



Correlates of Recurrence-Free Survival in Papillary Thyroid Carcinoma: A Cohort Study in an Iranian Population

Papiller Tiroid Karsinomunda Nüksüz Sağkalım ile İlişkili Faktörler: İran Popülasyonunda Bir Kohort Çalışması

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Abstract

Objective: Papillary thyroid carcinoma (PTC) is considered differentiated and has a good prognosis; however, the patient's survival differs from clinicopathological risk factors. This study is meant to assess factors predicting recurrence-free survival. **Material and Methods:** In this longitudinal study, we examined a cohort of 208 patients with PTC from 1977 to 2020. Patients who underwent total thyroidectomy entered the study. Thyroidectomy was considered the primary event, while the endpoint of the study was recurrence-free survival. A multivariate and univariate Cox regression test was used to identify independent risk factors in recurrence-free survival. **Results:** The 5-year recurrence-free survival was 90.5% [95% confidence interval (CI): 84.7-96.46]. Multiple regression models displayed that gender [p=0.01 hazard ratio (HR): 2.21, 95% CI 1.20-4.05] and tumor size (p=0.02 HR: 1.93, 95% CI 1.10-3.38) were the most significant factors influencing recurrence-free survival. The median recurrence-free survival among our patients was 12 years. According to the Kaplan-Meier tests, 5 and 10-year recurrence-free survival was 90.5% (95% CI: 84.7-96.46) and 51.7% (95% CI: 41.26-62.26), respectively. The median recurrence-free survival of the tumor was 24 years in tumors <1 cm and ten years in tumors in the range of 1-3.99 cm and ≥4 cm (p=0.02). **Conclusion:** The 5-year recurrence-free survival was 90.5% longer in women and those with tumors less than 1 cm. Tumor size and gender may affect the risk of recurrence/persistent disease.

Keywords: Differentiated thyroid carcinoma; papillary thyroid carcinoma; response to therapy; thyroidectomy; recurrence-free survival

Özet

Amaç: Papiller tiroid karsinomu (PTK) diferansiye kabul edilir ve iyi bir prognoza sahiptir; ancak hastanın sağkalımı klinikopatolojik risk faktörlerine göre farklılaşmaktadır. Bu çalışma, nüksüz sağkalımı öngördüren faktörleri değerlendirmeyi amaçlamaktadır. **Gereç ve Yöntemler:** Bu uzunlamasına çalışmada, 1977-2020 tarihleri arasında PTK'li 208 hastadan oluşan bir kohort çalışmasını inceledik. Çalışmaya total tiroidektomi yapılan hastalar dâhil edildi. Tiroidektomi primer olay olarak kabul edildi, çalışmanın sonlanım noktası ise nüksüz sağkalımdı. Nüksüz sağkalımda bağımsız risk faktörlerini belirlemek için çok değişkenli ve tek değişkenli Cox regresyon testi kullanıldı. **Bulgular:** Beş yıllık nüksüz sağkalım %90,5 idi [%95 güven aralığı (GA): 84,7-96,46]. Çoklu regresyon modelleri, cinsiyetin [p=0,01 tehlike oranı (hazard ratio "HR"): 2,21, %95 GA 1,20-4,05] ve tümör boyutunun (p=0,02 HR: 1,93, %95 GA 1,10-3,38) sağkalımı etkileyen en önemli faktörler olduğunu gösterdi. Hastalarımız arasında medyan nüksüz sağkalım 12 yıl idi. Kaplan-Meier testlerine göre 5 ve 10 yıllık nüksüz sağkalımlar sırasıyla %90,5 (%95 GA: 84,7-96,46) ve %51,7 (%95 GA: 41,26-62,26) idi. Medyan nüksüz sağkalım, boyutu <1 cm olan tümörlerde 24 yıl, boyutu 1-3,99 cm aralığında ve ≥4 cm olan tümörlerde 10 yıl idi (p=0,02). **Sonuç:** Beş yıllık nüksüz sağkalım kadınlarda ve 1 cm'den küçük tümörü olanlarda %90,5 daha uzun bulunmuştur. Tümör boyutu ve cinsiyet, nüks/persistan hastalık riskini etkileyebilir.

