men, this ratio has varied from 2.5 to 4 folds in women.

Mao et al reported an increasing prevalence of thyroid cancer in both sexes and its prevalence in women 2.5-folds more than men (10). The incidence of thyroid cancer in Semnan province was 1.44 per 100 000 people. A recent study estimates the prevalence of thyroid cancer at about 1.4 per 100 000 population.

Table 6. Correlation of age, tumor size, received iodine, biochemical and serological parameters

	Anti-TG 34.52 ± 71.96	**TG 24.17 ± 39.72**	**TSH 20.17 ± 26.57**	**T4 24.26 ± 45.13**	**Iodine 125.14 ± 44.01**	**Tumor Size 24.20 ± 12.61**	**Age 39.07 ± 13.93**
Age	R= -0.423 *P*= 0.005	R= 0.135 *P*= 0.389	R= 0.025 *P*= 0.873	R= -0.078 *P*= 0.579	R= -0.003 *P*= 0.987	R= -0.094 *P*= 0.547	
Tumor Size	R= -0.139 *P*= 0.373	R= 0.178 *P*= 0.253	R= 0.025 *P*= 0.875	R= 0.107 *P*= 0.493	R= 0.128 *P*= 0.457		
Iodine	R= -0.032 *P*= 0.853	R= 0.174 *P*= 0.310	R= 0.186 *P*= 0.278	R= -0.152 *P*= 0.375			
T4	R= -0.025 *P*= 0.875	R= 0.063 *P*= 0.687	R= -0.327 *P*= 0.033				
TSH	R= 0.060 *P*= 0.702	R= 0.068 *P*= 0.664					
TG	R= -0.383 *P*= 0.011						
Anti-TG							

In our study, the mean (±SD) age of patients was 39.07 ± 13.9 years (14-75 years) and 60% of patients were in the age range of 21 to 40 years. Orosco et al reported the mean age of most patients with thyroid cancer at diagnosis is less than 45 years and the mean age of patients at the time of diagnosis in their study was 45.6 years (11). Thyroid cancer is diagnosed at a young age, almost 70% of cases are younger than 55 years. About 2% of thyroid cancer occurs in children 13 to 19 years of age and the mortality rate in these patients is low, but the recurrent rate is higher than mortality.

The findings of our study are slightly different from other studies that examined all cases of thyroid cancer and not just papillary cancer. Papillary thyroid cancer accounts for 40%-80% of thyroid cancers (9). In previous studies which assessed tumor size, clinical, sonographic and histopathological features of papillary and micropapillary thyroid cancer, have described the prevalence rates, mean age of patients, multifocality, lymphatic, vascular and capsular invasion and differentiated lymph node metastasis (12).

Our findings showed a prevalence of thyroid papillary cancer ratio in women to men was 8.5, which is slightly different from other studies. In Pham et al study, the prevalence of papillary thyroid cancer in women was nearly 4.5-times higher than men (13).

In our study, lymph node metastasis was 23.3% and distant metastasis was 2.3%, which is almost similar to the results of the study by Schmid et al (14).

The prevalence of papillary type was higher than micropapillary in women. Frequency of lymphatic involvement, multifocal tumors, vascular, capsular and lymphatic invasion were not significantly different between papillary and micropapillary thyroid cancer, although in the papillary type, distance and lymph node metastasis, vascular invasion was reported more than the micropapillary group, and on the other hand, lymphatic and capsular invasion were multifocal, and the number of tumors and the mean age in patients with thyroid micropapillary cancers were higher than papillary thyroid cancers. These findings are similar to other studies. In the study of Seyrek et al, the relationship between tumor size and clinical, ultrasonographic and histopathological features of papillary (PTC) and micropapillary (PTMC) cancer was investigated and reported that vascular invasion and lymph node metastasis have been reported to be higher in the PTC group (12).

In our study, FNA findings in 85% of patients indicated to malignancy. In addition, some factors including higher mean tumor size, lower mean age, female gender, multifocal tumors and invasion to neck lymph node were associated with higher recurrent and in patients who underwent thyroidectomy recurrent rate was lower.

The study by Liu et al showed that long cell papillary cancer is associated with more invasive clinical-pathological features (extra-thyroid invasion, vascular invasion, lymph node metastasis) (15).

Likewise, Tam et al reported that the recurrent rate, extra-thyroid invasion, vascular invasion and lymph node metastasis are higher in multifocal tumors (16). In our study, the rate of recurrence, cervical lymph node metastasis, and vascular invasion was higher in multifocal tumors, which is similar to results of study by Tam et al. In our study only one case of distant invasion was existed which was not a multifocal tumor. This finding however is in contrary to the study by Tam et al. In our study no significant relationship between multifocal and distant invasion was detected ($P = 0.529$).

Zhu et al, evaluating of clinical and pathological features in papillary thyroid cancer showed that PTC recurrence was higher in larger tumors with extra-thyroid invasion, lymph node metastasis, in women and younger age. On the other hand, in patients who have undergone thyroidectomy and have a multifocal tumor, recurrent rate was lower and has a significant association with tumor variants (17). In our study, sample size was 43 while in the

study by Zhu et al was 335, since racial and geographical differences should also be taken into account (17). In the study by Magreni et al, the age-adjusted thyroid cancer incidence in whites was higher (5.6% per year), followed by blacks (4.8% per year), American Indian/Alaskan natives (3.2% per year), and Asians/Pacific Islanders (2.3% per year) (18).

