Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

What is the contribution of tumor capsule thickness and tumor nucleus diameter to differential diagnosis in encapsulated variant thyroid papillary carcinomas?

Aydan Kilicarslan[a,*], Rumeysa Kankoc[b], Ozge Eyeoglu[b], Ayca Dilsad Kuratmer[c], Nuran Sungu[a], Hayriye Tatli Dogan[a], Fazli Erdogan[a]

[a] *Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Pathology, Ankara, Türkiye*
[b] *Ankara Bilkent City Hospital, Department of Pathology, Ankara, Türkiye*
[c] *Ankara Etlik City Hospital, Department of Pathology, Ankara, Türkiye*

ARTICLE INFO

Keywords:
Computerized image analysis
Tumor capsule thickness
Tumor cell diameter
Encapsulated variant
Papillary thyroid carcinomas

Received: Oct 19, 2023
Accepted: Dec 25, 2023
Available Online: 27.12.2023

DOI:
10.5455/annalsmedres.2023.10.284

Abstract

Aim: Capsule thickness and papillary carcinoma nuclear features are common diagnostic criteria for invasive follicular variant papillary thyroid carcinoma (IEFVPTC), non-invasive follicular thyroid neoplasm with papillary nuclear features (NIFT-P), and encapsulated papillary thyroid carcinoma (E-PTC). Our goal in this study is to evaluate these two histomorphological criteria using computerized image analysis systems and to determine whether they can serve as auxiliary criteria for distinguishing these diagnostic groups.

Materials and Methods: 10 patients were selected from IEFVPTC, NIFT-P, and E-PTC diagnostic groups. Slides containing the largest tumor diameter were scanned and digitized. Using computerized image analysis systems, tumor capsule thickness was measured from 4 areas of 4 equal quadrants, and the average tumor capsule thickness (TCT) was determined. Furthermore, from these 4 equal quadrants, the nucleus diameter of 10 clearly distinguishable cells was measured to determine the average tumor cell nucleus diameter (ND).

Results: TCT and ND histomorphological criteria were statistically significant among the diagnostic groups. For IFVPTC diagnosis, both TCT and ND were found to be significant diagnostic tools. We demonstrated that ND can easily be used as a diagnostic tool for NIFT-P, whereas more caution is required for TCT.

Conclusion: Differentiating papillary nuclear feature-containing follicular variant thyroid papillary carcinomas is challenging. In this study with a limited number of patients, we demonstrated that the TCT and ND criteria can, to some extent, contribute to differential diagnosis between diagnostic groups. Future studies with larger patient groups and more advanced computerized image analysis programs will yield more promising results.

Introduction

The most common of thyroid carcinomas is PTC, constituting 85-90%. The second most common subtype of PTC is the follicular variant, accounting for 9-22% of cases [1, 2]. Among follicular variant papillary thyroid carcinoma (FVPTC) subtypes, the commonly encountered encapsulated follicular variant papillary thyroid carcinoma (EFVPTC) has been shown to have a much better prognosis than infiltrative follicular variant papillary thyroid carcinoma (IFVPTC) subtype in numerous studies [3, 4]. Additionally, while IFVPTC possesses a BRAF-like genetic profile, EFVPTC is characterized by a RAS-like genetic profile, indicating distinct molecular profiles for these two subtypes [5, 6, 7]. Based on the presence or absence of capsule and/or vascular invasion, EFVPTC has been divided into invasive and non-invasive subtypes. In 2016, the World Health Organization revised the non-invasive EFVPTC diagnostic group, identifying that they have a better prognosis. They added non-invasive follicular thyroid neoplasm with papillary nuclear features (NIFT-P) as a new entity in thyroid endocrine classification [8]. Different form this entity, the IEFVPC subtype with capsule and/or vascular invasion has been shown to have a higher recurrence and metastatic potential in some studies [4, 6].