Anahtar kelimeler: Diferansiye tiroid karsinomu; papiller tiroid karsinomu; tedaviye yanıt; tiroidektomi; nüksüz sağkalım

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Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 27 Feb 2021 **Received in revised form:** 10 Aug 2021 **Accepted:** 13 Sep 2021 **Available online:** 27 Sep 2021

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Introduction

Differentiated thyroid carcinoma (DTC) is a rapidly growing form of cancer in some populations and accounts for about 3.1% of universal cancer incidence (1).

Papillary thyroid carcinoma (PTC) constitutes about 80% of all thyroid cancers (2). PTC is considered differentiated and has a good prognosis with 10-year free survival ranges between 85 and 95% and 5-year disease-free survival (DFS) at 87.5%. The cancer-specific mortality after 5 years is at 0.8% (3).

Tumor persistence/recurrence is identified in up to 30% of patients. In almost all of these cases, a loco-regional disease without distant metastasis is detected (4).

Many factors correlate with increased risk of recurrence of PTC such as tumor size, patient's age, lymph node (LN) involvement, soft tissue invasion, tumor multifocality, specific subtypes of papillary thyroid cancers, including tall cell, insular, and hobnail variants, extrathyroidal extension (ETE), specific molecular profiles [e.g., BRAF, telomerase reverse transcriptase and gender (male)] (5). Two to ten percent of patients exhibit advanced thyroid cancer with distant metastases at the time of diagnosis, most commonly associated with lung and bone (6).

The American Thyroid Association (ATA) risk stratification predicts the risk of recurrence for thyroid cancer. However, the certainty of this risk stratification needs further improvement (7). For example, the biological progression of PTC can be clarified through ATA risk stratification (8). American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system was developed to predict mortality and is a standard system for the initial risk assessment of patients with DTC. However, TNM staging is not ideal for determining the risk of recurrence of DTC (9). Several factors such as histologic subtypes not included in AJCC affect the risk of recurrence (10).

The accepted treatment currently for PTC is total thyroidectomy followed by postoperative therapy with radioactive iodine (RAI). It aims to destroy residual remnant thyroid tissue and malignant cells, therefore reducing the risk of recurrence, followed by thyroxin suppression therapy (11).

During the follow-up, after initial risk stratification, serum thyroglobulin (Tg) level is used as an important tumor marker for ascertaining cases with persistent/recurrent disease (12). Ultrasonography (USG) is the key method for investigating cervical LN metastasis (13).

Patients with PTC should be assessed 6-12 months after the primary treatment, and a follow-up schedule should be adopted to determine the initial risk of persistent/recurrent disease and responses to therapy (12). This study investigated clinicopathological characteristics, response to initial therapy, recurrence-free survival (RFS), and factors influencing recurrence-free years.

Material and Methods

Study Patients

We studied 208 patients with PTC (166 females, 42 males) in the thyroid clinic of Imam Khomeini Hospital between 1977 and 2020. All patients underwent total thyroidectomy, and 160 received RAI (I131) ablative therapy. We excluded the patients who did not undergo full thyroidectomy, had a survival of fewer than 2 years and failed in the follow-up. Our patient's mean follow-up was 11 years after initial treatment, and their mean age (\pm SD) was 48.82 ± 14.29 years.

Subjects have given their written informed consent. This project was approved by the Ethics Committee of Imam Khomeini Hospital Complex of Tehran University of Medical Sciences (Approval ID: IR.TUMS.IKHC.REC.1398.078 on September 30th 2019). The study was conducted according to the Helsinki Declaration.

Study Protocol and Variables

The patient's clinicopathological characteristics such as (gender, median age, tumor size (<1 cm vs. 1-3.99 cm vs. \geq 4 cm), histological subtype, capsular invasion, extra thyroid extension (no vs. microscopic), lymphovascular invasion, local metastasis, distant metastasis, a biopsy of highly suspicious lymph nodes in postoperative USG, total I131 therapeutic dose, and post-operation unstimulated Tg level were collected and analyzed. After the preliminary treatment, each patient was subjected to risk stratification

using the modified risk stratification system from the ATA guidelines (8). The endpoint was RFS.

For low-risk patients, the initial follow-up was 3-6 months after risk stratification, with a thyroid-stimulating hormone (TSH) range between 0.5-1.5 mIU/L (14). Moreover, an USG of the neck was scheduled every 6 months (15). Diagnostic RAI scans were rarely required in the follow-up of low-risk patients because approximately all recurrences in these groups could be diagnosed by serum Tg and neck USG (16). The primary aim of early follow-up for low-risk patients was to find patients with excellent responses to initial therapy so their follow-up design could be changed to a much fewer vigor program (16).

