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Negative Histopathological Prognostic Factors Affecting Morbidity in T1 Differentiated Thyroid Carcinoma

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Abstract

Background: The aim was to evaluate (i) if multifocality is a negative prognostic factor, (ii) the association of diameter of the largest tumor, total tumor diameter, and the ratio of the largest tumor diameter to total tumor diameter (DR) with histopathological and clinical outcome parameters in T1 differentiated thyroid carcinoma (DTC).
Methods: In 1014 T1N0/1Mx patients, correlation between multifocality, contralateral lobe involvement, capsular-vascular invasion, diameter of the largest tumor, total tumor diameter, DR, and follow-up results were investigated.
Results: Persistent/recurrent disease and necessity for additional radioiodine treatment (RAIT) were more frequent in cases with multifocality and contralateral lobe involvement ($p=0.035$, $p=0.015$, $p=0.021$, and $p=0.04$). Persistence/recurrence, reoperation in the neck, and additional RAIT were more frequent in patients with the size of the largest tumor focus >1 cm ($p=0.024$, $p<0.001$, and $p=0.002$) and N1 status ($p<0.001$, $p<0.001$, and $p<0.001$). Mean total tumor diameter was higher in patients with capsular invasion, contralateral lobe, and lymph node involvement ($p=0.001$, $p=0.003$, and $p=0.013$).
Conclusion: Multifocality, contralateral lobe involvement, diameter of the largest tumor >1 cm, and N1 status are related with increased risk of disease persistence, recurrence, reoperation, and additional RAIT. Sum of diameter of all tumor foci are associated with capsular invasion.

Keywords: contralateral lobe involvement, dynamic risk stratification, multifocality, papillary thyroid cancer, radioiodine treatment, tumor size

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Introduction

Multifocality is defined as the coexistence of more than one independent tumoral foci.[1] Differentiated thyroid carcinoma (DTC) is a very frequent tumor, with high incidence of asymptomatic existence as revealed by autopsy series, as well as multifocal DTC, proving that multifocality is not a definitive risk factor for bad prognosis.[2] However, it has been proposed that multifocality may cause a worse clinical outcome if smaller tumor foci other than the dominant nodule are developed as a result of the intrathyroidal lymphatic spread from the primary tumor.[3–5] Most of the additional tumoral foci are usually smaller and their additive impact on clinical course of the disease is still a matter of debate. Evaluating only the diameter of the largest tumor may cause an underestimation and considering all measurable foci may in turn result in overestimation.[6–8]

Clinical relevance of multifocality in T2-3 tumors has been studied before. Incidence of relapse was higher, progression-free survival (PFS) and overall survival were shorter in patients with multifocal tumors, and multifocality was an independent risk factor for both PFS and disease-specific survival (DSS). Multifocality was also found highly associated with lymph node metastasis, extrathyroidal invasion, tumor size, and disease progression.[1,9–11] Some studies have investigated multifocality separately in two groups: microcarcinomas and larger tumors. In large series of papillary thyroid carcinoma, for instance, multifocality was proven to be an independent risk factor for persistence or recurrence in patients with tumors >1 cm size, but it was not the same for papillary microcarcinomas.[12] The question is, if multifocality is a negligible factor for deciding treatment and follow-up strategy in tumors located in the gray zone, that is tumors <2 cm in diameter (T1 tumors). Although T1 tumors are

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classified in low-risk group, persistence or recurrence can still be observed in some cases. Factors which may be indicative of disease progression or relapse (like diameters of tumor foci) are still of debate. Thus, the main aim of this study was to evaluate if multifocality and contralateral lobe involvement are related with biochemical and scintigraphic response on the 6th month of radioiodine treatment (RAIT), persistent or recurrent disease in the follow-up, and if necessity for further neck surgeries and RAIT is more frequent in T1 cases with multifocal and/or contralateral lobe involvement. Secondary objectives were investigating the relationship of diameter of the largest tumor and total tumor diameter as well as the ratio of the largest tumor diameter to total tumor diameter with histopathological parameters and follow-up results in T1 papillary thyroid carcinoma following RAI ablation in a large patient cohort with long-term clinical follow-up.