*Corresponding author:
Email address: dr.kilicaydan@gmail.com (Aydan Kilicarslan)

For differentiation within the FVPTC group, the tumor-parenchyma relationship and capsule continuity must be accurately assessed. However, when evaluation criteria are not clearly established, distinguishing between IFVPTC, NIFT-P, and E-PTC becomes challenging. Among pathologists who are not experts in endocrine pathology, evaluating capsule integrity and invasion status often presents a challenge. Numerous sections need to be prepared from blocks containing suspicious areas to assess capsule invasion, increasing costs and prolonging the diagnostic process. Furthermore, the diagnostic criteria used in this group of thyroid tumors, namely the nuclear cytological atypia of papillary tumor cells, are heterogeneous within the tumor. Nuclear atypia evaluation criteria and definitions can vary between pathology clinics [9].

Chevillar et al. identified over 43 different genes between follicular adenoma and FVPTC in a study [10]. Molecular tests for differential diagnosis are not widely available and increase healthcare costs.

The role of computerized image analysis systems is expanding in pathology practice [11, 12, 13]. In challenging cases like IEFVPTC, NIFT-P, and E-PTC, computerized image analysis can be used to precisely measure the nuclear diameters of follicular tumor cells and capsule thicknesses. In our research, we aimed to quantify these histomorphological criteria, compare them across IEFVPTC, NIFT-P, and E-PTC diagnoses, and determine their potential contributions to diagnosis.

Materials and Methods

Between the years 2019 and 2022, out of 2310 thyroidectomy specimens conducted at our institution, 580 of them contained follicular neoplasm. For our research, we needed to take a more limited number of cross-sectional samples from NIFT-P, IEFVPTC, and E-PTC patient groups within these follicular neoplasms. Therefore, the G*Power Ver. 3.1.9.6 (G*Power, Franz FAUL, Universität Kiel) software was utilized to determine the necessary sample size for the study. The effect size for a significant difference between research groups was calculated using values from the article https://doi.org/10.1177/1066896919859085. In the study, it was determined that to discern a difference with an effect size of f=0.90 among the three groups at an =0.05 type I error and 95% power, at least 8 samples from each group and a minimum of 24 samples in total were required. It was decided that for the retrospective study, taking at least 10 samples from each group, totaling 30 samples, would be sufficient. No random sampling was applied; the quota sampling method was used. Starting from January 2022, records were reviewed from the most recent to the past until the quota for each group was met.

Demographic information, tumor diameter, and tumor localization of the cases were obtained from the hospital information system. The specimens of the cases were re-examined by two pathologists (AK, ÖE), and the diagnoses were revisited. Cases with multiple tumors and those with a tumor diameter of 5mm or smaller were excluded from the study. The invasion was evaluated as the tumor's invasion outside the capsule and/or the presence of vascular invasion. If there was suspicion of invasion, these cases (well-differentiated tumor of uncertain malignant potential) were excluded from the study. The differential diagnosis separating NIFT-P from EFVPTC was made using the criteria specified in WHO Endocrine and Neuroendocrine Tumours (5th ed.) (criteria in favor of NIFT-P; <1% true papillae, no psammoma bodies, <30% solid/trabecular/insular growth pattern, no tumor necrosis, low mitotic count <3 mitosis/ 2mm^2, lack of morphologic characteristics of other PTC variants, e.g., tall cell features). The diagnostic criteria for IEFVPTC cases were; they were encapsulated tumors consisting of follicular structures with papillary nuclear features and the tumor showed capsular invasion. The diagnostic criteria for E-PTC cases were encapsulated tumors with papillary nuclear features. Among these E-PTC cases, those without capsule invasion were selected for the study.

Specimens stained with H&E, where the tumor diameter was the largest, were selected and images were transferred electronically. Using a software analysis system (Virasoft Software Trading Joint Stock Company/İstanbul/Turkey), the capsule thickness was measured from 4 areas over the 4 equal quadrants. On the same images, groups of cells showing the most nuclear enlargement and nuclear clarity in 4 different areas were identified. The largest nuclear diameter of 10 cells in this area was measured and recorded.

In 19075 Declaration of Helsinki performed all procedures. The study was approved by the Local Institutional Clinical Research Ethics Committee (Ankara City Hospital no. 1 Clinical Research Ethics Committee Chairmanship, E. Kurul-E1-23-3286, 08.02.2023).