The initial follow-up program had a visit scheduled 3-6-months after completion of treatment with a risk stratification target range of TSH between 0.1-0.5 mIU/L for intermediate-risk patients (16). Neck USG was performed every 6 months, and sometimes earlier (16). RAI scans were generally not used as a screening method for recurrence. Still, RAI scans might be used to identify the functional status of structural disease detected during follow-up or to localize the origin of significant serum Tg levels elevation (14).

In high-risk patients, follow-up programs were more customized and dynamic than patients in intermediate-and low-risk stratification groups (16). Commonly, most of these patients got their initial imaging (consisting of the neck and chest along with the imaging of any residual disease after initial therapy) approximately three months after initial therapy (16). In such patients, diagnostic RAI scans were performed more frequently to detect patients with early disease progression (16). Follow-up programs for the rest of the first year were dependent upon the images obtained during these 2-3-month and could not be generalized for all patients as a fixed program (16). In high-risk patients, the target TSHs was usually 0.1 mIU/L, except for patients whose comorbidities caused contraindication (14).

Regarding the assessment of response to the total thyroidectomy and RAI ablative therapy as initial therapy, we used a combination of biochemical and imaging studies,

including serum Tg, neck USG, and classified patients into 3 categories:

Excellent response (unstimulated Tg < 0.2 ng/dL, stimulated Tg < 1 ng/mL, and negative neck USG for structurally identifiable disease),

Biochemical incomplete response (unstimulated Tg > 1 ng/dL, stimulated Tg ≥ 10 ng/mL, and absence of structurally identifiable disease in neck USG),

Structural insufficient response (persistent/recurrent structurally detectable disease in neck USG or physical examination with or without unstimulated Tg elevation (7).

Definition of the endpoint in this study (Recurrence-Free-Survival) means the length of time after primary treatment that the patient survives without any signs or symptoms of that particular cancer.

Statistical Analysis

Mean (±SD) and frequencies (%) were used to describe each patient group's characteristics. Chi-square tests, one-way ANOVA tests were used to analyze categorical and continuous variables between the 2 groups, respectively.

The Kaplan-Meier test was conducted to estimate the RFS and the median time to recurrence after total thyroidectomy.

The Cox proportional hazard regression model determined the chance of factors on RFS. Variables ≤ 0.200 in the univariate Cox regression were considered potentially significant and were included in the multivariate Cox regression. The hazard ratio (HR) and its 95% confidence interval (CI) were projected.

All analyses were conducted using Stata version 12. A p value of less than 0.05 was considered statistically significant.

Results

Basic demographic and treatment data are depicted in Table 1. Out of 208 patients with PTC registered in our study, 166 (79.8%) were female, and 42 (20.1%) were male. The mean age of our patients was 48.82±14.29 years, and the mean tumor size was 1.73 (±1.19) (Table 1, Table 2). The total number of I131 ablative therapy was 158.19±63.63 in patients with tumors < 1 cm, 164.73±97.88 in those with tumors in

Table 1. Baseline characteristics and treatment data in the study population (n=208).

Variables	n (%)
Gender	
Male	42 (20.1)
Female	166 (79.9)
Age¶	48.82±14.29
Tumor size	
<1 cm	42 (20.1)
1-3.99 cm	145 (69.7)
≥4 cm	21 (10.0)
Local metastasis	35 (16.8)
Distant metastasis	8 (3.8)
Capsular invasion	40 (19.2)
Extra thyroid extension	23 (11.0)
Lymphovascular invasion	76 (36.5)
Risk group	
Low risk	83 (39.9)
Intermediate risk	72 (34.6)
High risk	53 (25.4)

Data presented as n (number) and % (percentage); ¶Ages present as mean±standard deviation.

the range of 1-3.99 cm, and 129.54±60.01 among patients with tumors of 4 cm and greater than 4 cm (p=0.978) (Table 2). The mean tumor size was 1.97±1.28 cm among males and 1.67±1.16 cm among fe-

males (p=0.16). The mean I131 therapeutic dose was 167±151 mild cognitive impairment (MCI) among males and 127±122 MCI in female patients (p=0.08) (Table 3).

Among the other patients, only 8 (3.8%) had advanced thyroid cancer, which mostly metastasized to the bone and lung.