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Materials and Methods

Patients

Following Ethics Committee approval (İlI-704-20), clinical data of 3050 consecutive DTC patients, who received RAIT in the department following thyroidectomy between January 1998 and January 2015, were retrospectively reviewed. Among these, a total of 1014 patients aged >18 (155M, 859F, mean age: 44.97 ± 11.89 years min:20, max:83) with T1N0/N1Mx (TNM classification of American Joint Committee on Cancer, Chicago, IL) tumors according to histopathological examinations of thyroidectomy materials were selected as the study group.

All patients underwent RAIT 4–6 weeks after thyroidectomy with T4 withdrawal, provided serum thyroid-stimulating hormone levels were >30 IU/mL. Preablative stimulated serum Tg and Tg antibody (TgAb) levels were recorded. LT4 suppression therapy was started at 24th hour after treatment. Postablative I-131 whole body scan (WBS) was performed on 5–7th days after RAIT. All patients were reevaluated by 185MBq I-131 diagnostic WBS with T4 withdrawal 6–12 months later and stimulated serum Tg and TgAb levels were measured again. Patients with excellent response (a negative diagnostic WBS with undetectable stimulated serum Tg and TgAb) were followed up every 6 months by serum Tg and TgAb measurements under T4 suppression and annual neck ultrasonography (US). The presence of a positive Tg, persisting/increasing TgAb levels or development of structural disease within 1 year after RAIT was defined as "persistent disease." If structural or biochemical relapse was detected following a disease-free status of 1 year, this condition was then defined as "recurrent disease." Patients with persistent or recurrent disease (structural and/or biochemical) were further evaluated with neck US, thorax computerized tomography (CT), or 18F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). Follow-up data were also recorded, including the localization of persistence, recurrence or metastasis, total follow-up time, need for extra surgery, or further RAI administration.

Data analysis

Age, gender, histopathological variant of the tumor (tall cell, columnar cell, and oncocytic variants were classified as aggressive variants), existence of multifocality, contralateral lobe involvement, capsular or vascular invasion, diameter of the largest tumor focus and in multifocal cases, sum of the largest diameter of all tumor foci and diameter ratio (DR = the largest tumor diameter/total tumor diameter), and biochemical and scintigraphic response on 6th month of RAIT were recorded. Follow-up results, including the status of persistence or recurrence and the need for additional RAIT or neck surgery, were also noted. The relationship of these parameters with each other was investigated. In multifocal cases; sum of the diameter of all tumor foci and DR were further analyzed to determine if the probability of undergoing further neck surgeries or receiving additional RAIT in the follow-up can be estimated at diagnosis by these parameters. Patients were divided into two groups as DR values and preablative serum Tg levels below and above the mean levels. Additional subgroup analyses were performed for total diameter and largest tumor diameter below and above 1 cm.

Statistical analysis

Descriptive data were expressed as mean ± standard deviation (SD) values. Chi-square test was used to determine univariate relationships and risk estimation for persistence/recurrence and probability of necessity for additional surgery or RAIT in the follow-up. *T*-test was used to compare the mean values of two independent groups. Values of $p < 0.05$ were significant. Statistical analysis was conducted using the Statistical Package for Social Sciences - SPSS 17.0 (Chicago, IL).

Results

Total thyroidectomy was performed in 740/1014 (72.9%), subtotal thyroidectomy was completed in 135/1014 (13.5%), central neck node dissection was added to total thyroidectomy in 100/1014 (9.8%), and lateral neck dissection was needed in 39/1014 (3.8%) of the patients. Of the patients, 896/1014 (88%) had a lymph node status "N0." In 118/1014 (12%) patients, lymph node metastasis was detected in 79/118 (67%) in the central compartment and in 39/118 (33%) in the lateral compartment.