Statistical analysis

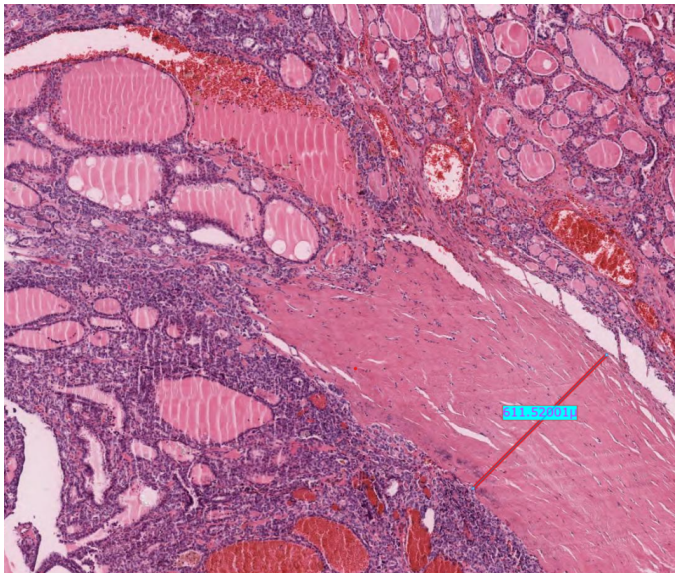
The conformity of measurement values to the normal distribution was checked with the Shapiro-Wilk test. In the presentation of descriptive statistics, numbers (%) were used for gender and pathological diagnosis; mean ± standard deviation and [95% CI] was used for age, capsule thickness, and average nucleus diameter which followed a normal distribution. For the tumor diameter which did not follow a normal distribution, the median (IQR-InterQuartile Range) values and [95% CI] were used. One-way analysis of variance (ANOVA) was utilized to compare capsule thickness and average nucleus diameter, which conformed to a normal distribution, among diagnostic groups. When a difference was found, the Bonferroni test was applied for post-hoc pairwise comparisons. The non-parametric variance analysis (Kruskal-Wallis) test was used to compare the tumor diameter variable, which did not conform to a normal distribution, among diagnostic groups. ROC analysis was conducted to diagnose using tumor capsule thickness (TCT) and average tumor nucleus diameter (ND), and AUC (Area Under Curve) and cut-off point values were determined. Sensitivity, specificity, and Youden index values were calculated for the specified different cutoff points. Statistical analysis and calculations were performed using Ms-Excel 2016 and IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp.). In statistical decisions, p<0.05 was considered as an indicator of significant difference.

Results

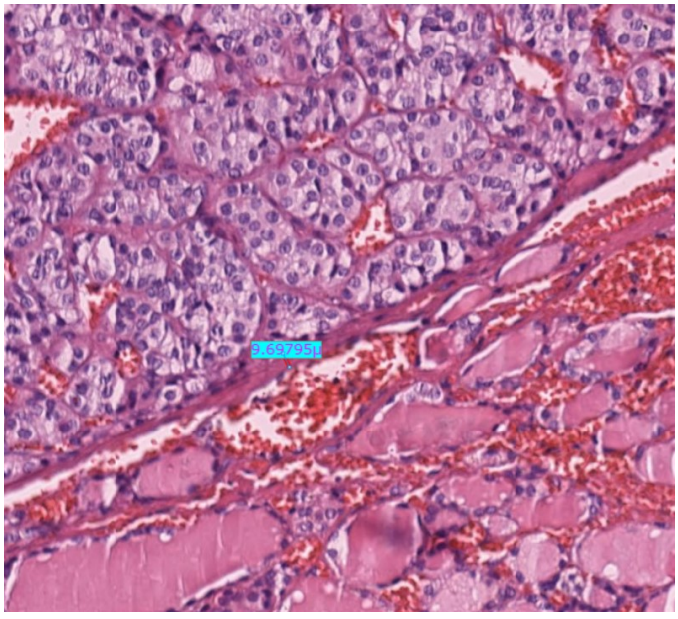
In the study, samples from a total of 30 patients, 9 (30%) male and 21 (70%) female, ranging in age from 25 to 78 were used. The age and gender distribution of the samples examined within the scope of the study were not different between groups (respectively F = 0.310; p = 0.737 and 2= 0.966; p = 0.617).