In total, 126 (60.5%) patients had excellent response [101 female (80.1%) and 25 (19.8%) male], 32 (15.3%) had biochemical incomplete response [25 (78.1%) female and 7 (21.8%) male], and 50 (24.0%) had structural incomplete response [40 (80.0%) female and 10 (20.0%) male] (Table 1, Table 3).

In the multivariate Cox regression model, these variables, including gender (p=0.01 HR: 2.21, 95% CI 1.20-4.05) and tumor size (p=0.02 HR: 1.93, 95% CI 1.10-3.38) were recognized as an independent risk factor in RFS (Table 4).

Recurrence rate was 26 (49.0%) in high risk group and 13 (18.0%) in intermediate-risk patients (p=0.001). As per the response to therapy, the recurrence rate was 33 (66%) in incomplete structural response and 6 (18.7%) in incomplete biochemical response and was not visible in patients with excellent response to therapy (Table 5).

Here, the recurrence rate of patients was 39 (18.7%). Recurrence occurred in 31

Table 2. Relationship between clinicopathological variables and the tumor size.

Variable	<1 cm (n=42)	1-3.99 cm (n=145)	≥4 cm (n=21)	p value
Gender				
Male	8 (19.0%)	31 (21.3%)	3 (14.2%)	0.73 [†]
Female	34 (80.9%)	114 (78.6%)	18 (85.7%)	
Risk group				
Low	19 (45.2%)	56 (38.6%)	8 (38.0%)	0.319 [†]
Intermediate	9 (21.4%)	55 (37.9%)	8 (38.0%)	
High	14 (33.3%)	34 (23.4%)	5 (23.8%)	
Metastasis				
Local metastasis	8 (19.0%)	22 (15.1%)	5 (23.8%)	0.27 [†]
Distant metastasis	1 (2.3%)	6 (4.1%)	1 (4.7%)	0.708 [‡]
Capsular invasion	7 (16.6%)	27 (18.1%)	6 (28.5%)	0.268 [‡]
Extra thyroidal extension	5 (11.9%)	14 (9.6%)	4 (19.0%)	0.229 [‡]
Lymphovascular invasion	14 (33.3%)	54 (37.2%)	8 (38.0%)	0.844 [‡]

[†]Pearson's chi-square test; [‡]Fisher's exact test.

(18.6%) women, 8 (19.0%) men ($p=0.42$), 9 (39.13%) patients with ETE ($p=0.022$) and 23 (58.97%) patients with tumors in the range of 1-3.99 cm ($p=0.27$). The tumor size was not the factor in predicting capsular invasion, lymphovascular invasion, extrathyroidal extension, metastasis, and response to initial therapy. In the present study, univariable and multivariable Cox proportional hazard regressions recognized factors that influenced the RFS.

According to the univariable Cox proportional hazard regression model, factors such as tumor size [$p=0.02$ (HR): 1.86, 95% CI 1.09-3.18], gender [$p=0.02$ (HR): 1.93, 95% CI 1.08-3.44], extra thyroid extension [$p=0.01$ (HR): 3.13, 95% CI 1.32-7.43] and lymphovascular invasion [$p=0.03$ (HR): 2.13, 95% CI 1.28-3.53] had important association with recurrence-free years. The median RFS among our patients was 12 years. As per the Kaplan-Meier tests, 5 and

Table 3. Baseline characteristics of the studied population 3-6 months after total thyroidectomy and radioactive iodine ablative therapy according to the response to initial therapy.

Variable	Structural incomplete response 50 (24.03%)	Biochemical incomplete response 32 (15.3%)	Excellent response 126 (60.5%)	p value
Gender n (%)				
Male	10 (20.0)	7 (21.8)	25 (19.8)	0.976 [†]
Female	40 (80.0)	25 (78.1)	101 (80.1)	
Tumor size n (%)				
<1 cm	11 (20.8)	8 (25.0)	23 (17.9)	0.736 [†]
1-3.99 cm	33 (66.7)	22 (68.7)	90 (73.2)	
≥4 cm	6 (12.5)	2 (6.2)	13 (8.9)	
Risk group n (%)				
Low	4 (8.0)	1 (3.1)	78 (61.9)	<0.001 [†]
Intermediate	23 (46.0)	1 (3.1)	48 (38.09)	
High	23 (46.0)	30 (93.7)	0 (0)	
Metastasis n (%)				
Local metastasis	30 (60.0)	5 (15.6)	0 (0)	<0.001 ^{*†}
Distant metastasis	7 (14.0)	1 (3.1)	0 (0)	<0.001 ^{*†}
Capsular invasion n (%)	14 (28.0)	4 (12.5)	22 (17.4)	0.174 [†]
Extra thyroidal extension n (%)	10 (20.0)	2 (6.2)	11 (8.7)	0.64 [†]
Lymphovascular invasion n (%)	26 (52.0)	10 (31.2)	40 (31.7)	0.030 ^{*†}

†Pearson's chi-square test; †Fisher's exact test; * $p<0.05$ was significant.