Fixed dose ablation protocol was followed and administered RAI activities ranged between 1110 and 5500MBq according to risk groups. (patients with intrathyroidal tumors with no lymph node metastasis or <5 micrometastasis and no other risk factors received 1110–3700MBq. RAI doses of 4625–5550Mq were applied for a relatively higher risk histopathology: extrathyroidal invasion, aggressive histology, existence of >5 lymph node metastasis, and vascular invasion). Preablative serum TgAb was positive in 150/1014 patients (15%). Metastatic disease was found in 20/1014 (2%) patients on postablation scan (10 in the lungs, 10 in the lymph nodes). Duration of mean follow-up was 189.51 ± 116.53 months (min:20, max:563). During follow-up period, 916/1014 (90.3%) of the patients were under remission with an excellent therapy response, but disease remained persistent in 90/1014 (8.8%) patients. Among these, persistent disease was in the lungs in 10/90 (11%) patients and in the lymph nodes, which could not be removed by surgery (due to high complication risk of reoperation of the neck) or treated by RAI in 55/90 (61%) patients. Biochemical

persistence with no detectable structural disease was found in 25/90 (28%) patients. Recurrence was observed in 8/1014 (0.8%) patients. In 1/8 patients (12.5%) lung metastasis, and in 6/8 (75%) patients, lymph node metastasis developed in the follow-up. In 1/8 (12.5%) patients, only biochemical recurrence was found with a gradual increase in serum Tg levels and no identifiable disease focus. Of the patients, 49/1014 (4.8%) with recurrence or persistent disease had to undergo further surgery for lymph node spread and 68/1014 (6.7%) received additional high-dose RAIT. Descriptive data are summarized in Table 1.

Persistent or recurrent disease in the follow-up and necessity for additional RAIT sequences were more frequent in cases with multifocal tumors (14.3% vs. 8.3%, $p=0.035$, and 11% vs. 5.3% $p=0.015$, respectively). The same was also true for contralateral lobe involvement (15.5% vs. 8.9% $p=0.021$ and 12.1% vs. 5.8% $p=0.004$) (Table 2). However, biochemical or scintigraphic response rates on the 6th month of RAIT did not differ among groups with multifocal or unifocal tumors.

TABLE 1. DESCRIPTIVE DATA OF THE PATIENTS AND CLINICAL FOLLOW-UP RESULTS

Age	44.97 ± 11.89 (min:20, max:83)
Diameter of the largest tumor (cm)	1.04 ± 0.52 (min:0.1, max:2)
Sum of all tumor foci (cm)	1.75 ± 1.02 (min:0.1, max:7.1)
DR	0.88 ± 0.19 (min:0.14, max:1)
Preablative Tg (ng/mL)	12.15 ± 39.5 (min:0.1, max:467)
Ablation dose (MBq)	4230.21 ± 907.98 (min:1110, max:5550)
Preablative TgAb positivity	150 (15%)
Surgery	
TT	740 (72.9%)
STT + CT	135 (13.5%)
TT + CLND	100 (9.8%)
TT+ CLND + LLND	39 (3.8%)
Capsular invasion	350 (34.5%)
Vascular Invasion	45 (4.3%)
Multifocality	359 (35.3%)
Contralateral lobe involvement	232 (22.9%)
Histopathological type	
Papillary cancer classical variant	654 (64.5%)
Follicular cancer	112 (11%)
Papillary cancer follicular variant	105 (10.3%)
Papillary cancer Hurthle cell variant	81 (8%)
Papillary cancer tall cell variant	37 (3.7%)
Papillary cancer oncocytic variant	25 (2.5%)
LN metastasis	
Central LN metastasis	79 (7.7%)
Lateral LN metastasis	39 (3.8%)
Clinical follow up	
Remission	916 (90.3%)
Persistent disease	90 (8.8%)
Recurrent disease	8 (0.8%)
Reoperation in the neck	49 (4.8%)
Additional RAIT	68 (6.7%)

DR, diameter ratio; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TT, total thyroidectomy; STT, subtotal thyroidectomy; CT, completion thyroidectomy; CLND, central lymph node dissection; LLND, lateral lymph node dissection; LN, lymph node; RAIT, radioiodine treatment.