In the examined samples, while patients' diagnosis ages ranged from 25 to 78, the average diagnosis age was found to be 48.5±13.4 years. Tumor diameters ranged between 6-50 mm, and the median of the tumor diameter was calculated to be 21.0 (IQR=30.0) mm. Findings related to the examined samples and the results of group comparisons are summarized in Table 1.

After significant differences were observed among tumor types in terms of TCT (Figure 1) and average ND (Figure 2), it was investigated whether these two variables could be used to determine the type of tumor. As a result of the ROC analysis, both variables were found to have sufficient sensitivity and specificity power to determine the type of "follicular neoplasms with papillary nuclear features" (Figure 3).

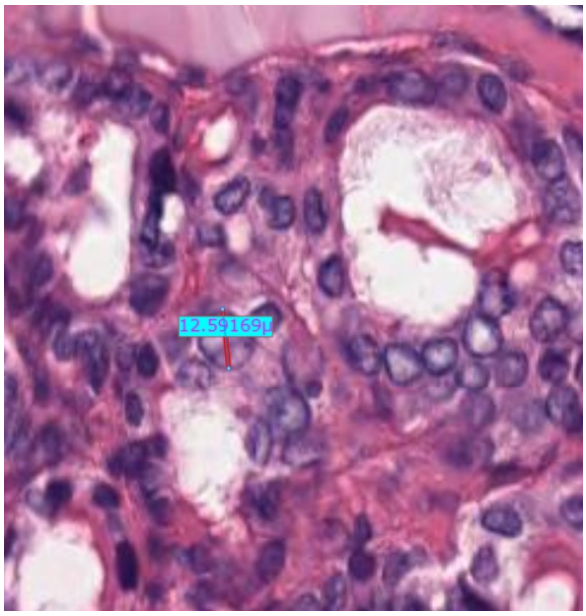


(a) Focus where the capsule of IEFVPTC is fully invaded (HEx10).

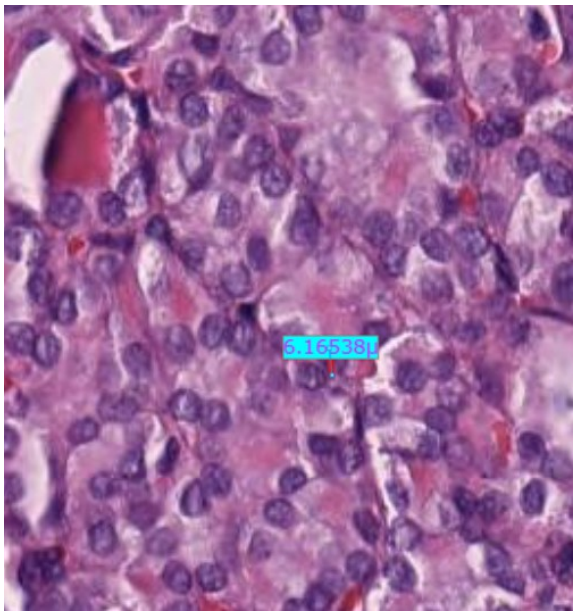


(b) Tumor capsule thickness of NIFT-P (HEx40).

Figure 1. A: Where the capsule of IEFVPTC is fully invaded, B: Tumor capsule thickness of NIFT-P.



(a) Tumor nucleus diameter of IEFVPTC (HEx100).



(b) Tumor nucleus diameter of NIFT-P (HEx100).

Figure 2. Tumor nucleus diameter of IEFVPTC and NIFT-P.

Sensitivity and specificity values for different cutoff points of TCT and average NC were calculated, and with the combination of these values, the Youden index value was determined (Table 2).

Cutoff points that could be used for diagnosis based on the tumor capsule thickness and tumor cell nucleus diameter variables, which are shown in Table 2, were calculated. The area under the ROC curve (AUC) values for these calculated cutoff points and their statistical significance

Table 1. Demographic and pathological findings related to the samples.