Table 4. Cox proportional hazard models predicting the recurrence-free survival.

Variable	Univariate Cox regression			Multivariate Cox regression			
		Hazard ratio	p value	95% CI	Hazard ratio	p value	95% CI
Gender*		1.93	0.02*	1.08-3.44	2.21	0.01*	1.20-4.05
Tumor size	<1 cm	Ref.					
Capsular invasion	1-3.99 cm	1.86	0.02*	1.09-3.18	1.93	0.02*	1.10-3.38
	≥4 cm	2.17	0.10	0.84-5.58	2.02	0.16	0.75-5.42
Extra thyroidal extension		1.56	0.16	0.83-2.90	1.18	0.61	0.61-2.28
Extra thyroidal extension		3.13	0.01*	1.32-7.43	1.98	0.12	0.77-5.06
Lymphovascular invasion		2.13	0.003	1.28-3.53	1.58	0.11	0.89-2.81
Mean total I131 dose (mci)		0.99	0.66	0.99-1.002	-	-	-

* $p<0.05$ was significant; *Recurrence-free survival was shorter in the male gender; Reference group is female; CI: Confidence interval.

Table 5. Recurrence rate according to tumor size, risk groups, and response to treatment.

Variables	Recurrence n (%)	p value
Gender		
Male (n=42)	8 (19.0)	ns
Female (n=166)	31 (18.6)	
Age	50.49 years old	ns
Risk		
High (n=53)	26 (49.0)	<0.001 ^{†*}
Intermediate (n=72)	13 (18.0)	
Low (n=83)	0	
Response to therapy		
Excellent (n=126)	0	<0.001 ^{†*}
Biochemical incomplete (n=32)	6 (18.7)	
Structural incomplete (n=50)	33 (66.0)	
Tumor size		
<1 cm (n=41)	10 (25.6)	ns
1-3.99 cm (n=145)	23 (58.9)	
≥4 cm (n=21)	6 (15.3)	
Capsular invasion		
Negative (n=168)	26 (15.4)	0.021 ^{‡*}
Positive (n=40)	13 (32.5)	
Extra thyroid extension		
Negative (n=185)	30 (16.2)	0.022 ^{§*}
Positive (n=23)	9 (39.1)	
Lymphovascular invasion		
Negative (n=132)	12 (9.0)	<0.001 ^{†*}
Positive (n=76)	27 (35.5)	

*p<0.05 was significant; †ANOVA test; ‡Pearson's chi-square; §Fisher's exact test, ns: not significant.

10-year RFS was 90.5% (95% CI: 84.7-96.46) and 51.7% (95% CI: 41.26-62.26) (Figure 1). RFS in women with PTC is significantly higher than in men (p=0.01) (Figure 2). The median RFS as per the tumor size was 24 years in tumors <1 cm, 10 years in tumors in the range of 1-3.99 cm, and ≥4 cm (p=0.02) (Figure 3). Patients with tumor size less than 1 cm had a RFS that was longer than those with tumors in the range of 1-3.99 cm (Table 4). Women's 5-year RFS was longer than men's (Figure 2, Table 4).

Discussion

In the present group of patients with PTC, the median RFS was 12 years. RFS was longer in women with a tumor less than 1 cm. Mean RFS was 15 years in females, 6

years in males, and 24 years in those with a tumor less than 1 cm. The gender, tumor size, and ETE were correlated with RFS in univariate analysis. However, for multivariate analysis, only gender and tumor size were defined as factors influencing RFS.

The tumor size was not an aspect in predicting capsular invasion, lymphovascular invasion, extrathyroidal extension, metastasis, and response to initial therapy.

In the low-risk patient group, 45.2% had tumor size less than 1 cm. Meanwhile, 33.3% in the high-risk group had tumors less than 1 cm. Tumors greater than 4 cm were recognized in 38.0% of low-risk patients and 23.8% of high-risk patients.