The correlation analysis of diameter of the largest tumor revealed that capsular invasion, contralateral lobe involvement, multicentricity, vascular invasion, and lymph node metastasis were significantly more frequent in patients with diameter of the largest tumor >1 cm compared to patients with tumor size <1 cm ($p<0.001$, $p=0.021$, $p=0.035$, $p<0.001$ and $p<0.001$, respectively) (Table 3). Persistence or recurrence, reoperation, and additional RAI were also more frequent in patients with the size of the largest tumor focus larger than 1 cm (9.7% vs. 4.4% $p=0.024$, 6.8% vs. 2% $p<0.001$, and 8.7% vs. 3.9% $p=0.002$, respectively) (Table 2). Logistic regression analysis results showed that in patients falling in the group with the largest tumor size >1 cm were more likely to undergo further surgeries in the neck and receive additional RAIT (OR: 3.49, 95% CI: 1.675–7.272, $p=0.001$ and OR: 2.359, 95% CI: 1.343–4.146, $p=0.003$) (Table 4).

Total tumor diameter and the ratio of the largest tumor diameter to total tumor diameter (DR) were investigated in the separate analysis, including only patients with multifocal tumors ($n=359$). Mean values of total tumor size were higher in patients with capsular invasion, contralateral lobe involvement, and N1 disease status ($p=0.001$, $p=0.003$, and $p=0.013$). The only significantly important result obtained from chi-square tests was that the frequency of capsular invasion was higher in patients with total tumor size >1 cm ($p=0.001$) No relationship was found between DR and histopathological characteristics of tumor, and it was not indicative of any of the follow-up endpoints.

In patients with lymph node metastasis at initial diagnosis (T1N1), occurrence of disease persistence or recurrence was more frequent ($p<0.001$). Reoperation and additional RAIT were also more recently needed in the follow-up in these patients ($p<0.001$) (Table 2).

In the separate analysis conducted by excluding patients who already had lymph node metastasis at initial diagnosis and only T1N0 patients are analyzed, chi-square test revealed that capsular invasion, contralateral lobe involvement, and vascular invasion were more frequent in patients with the size of the largest tumor >1 cm ($p<0.001$, $p=0.021$ $p=0.001$, respectively). According to follow-up results, necessity for reoperation and/or additional RAIT was more frequent in patients with the size of the largest tumor >1 cm ($p=0.002$ and $p=0.011$). Logistic regression revealed that in patients with the largest tumor size >1 cm had a higher risk of undergoing reoperation (OR: 4.59, 95% CI: 1.57–13.44, $p=0.005$) and additional RAIT (OR: 2.51, 95% CI: 1.212–5.199, $p=0.013$), Among 304 T1N0 patients who have multifocal tumors, capsular invasion and contralateral lobe involvement were more common in patients with calculated sum of diameter of all tumor foci ($p<0.0001$ and $p=0.013$).

By excluding aggressive variants, follicular cancer and follicular subgroup of papillary cancer, statistical analysis focusing on only 654 patients with classical variant of

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Table 2. Chi Square Analysis Results for Disease Persistence/Recurrence, Reoperation in the Neck, and Necessity for Additional Radioiodine Treatment in the Whole Study Group

	Persistence/recurrence			*Reoperation in the neck*			*Re-RAIT*		
	n	%	P	n	%	p	n	%	p
Multifocality									
Pos	52	14.3	0.035	23	6.8	0.21	35	11	0.015
neg	46	8.3		26	4.1		33	5.3	
LN metastasis									
pos	37	28.4	<0.001	23	19.3	<0.001	28	23.5	<0.001
neg	61	7.3		26	2.9		40	4	
Contralateral lobe involvement									
pos	34	15.5	0.021	16	7.4	0.09	25	12.1	0.004
neg	64	8.9		33	4.4		43	5.8	
Diameter of the largest tumor									
>1 cm	74	9.7	<0.001	40	6.8	<0.001	51	8.7	0.002
≤1 cm	24	4.4		9	2		17	3.9	