Variables	NIFT-P	IEFVPTC	E-PTC	Group Comparison*
Age, year (mean±Sd)	51.0±15.6	48.8±11.2	45.8±13.4	F=0.310
[95% CI]	[39.8 – 66.2]	[40.8 – 56.8]	[35.9 – 55.7]	p=0.737
Gender				
Male (n=9, 30%)	2 (20%)	3 (30%)	4 (40%)	X^2=0.966;
Female (n=21, 70%)	8 (80%)	7 (70%)	6 (60%)	p=0.621
Tumor localization				
Isthmus (n=6, 20%)	2 (20.0%)	3 (30.0%)	1 (10.0%)	
Right (n=9, 30%)	2 (20.0%)	3 (30.0%)	4 (40.0%)	X^2=2.129;
Left (n=15, 50%)	6 (40.0%)	4 (40.0%)	5 (50.0%)	p=0.712
Tumor Diameter (mm) (Median (IQR))	14.0 (IQR=24.8)	11.5 (IQR=18.8)	32.5 (IQR=23.0)	2=3.376;
[95% CI]	[10.0 – 31.2]	[9.9 – 29.5]	[21.6 – 41.0]	p=0.185
Tumor Capsule Thickness (mean±Sd)	31.1±27.0	182.6±173.9[a]	25.3±12.7	F=7.663;
[95% CI]	[11.8 – 50.4]	[58.2 – 307.0]	[16.2 – 34.4]	**p=0.002**
Average Tumor Nucleus Diameter (mean±Sd)	6.8±0.7	8.0±0.7[a]	7.1±0.7	F=7.236;
[95% CI]	[6.3 – 7.3]	[7.5 – 8.5]	[6.6 – 7.7]	**p=0.003**

[a]: The IEFVPTC group has a higher average capsule thickness and tumor cell nucleus diameter compared to the other NIFT-P and non-IEFVPTC groups. The NIFT-P and E-PTC groups are statistically indistinguishable.
* F: One way ANOVA test, X^2: Kruskal-Wallis test.

Table 2. Sensitivity and Specificity values for different tumor capsule thickness and tumor cell nucleus diameter cutoff points.

Diagnosis	Tumor Capsule Thickness				Tumor Nucleus Diameter			
	Cutoff Point (μm)	Sensitivity (%)	Specificity (%)	Youden Index	Cutoff Point (μm)	Sensitivity (%)	Specificity (%)	Youden Index
IEFVPTC	≥ 94.88	70	100	1.700	≥ **7.36**	**90**	**80**	**1.700**
	≥ **34.00**	**90**	**75**	**1.650**	≥ 7.25	90	75	1.650
	≥ 39.75	80	85	1.650	≥ 7.17	90	70	1.600
	≥ 78.00	70	95	1.650	≥ 7.47	80	80	1.600
	≥ 30.75	90	70	1.600	≥ 7.53	70	80	1.500
	AUC=0.900; **p<0.001**				AUC=0.850; **p=0.002**			
NIFT-P	≤ 94.88	100	35	1.350	≤ **6.88**	**70**	**80**	**1.500**
	≤ 13.63	40	90	1.300	≤ 7.17	80	65	1.450
	≤ 38.88	80	50	1.300	≤ 7.02	70	75	1.450
	≤ 117.88	100	30	1.300	≤ 6.81	60	80	1.400
	≤ **30.75**	**70**	**60**	**1.300**	≤ 7.25	80	60	1.400
	AUC=0.705; p=0.071				AUC=0.760; **p=0.022**			
E-PTC	≤ 60.00	100	45	1.450	≤ **7.36**	**80**	**55**	**1.350**
	≤ **34.00**	**80**	**60**	**1.400**	≤ 7.47	80	50	1.300
	≤ 39.75	90	50	1.400	≤ 7.25	70	55	1.250
	≤ 78.00	100	40	1.400	≤ 7.53	80	45	1.250
	≤ 27.50	70	65	1.350	≤ 8.03	90	35	1.250
	AUC=0.695; p=0.086				AUC=0.590; p=0.428			

levels are also provided in Table 2. Upon examining the AUC values, it was observed that the TCT and tumor cell ND values can comfortably be used to diagnose IEFVPTC (AUC=0.900; p<0.001, AUC=0.850; p=0.002). The ND variable was identified as a good marker when diagnosing NIFT-P (AUC=0.760; p=0.022). However, caution should be exercised when using the TCT value in diagnosing NIFT-P (AUC=0.705; p=0.071). For diagnosing E-PTC, it was noted that the TCT and ND diameter variables might not provide sufficient evidence, and a diagnosis based on these variables might not achieve satisfactory sensitivity and specificity levels (AUC=0.695; p=0.086, AUC=0.590; p=0.428).