In our study, five patients have been complicated after thyroidectomy, of which two were transient hypoparathyroidism (4.7%) and three were laryngeal recurrent nerve damage (7%). The incidence of transient hypoparathyroidism was lower in our study than in other studies, but the transient damage to the laryngeal recurrent nerve was similar. Benkhadoura et al reported a prevalence of thyroidectomy complications including transient hypoparathyroidism in nine patients (12.3%), transient laryngeal recurrent nerve damage in five patients (6.8%) and permanent laryngeal recurrent nerve damage in one patient (1.4%) (19).

In our study, we also examined the levels of thyroid hormones and some biochemical and serological parameters. T4 hormone levels were higher than normal in 86% of patients and were significantly higher in patients with a family history of thyroid cancer and cervical lymph node metastasis (respectively: $P=0.031$ and $P=0.023$). TSH level was higher than normal in 52.2%. There were not any significant different between T4 and TSH levels do not differ in various age groups, male and female, various types of therapy, FNA results, tumor invasion pattern, papillary and micropapillary thyroid cancer and patients with or without family history, multifocal tumor, distant and neck lymph nodes metastasis.

Thyroxin levels increase after thyroidectomy compared to before and TSH levels decrease and remain within the normal range (20). Ito et al reported that after total thyroidectomy, in papillary thyroid cancer, free T4 levels were higher than control group who were matched for TSH levels, in the other hand, free T3 levels were lower than those in the control group. In patients who underwent partial thyroidectomy and received levothyroxine, thyroid hormone levels were not significantly different from the control group. Patients who had partial thyroidectomy and received levothyroxine had significantly lower free T4 but free triiodothyronine was not significantly different from the control group (20).

Euthyroidism is very important issue after total thyroidectomy. Ignoring this issue can be resulted in hypothyroidism or thyrotoxicosis and its complications. Inadequate thyroid hormone levels in these patients can be due to several factors. The most common causes of inadequate thyroid hormone levels in these patients include incorrect doses of levothyroxine, elevated serum thyroglobulin levels, changes in body mass, and eating habits. In addition, concomitant use of calcium supplements, iron sulfate, proton pump inhibitors, bile acid sequestrant, and sucralfate may affect levothyroxine uptake or metabolism (21).

In our study, the level of thyroglobulin was at normal range in 33 patients (76.7%) and higher than normal in 10 patients (23.3%). In other hand, the level of anti-thyroglobulin was normal in 11 patients (25.6%) and higher than normal in 32 patients (74.4%). There was a significant inverse correlation between age and anti-thyroglobulin ($P=0.005$). In other cases, thyroglobulin and anti-thyroglobulin levels are not different between various age and gender groups and had not any correlation with type of treatment, family history, multifocality, papillary and micropapillary types, FNA results, tumor invasion pattern, distant and neck lymph nodes metastasis.

Anti-thyroglobulin antibody is a valuable marker for the follow-up of PTC and changes in anti-thyroglobulin levels in the first year after surgery can be a predictor for the risk of persistence or recurrence in PTC patients with positive anti-thyroglobulin (22).

In our study, the recurrence rate was 35% and all cases were seen in women and most recurrences were nodal type. PTCs typically have a good prognosis; however, recurrence is still a major concern and between 8 to 28% of patients develop recurrent after treatment (23). The average recurrence time is six months to several decades and is related to some factors such as lymph node metastasis, histological type, tumor size, extra-thyroid invasion, extra-lymph node invasion, male gender and age over 45 years at diagnosis (24). The recurrence rate in our study is higher than other studies, which can be related to several factors which mentioned.

The American Thyroid Association (ATA) system classified the patients as low, medium and high risk based on clinical and pathological findings, including tumor size, histological type, vascular or lymph node involvement, local invasion, distant metastases, extent of tumor resection, thyroglobulin levels, and postoperative uptake of radioactive iodine in the thyroid bed (25). Elevated serum thyroglobulin with a negative titer of anti-thyroglobulin antibody or increased serum anti-thyroglobulin titer can be a biochemical disorder in patients who have undergone thyroidectomy due to thyroid cancer. Thyroglobulin is known as the best marker in the follow-up of patients with thyroid cancer after thyroidectomy who received radioactive iodine. Thyroglobulin measurement and neck ultrasound are recommended every 6-12 months and then annually in the absence of symptoms (1).

Conclusion

Our findings showed that papillary thyroid cancer with a prevalence of 1.1 per 100 000, is more frequent in young female, with a recurrence rate of 35%, which indicates a relatively low prevalence but high recurrence rate. The incidence of complications after thyroidectomy in our study was less than 12%, without mortality. The FNA had high diagnostic value equal to 85% in detecting of malignancy. Serological and biochemical markers

including serum anti-thyroglobulin, TG, TSH, T4 concentrations are valuable in following up the course of treatment and recurrence and have the ability to predict the adequacy of treatment and the occurrence of complications. Due to the high recurrence rate, follow-up of patients after thyroidectomy and complementary therapies is very important.

Limitations of the study

There were few limitations in this study including retrograde data collection, exclusion of some of the cases during study and incompletion of some of the data. The data were completed, as much as possible by calling patients.

Authors' contribution

AN and MF participated in conceptualization, validation, investigation, resources, supervision, project administration and funding acquisition. MRRM was included in data curation and writing (original draft preparation). MM was included in methodology and formal analysis. All authors participated in preparing the final draft of the manuscript, review and editing.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Semnan University of Medical Sciences approved this study (IR.SEMUMS.REC.1400.214). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Mohammad Reza Rahimi Majd at this university (Thesis#245). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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