Pos, positive; neg, negative; LN, lymph node; RAIT, radioiodine treatment.

papillary cancer was also performed. Capsular invasion, vascular invasion, and lymph node metastasis were more frequent in cases with size of the largest tumor >1 cm ($p<0.001$, $p=0.007$ and $p=0.007$, respectively) and only capsular invasion was more frequent in cases with total tumor diameter >1 cm ($p=0.027$). In the follow-up, persistant or recurrent disease was more frequent in multicentric tumors, contralateral lobe involvement, lymph node involvement, in tumors with size >1 cm, and in cases with total tumor diameter >1 cm ($p=0.043$, $p=0.022$, $p<0.001$, $p<0.001$ and $p=0.03$, respectively). Additional surgery and RAI requirements were also more frequent in patients with capsular invasion, lymph node metastasis, size of the largest tumor >1 cm, and total tumor diameter >1 cm ($p=0.006$ and $p=0.008$, $p<0.001$ and $p<0.001$, $p=0.005$ and $p=0.021$, $p=0.001$ and $p=0.003$, respectively). Therapy response evaluated by I-131 whole-body scintigraphy and stimulated Tg levels on 6th month of therapy was indicative of clinical outcome in papillary cancer classical variant cases. Persistant or recurrent disease was more common in nonresponders ($p<0.001$ for both). Reoperation and additional RAIT requirements were less frequent in patients with scintigraphic or biochemical response ($p=0.01$ and $p<0.001$, $p<0.001$, and $p=0.003$).

Mean values of preablative stimulated serum Tg levels were significantly higher in recurrent or persistent cases ($p<0.001$ and $p<0.001$) and in patients who underwent additional surgeries in the neck and/or received further RAIT ($p<0.001$ and $p<0.001$). Scintigraphic and biochemical response evaluated 6 months later and existence of aggressive tumor variants were not statistically significant parameters in the clinical follow-up for the whole study group.

Table 3. Chi-Square Analysis Results for Diameter of the Largest Tumor >1 cm

	Diameter of the largest tumor		
	<1 cm n *(%)*	*>1 cm* n *(%)*	
Capsular invasion	101 (23.3)	249 (43)	$p<0.001$
Contralateral lobe involvement	85 (19.6)	145 (25)	$p=0.021$
Multicentricity	146 (33.7)	212 (36.5)	$p=0.035$
Vascular invasion	7 (1)	37 (6.3)	$p<0.001$
Lymph node metastasis	34 (7.8)	85 (14.6)	$p<0.001$

Discussion

Multifocality is not recognized as an independent risk factor of DSS in low-risk tumors at any T stage, and less aggressive treatment is advised, even if there is lymph node involvement.[13,14] Almost all published series investigating multifocality in DTC included tumors of any size, some of which divide into two as tumors <1 cm and >1 cm.[12] However, clinical outcome in all tumors exceeding 1 cm are not the same and this heterogeneity may be the reason for reports with conflicting results. It is obvious that for tumors in higher T stages, multifocality is an independent prognostic parameter to administer more aggressive treatments (like completion thyroidectomy and/or RAI).[1,9]

The objective of this study was to investigate the prognostic significance of multifocality, contralateral lobe involvement, diameter of the dominant nodule, and total tumor diameter as well as the ratio of the largest tumor diameter to total tumor diameter in T1N0 and T1N1 DTC following radioiodine ablation. Survival analysis was not conducted in this series because the chosen study group was already proven to be in a very low risk of disease-specific mortality.[13] Instead, the authors investigated if persistence

Table 4. Odds Ratios for Risk of Undergoing Further Surgeries or Additional Radioiodine Treatment for Diameter of the Largest Tumor >1 cm