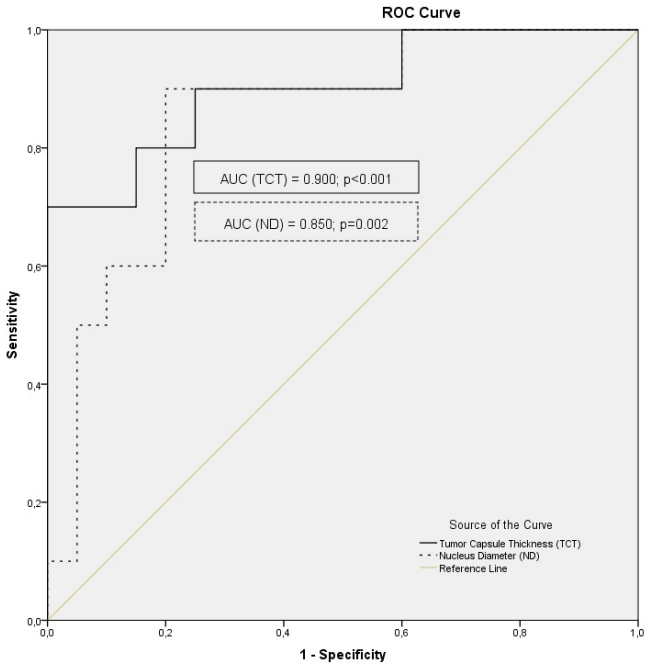


Figure 3. ROC Curve of Tumor Capsule Thickness (TCT) and Tumor Cell Nucleus Diameter (ND).

Discussion

Encapsulated papillary nuclear feature-bearing follicular neoplasms (NIFT-P, IEFVPTC, and E-PTC) require evaluation of a series of complex qualitative and quantitative histological parameters when differentiating between them. There is a need for simpler and more repeatable diagnostic methods to distinguish these group diagnoses. In our research, we found that the numerical values of tumor cell ND and TCT obtained with the help of an image analysis software were statistically significant in distinguishing IEFVPTC from NIFT-P and E-PTC. Thus, we demonstrated that these two histomorphological criteria can be useful additional diagnostic tools during routine pathological examination.

The common diagnostic criterion in follicular neoplasms with papillary nuclear features, including the diagnoses of NIFT-P, IEFVPTC, and E-PTC, is the resemblance of the tumor cell nuclei to papillary carcinoma. Nuclear scores of 2-3 for nuclear features of thyroid papillary carcinomas are criteria also used in the diagnosis of this group of carcinomas [14]. However, this histological criterion does not contribute to the differential diagnosis between follicular neoplasms with papillary nuclear features when using routine pathological examination methods. The findings of cytological atypia are heterogeneous within the neoplasm and require challenging and high-level specialist training for evaluation [15]. Small changes in the diameters of tumor cell nuclei between diagnostic groups would be hard to perceive and interpret by the human eye. Computer software programs that can overcome these challenges can convert the features of these similar-looking cells into parameters that can assist in diagnosis. In our study, we demonstrated that ND values were statistically significant for differential diagnosis for IEFVPTC and NIFT-P (AUC=0.850; p=0.002, AUC=0.760; p=0.022). We revealed that if the ND is 7.36 µm, there is a high probability of IEFVPTC diagnosis, and if it is 6.88 µm, the likelihood of NIFT-P diagnosis is high.

In their study, R. Yashaswini and colleagues measured nuclear dimensions (nuclear diameter, nuclear area, and nuclear circumference) on thyroid cytologic materials using computerized image analysis for nuclear morphometric studies [16]. They identified the maximum nuclear diameter of tumor cells diagnosed as malignant to be 8.67 µm. In our study, we similarly determined the tumor cell nuclear diameter in IEFVPTC to be 7.36 µm.