As per the ATA risk stratification, tumor size does not play a key role in determining the risk stratification of patients (17).

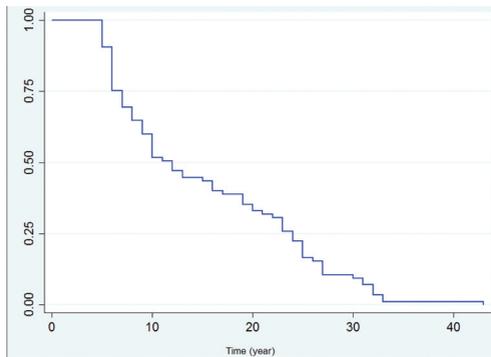


Figure 1. Kaplan-Meier recurrence-free survival in the papillary thyroid carcinoma patients.

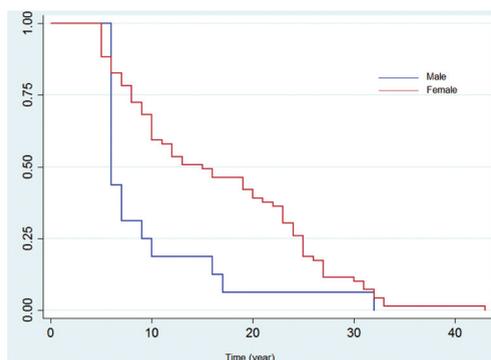


Figure 2. Kaplan-Meier recurrence-free survival in the papillary thyroid carcinoma patients according to gender.

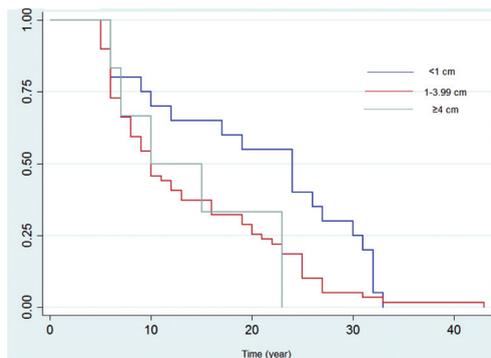


Figure 3. Kaplan-Meier recurrence-free survival in the papillary thyroid carcinoma patients according to tumor size.

In the present study, recurrence was more loco-regional (16.82%) and found commonly in the lateral neck lymph nodes than in the thyroid bed.

Medas et al., in a retrospective study, assessed patients after thyroidectomy for DTC from 2011 to 2016 at their institution.

They identified the biochemical or structural recurrent disease in 36 (6.2%) patients. The 5-year DFS was 94.1%. In this research, for univariate analysis, male sex, histotype, LN yield, LN metastasis at the time of surgery, extrathyroidal invasion, and multicentricity were correlated with a significantly higher risk of recurrence. In comparison, microcarcinoma was associated with a substantially lower risk of recurrence. In multivariate analysis, only LN metastases [odds ratio (OR) 4.724, $p=0.012$] and microcarcinoma (OR 0.328, $p=0.034$) were detected as independent predictive factors of recurrence (18).

In patients with excellent responses to therapy, no recurrence was observed during follow-up. Jeon et al. investigated DTC in patients who had an excellent response to treatment during a median follow-up of 8.7 years. They also showed that recurrences of DTC in patients with an amazing response to initial therapy were detected almost late. The intensity and frequency of follow-up of neck USG and serum Tg and anti-Tg antibody measurements should be reduced, especially within 5 years of the initial therapy (19).

We found that among patients with a structural incomplete response group, recurrence happened in 66% of patients. Further, capsular invasion, extrathyroidal extension, and lymphovascular invasion were more common in patients with incomplete structural responses. Local and distant metastases also were noticed more in patients with incomplete structural responses. Moreover, tumors with more aggressive behavior were seen in this group. The incomplete biochemical response to initial therapy recurrence was less common (18.0%) than incomplete structural response. This result indicates that a high Tg level does not mean a higher probability of repetition in the patient. Vaisman et al., in a retrospective study, evaluated 192 adult thyroid cancer patients following total thyroidectomy and RAI ablation with biochemical and structural incomplete response to initial therapy (20). Clinical outcomes evaluated include structural disease progression, biochemical disease progression, and overall survival (OS) (20). They showed that a structural response to initial treatment is associated with

a significantly worse clinical outcome than an incomplete biochemical response to therapy (20).