		95% CI		
	OR	*Lower*	*Upper*	p
Reoperation	3.49	1.675	7.272	0.001
Re-RAI	2.35	1.34	4.14	0.003

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or recurrence was observed more frequently and if any of these morbidities lead to further surgeries or RAIT in patients with multifocal tumors. Unlike previous studies, instead of grouping roughly as microcarcinomas and others (all T stages), they focused on a relatively more specific and homogenous group (patients with T1 tumors) extracted from other low-risk patients and aimed to enlighten the gray zone where the prognostic significance of multifocality is still scarce. Enrolling 1014 T1 patients, a large study population for this specific inclusion criterion, strengthened the accuracy of the obtained statistical results.

These results seem to enlighten the gray zone, proving that morbidity can still be higher in some cases with T1 tumors although they may have a low risk of disease specific death.[13] Multicentricity and contralateral lobe involvement were statistically significant predictors of persistent or recurrent disease in the follow-up and the need for repetitive RAIT sequences was more frequent in cases with multifocal T1 DTC. Contralateral lobe involvement has not been studied much, except for one study, suggesting that bilateral multifocality was an indicator of more extensive disease, higher risk of recurrence and mortality, consistent with the authors' findings.[10]

Multifocal tumors with the largest tumor <1 cm were found to become rarely persistent or recurrent after RAI, in contrast to some previous studies suggesting that recurrence rates were higher in multifocal microcarcinomas compared to unifocal tumors.[15] One possible explanation for this discrepancy may be that the extent of surgery differs in this series, and the investigators reported that lobectomy was performed in some of the multifocal cases if contralateral lobe involvement was not clinically overt. This approach may have increased the recurrence rates. As papillary microcarcinomas are still a matter of debate in many ways, there are also many other studies supporting their data.[12,16–18] Consistently, recent recommendations do not recognize multifocality as a separate determinant of DSS in microcarcinomas.[13]

In patients with largest tumor size >1 cm, disease persistence and recurrence was more frequently seen in the follow-up. Diameter of the largest tumor size was also correlated with capsular invasion, vascular invasion, contralateral lobe involvement, lymph node metastasis, and multifocality. Disease management according to the size of the dominant nodule is a common clinical approach in multifocal DTC, based on the fact that they present with more extensive disease and show a more aggressive trend compared to microcarcinomas.[1,12] But the data about further clinical management in long-term follow-up have not been reported before. The risk of persistence or recurrence, thus, undergoing further neck surgeries and RAIT was also increased compared to the patients with smaller tumors in this study.

Statistical analysis also revealed that the sum of the diameters of all tumor foci was significantly higher in patients with contralateral lobe involvement, capsular invasion, and lymph node metastasis. Frequency of capsular invasion was also found higher in patients with calculated sum of diameter of all tumor foci >1 cm. In other studies investigating if the sum of the diameters of the multiple tumor foci may be important in decision-making, some authors concluded that papillary microcarcinomas with total tumor diameter >1 cm had a similar risk of lymph node metastasis and other aggressive histopathological features (capsular invasion and extrathyroidal invasion) compared to those with total tumor diameter <1 cm at initial diagnosis.[8,19,20] The scope of this study, however, was not papillary microcarcinomas but all T1 tumors, as already explained above. So this discrepancy can be attributable to different patient selection criteria. Although a close relationship between sum of diameter of all tumor foci and other well-known determinants of aggressive disease, no correlation was found between persistence or recurrence and risk of developing necessity for additional surgery and RAIT in patients with multifocal T1 tumors. In a relatively smaller series, T1a and T1b multifocal tumors were compared and recurrence rates were found higher if total calculated tumor diameter was exceeding 1 cm, contrary to these results.[19] Considering that there are no other studies where total tumor diameter is associated with long-term clinical outcome before, data presented here, belonging to a larger patient population, will hopefully contribute to the literature.