In the literature, several studies have demonstrated that nuclear size measurements on thyroid cytology materials, when done with computerized image analysis, can serve as a diagnostic tool to differentiate malignant lesions from benign ones [17, 18, 19, 20]. Another study, using the Aperio imaging system on cytology materials, has shown that the nuclear elongation values derived from the ratio of nuclear area to maximum and minimum diameters can be utilized to distinguish between NIFT-P and PTC [21].

Furthermore, in a study conducted on tissue samples using computerized image analysis, it was revealed that the chromatin textural characteristics (grey intensity) of tumor cell nuclei in NIFT-P were different from those of tumor cell nuclei in IEFVPTC [22].

During tissue processing, inadequate hydration can cause contractions and shrinkages in nuclei. Thus, ensuring the accuracy of morphometric measurements is closely related to the standardization of tissue processing. Pathology clinics that will use computerized image analysis should prioritize establishing this standardization.

The clinical behavior and genotypic characteristics of NIFT-P are distinct from IEFVPTC and are regarded as an entity to be managed conservatively [8, 23]. In cases with unclear capsular and vascular invasion, the presence of invasion is clearly detected with new serial sections, thus NIFT-P and E-PTC can be differentiated and IEFVPTC can be diagnosed. However, it's crucial for managing the patient's clinical treatment post-surgery. In our study, we demonstrated that TCT could be utilized to distinguish between IEFVPTC, NIFT-P, and E-PTC ($p<0.001$). Specifically, the optimal cut-off point for TCT was determined to be 94.9 µm. However, considering this as a significantly high value, it is recommended to use a TCT value of 34.0 µm, sacrificing some of the test's diagnostic power for more consistent results. A TCT of 34.0 µm should raise suspicion of IEFVPTC, whereas the possibility of NIFT-P and E-PTC should be viewed with caution. Pathologists should continue their pathological examination with additional leveled tissue sections, presuming the potential oversight of a minor invasion focus in these cases.

There are limited studies in the literature about TCT in follicular variant papillary carcinomas. One study demonstrated that TCT could be a criterion to differentiate NIFT-P from IEFVPTC, suggesting suspicion of IEFVPTC when the TCT exceeds 0.2 mm [24]. However, the TCT values found in this study for NIFT-P, IEFVPTC, and E-PTC are higher than in our study. The software we used in our study might provide more precise measurements. In another study, TCT was measured ul-

trasonographically and microscopically, considering it an independent risk factor for distal metastasis if it was 1mm [25].

Our study is limited by the small number of cases included in the diagnostic groups. Although larger-scale studies are needed to validate this technique for routine clinical use, we've shown that when used together ND and TCT are helpful quantitative measures in routine pathology practice to determine NIFT-P and IEFVPTC. As a result, unnecessary lymph node dissection, radioactive iodine treatment, and frequent clinical follow-ups are avoided when NIFT-P cases are clearly distinguished from IEFVPTC cases.

To summarize, the ability to distinguish between different encapsulated papillary nuclear feature-bearing follicular neoplasms is crucial in pathology. Our study highlights the potential utility of specific quantitative measurements, such as tumor cell ND and TCT thickness, as aids in making these differential diagnoses. Using modern tools like software analysis can help in making these determinations more accurate and consistent.

Acknowledgments

We thank Virasoft Software Trading Joint Stock Company and its employees for their contributions.

Ethical approval

The study was approved by the Ankara City Hospital no. 1 Clinical Research Ethics Committee Chairmanship (Ethics form no: E. Kurul-E1-23-3286, date 08.02.2023).