Ahn et al. evaluated 102 patients with PTC showing an incomplete biochemical response during the first 12-24 months after total thyroidectomy and RAI therapy. PTC patients with incomplete biochemical reactions showed a high rate of persistent structural disease. The Tg change after initial therapy was the most vital prognostic factor for determining clinical outcomes of patients (21).

Ito et al. assessed PTC patients who underwent initial surgery. The median postoperative follow-up duration was 177 months. They showed that the most significant prognostic factor for OS was patient age, demonstrating PTC is generally indolent (22).

Risk groups had a massive effect on the recurrence rate. Most patients were in the low-risk group in the present study, and recurrence happened in 19.7% of the patients.

Wang et al. assessed patients with PTC after total thyroidectomy between 2000 and 2010 in 36 months of follow-up. Among the total patients in their study, most of them were in the intermediate-risk group, 362 (31.1%) patients were low risk, 561 (51.6%) intermediate-risk, and 164 (15.1%) high risk according to ATA risk (23). The ATA recurrence risk stratification can foresee the risk of recurrence for thyroid cancer, but the accuracy of this risk stratification needs improvement (9). For example, through the ATA risk Stratification, the biological progression of PTC and fundamental processes such as cell growth, the transformation of normal cells to cancer cells, the spread (metastasis) of cancer cells, age, sex, and tumor size can be clarified. AJCC/UICC staging system, consisting of Clinicopathological factors, can estimate the mortality associated with PTC. Still, it does not predict disease recurrence risk (8).

Banerjee et al., in a population-based study, evaluated treatment-free survival in patients with PTC. According to their analysis, the significant factors for predicting treatment-free survival were disease stage, tumor size, and receiving RAI (24). After initial surgery and preparation of patients, 79.93% of patients in intermediate and high-risk cate-

gories and those with invasive pathologic features received RAI ablative therapy. Mean radioiodine dose administered to the patients had no significant impact on RFS. At the first follow-up, 3-6 months after thyroidectomy, patients were re-stratified as per their clinical status. ATA risk stratification is based on histology and whole-body scan results. Dynamic risk stratification of DTC patients, once the response to surgery and radioiodine ablation is evident, allows us to define individual risk better and modulate the subsequent follow-up (25).

Advanced thyroid cancer cases, including those presenting with locally advanced disease or distant metastatic thyroid cancer, comprise 10-15% of total thyroid cancer patients. Only 4% of patients with thyroid cancer present with distant metastasis at the time of diagnosis (26). The management of these patients requires a multidisciplinary group of specialists (26).

With the rapidly increasing number of PTC cases, adequate treatment and patient surveillance have become crucial. The strength of this study had a mean follow-up of 11 years, with more than fifty percent of patients having at least 6 years of follow-up. This is the first report of a group study in the Iranian population. The major limitation of this study is that the various pathologic subtypes are not included since the previous year's pathologic reports were not according to the ATA system and the details of tumor pathology.

Conclusion

We demonstrate disease recurrence in 39 (19.7%) patients. The 5-year RFS was 90.5% and was longer in women and those with less than 1 cm tumors. Gender and tumor size exhibited the highest coefficient for predicting RFS.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Manouchehr Nakhjavani, Bahareh Shateri Amiri, Mahboobeh Hemmatabadi; Design: Manouchehr Nakhjavani, Bahareh Shateri Amiri, Mahboobeh Hemmatabadi; Control/Supervision: Manouchehr Nakhjavani; Data Collection and/or Processing: Bahareh Shateri Amiri, Manouchehr Nakhjavani; Analysis and/or Interpretation: Bahareh Shateri Amiri, Hamideh Hasannejad; Literature Review: Bahareh Shateri Amiri, Mahboobeh Hemmatabadi, Manouchehr Nakhjavani; Writing the Article: Bahareh Shateri Amiri, Mahboobeh Hemmatabadi, Soghra Rabizadeh, Manouchehr Nakhjavani; Critical Review: Manouchehr Nakhjavani, Bahareh Shateri Amiri, Mahboobeh Hemmatabadi, Soghra Rabizadeh; References and Fundings: Manouchehr Nakhjavani, Mahboobeh Hemmatabadi; Materials: Manouchehr Nakhjavani, Bahareh Shateri Amiri, Mahboobeh Hemmatabadi.

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