Lymph node positivity at initial diagnosis was also correlated with persistent or recurrent disease in the follow-up and frequency of recurrent surgery or RAIT was higher in these patients. To achieve reliable results about the impact of multifocality, contralateral lobe involvement and defined parameters subside the effect of lymph node involvement, the authors also conducted a separate analysis of a more homogenous subgroup, T1N0 patients. The authors' results still pointed out that size of the largest tumor can be proposed as an important parameter to consider for clinical management of T1N0 patients. Size of the largest tumor was significantly associated with capsular invasion, vascular invasion, involvement of the contralateral lobe, and development of persistent or recurrent disease in the follow-up. These patients were also under higher risk of undergoing additional surgery or RAIT in the long term. Total tumor diameter was studied before, but for papillary microcarcinomas with any N and M stage or for tumors of all T stages. The authors found that in capsular and lymphovascular invasion, lymph node metastasis was higher in patients with total tumor diameter >1 cm.[19,21] It is important to mention that this generalized argument is now proven to be only partly valid for subgroup of tumors at T1N0. They tend to show capsular invasion and spread to the contralateral lobe more commonly even if there is no lymph node metastasis (N0).

With an intent to focus on a homogenous, histopathologically low-risk subgroup, same statistical analysis was also performed for the patients with papillary cancer classical variant. Subsiding the role of possible aggressive behavior of other histopathological variants, the results were pretty much similar to the whole study group. Multicentricity, contralateral lobe involvement, capsular invasion, lymph node metastasis, size of the largest tumor, and total tumor diameter were indicative of recurrent/persistant disease and additional surgery/RAIT requirements. Different from the whole study population, in this subgroup, scintigraphic and biochemical responses evaluated on 6th month of therapy were also significant predictors of clinical outcome. This difference may be attributable to the previously reported fact that there is a high incidence of radioiodine resistance among aggressive variant papillary carcinomas.[22]

DR is a recently presented parameter, which counts in both the largest size of the dominant tumor and the sum of diameters of all

tumor sizes. Previous investigators have found that decreased tumor diameter ratio was associated with capsular invasion, extrathyroidal extension, and lymph node metastasis in patients with multifocal papillary carcinomas and microcarcinomas.[23]

Preablative Tg is one of the most studied parameters in prognostication in DTC. In this study, it is also found that preablative levels were closely related with follow-up outcome results, which was an expected finding considering many similar previous reports.[24]

The main limitation of this study was that it had a retrospective design. Some other parameters which may be important to mention could not be accessed from the medical records. For instance, the relationship between the localization of largest tumor and thyroid capsule invasion would be worthy to discuss. Another thing is that all included patients received RAI, although the recent approach to T1 tumors is not the same any more. However, the study group involved patients under follow-up for a long time (mean follow-up was 189.51 ± 116.53 months (min:20, max:563) and RAI treatment was not inappropriate then. A prospectively designed study investigating the same parameters among patients who did not receive radioiodine would also be very interesting. A small percentage of patients had an antithyroglobulin positivity at baseline. Although this can be evaluated as a reason for heterogeneity, the existence of these cases do not seem to affect the statistical results, probably due to low frequency. Preablative thyroglobulin levels were still found to be strong predictor of clinical outcome.

Conclusion

Multifocality, contralateral lobe involvement, the diameter of the largest tumor >1 cm, and N1 status at initial diagnosis are related with increased risk of disease persistence, recurrence, reoperation in the neck, and need for additional RAIT in the follow-up of patients with T1 DTC. Diameter of the largest tumor >1 cm and calculated sum of diameter of all tumor foci are associated with capsular invasion in multifocal cases. Despite reported low disease-specific mortality rates in T1 DTC, keeping in mind the increased risk of morbidity in existence of these mentioned parameters, clinical decision-making should be made accordingly.

Authors' Contributions

Conception and design: M.A., C.S., and E.O.; Acquisition, analysis, and interpretation of data: P.G., M.A., and C.S.; Drafting the article: M.A.; Revising the article critically for important intellectual content: C.S. and E.O.; Final approval of the version to be published: C.S., E.O., N.O.K., and K.M.K.

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