References

1. Passler C, Prager G, Scheuba C, et al. Follicular variant of papillary thyroid carcinoma: a long-term follow-up. Arch Surg. 2003;138(12):1362-6.
2. Sebastian SO, Gonzalez JM, Paricio PP, et al. Papillary thyroid carcinoma: prognostic index for survival including the histological variety. Arch Surg. 2000;135(3):272-7.
3. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: A name change to Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features would help prevent overtreatment. Mod Pathol. 2016;29(7):698-707.
4. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid. 2013;23(3):273-9.
5. Kim TH, Lee M, Kwon AY, et al. Molecular genotyping of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma. Histopathology. 2018;72(4):648-61.
6. Sohn SY, Lee JJ, Lee JH. Molecular Profile and Clinicopathologic Features of Follicular Variant Papillary Thyroid Carcinoma. PatholOncol Res. 2020;26(2):927-36.
7. Howitt BE, Jia Y, Sholl LM, Barletta JA. Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. Thyroid. 2013;23(10):1256-62.
8. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. JAMA Oncol. 2016;2(8):1023-9.
9. Valderrabano P, Khazai L, Thompson ZJ, et al. Cancer Risk Associated with Nuclear Atypia in Cytologically Indeterminate Thyroid Nodules: A Systematic Review and Meta-Analysis. Thyroid. 2018;28(2):210-9.
10. Chevillard S, Ugolin N, Vielh P, et al. Gene expression profiling of differentiated thyroid neoplasms: diagnostic and clinical implications. Clin Cancer Res. 2004;10(19):6586-97.
11. Hernandez A, Miranda DA, Pertuz S. Algorithms and methods for computerized analysis of mammography images in breast cancer risk assessment. Comput Methods Programs Biomed. 2021;212:106443.
12. Kong J, Cooper L, Kurc T, et al. Towards building computerized image analysis framework for nucleus discrimination in microscopy images of diffuse glioma. Annu Int Conf IEEE Eng Med Biol Soc. 2011;2011:6605-8.
13. Um IH, Scott-Hayward L, Mackenzie M, et al. Computerized Image Analysis of Tumor Cell Nuclear Morphology Can Improve Patient Selection for Clinical Trials in Localized Clear Cell Renal Cell Carcinoma. J Pathol Inform. 2020;11:35.
14. Lloyd RV, Osamura RY, Günter K, Juan R, Who Classification of Tumours of Endocrine Organs, 4th edition, Lyon(France), 2017, 78-80.
15. Mai KT, Yazdi HM, Perkins DG, et al J. Papillary thyroid carcinoma and related thyroid neoplastic lesions: a light microscopic study with emphasis on nuclear changes. Tumori. 2000;86(3):238-49.
16. Yashaswini R, Suresh TN, Sagayaraj A. Cytological Evaluation of Thyroid Lesions by Nuclear Morphology and Nuclear Morphometry. J Cytol. 2017;34(4):197-202.
17. Celik ZE, Altinay S, Kilinc F, et al. Using Computerized Cytomorphometry to Distinguish between Benign and Malignant Cases in Thyroid Fine-Needle Aspiration Cytology. DiagnCytopathol. 2016;44(11):902-11.
18. Tseleni-Balafouta S, Kavantzas N, Paraskevakou H, Davaris P. Computerized morphometric study on fine needle aspirates of cellular follicular lesions of the thyroid. Anal Quant CytolHistol. 2000;22(4):323-6.
19. Aiad H, Abdou A, Bashandy M, et al. Computerized nuclear morphometry in the diagnosis of thyroid lesions with predominant follicular pattern. Ecancermedicalscience. 2009;3:146.
20. Karslioglu Y, Celasun B, Gunhan O. Contribution of morphometry in the differential diagnosis of fine-needle thyroid aspirates. Cytometry B ClinCytom. 2005;65(1):22-8.
21. Chain K, Legesse T, Heath JE, Staats PN. Digital image-assisted quantitative nuclear analysis improves diagnostic accuracy of thyroid fine-needle aspiration cytology. Cancer Cytopathol. 2019;127(8):501-13.
22. Coelho BP, de Oliveira Valentim F, Miot HA, et al. Follicular Lesions with Papillary Nuclear Characteristics: Differences in Chromatin Detected by Computerized Image Analysis. Arch EndocrinolMetab. 2021;64(5):630-5.
23. Chung R, Guan H, Ponchiardi C, et al. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: Epidemiology and Long-Term Outcomes in a Strictly Defined Cohort. Thyroid. 2021;31(1):68-75.
24. French B, Hattier G, Mardekian SK. Utility of Tumor Capsule Thickness as a Predictor of Invasion in Encapsulated Follicular Variant of Papillary Thyroid Carcinoma and a Diagnostic Tool for Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features. Int J SurgPathol. 2020;28(1):13-9.
25. Shimbashi W, Sugitani I, Kawabata K, et al. Thick tumor capsule is a valuable risk factor for distant metastasis in follicular thyroid carcinoma. Auris Nasus Larynx. 2018;45(1):147-55.