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NON-INVASIVE ENCAPSULATED FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA: A LOCAL EXPERIENCE AND A PARADIGM SHIFT.

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Abstract:

Introduction: *Encapsulated follicular variant of papillary thyroid carcinoma [EFV-PTC] is an indolent variant of papillary thyroid carcinoma [PTC]. Based on capsular and vascular invasion, EFV-PTCs are divided into non-invasive [NIEFV-PTC] and invasive [IEFV-PTC] subtypes. Recently, NIEFV-PTC was re-classified as a non-malignant thyroid neoplasm. This study evaluates the clinicopathological characteristics and management of NIEFV-PTC among patients treated at King Abdulaziz Medical City, Jeddah, Saudi Arabia*

Methods: *A Retrospective cross-sectional study involving 44 cases of NIEFV-PTCs. They were identified after reviewing the pathology reports of all thyroid gland surgeries performed from January 2011 to December 2015 at King Abdulaziz Medical City. Clinical data and follow up were obtained from patient's records.*

Statistical analysis used: IBM SPSS 22 [SPSS Inc., Chicago, Il, USA] was used. Chi-square and one-way ANOVA tests were used to delineate statistical significance.

Results: *Cases included 40 women and 4 men, with a mean age of 35-years-old. All had a unilateral tumor[s] [37 unifocal and 7 multifocal], with an average tumor size of 3.4 cm. Histologically, these tumors were surrounded by a well- defined capsule, with no capsular or vascular invasion and all lacked extrathyroidal extension, perinural invasion, positive resection margins, and/or high mitotic activity. No lymph node or distant metastases were identified. Patients were treated by total thyroidectomy [n=24], completion thyroidectomy [n=19], or lobectomy [n=1] combined with radioactive iodine ablation in 25 patients with a mean dose of 92.8 ±25.4 mCi. A median follow-up of 19 months was available for 95.5% patient, none of them demonstrated any evidence of disease recurrence/metastasis.*

Conclusions:

NIEFV-PTC is an indolent thyroid tumor with very low-likelihood of metastases. To avoid over-treatment, we recommend the incorporation of the recently coined term [NIFTP] into the management algorithms for patients with thyroid tumors.

Key-words: *NIFTP, Thyroid neoplasm, NIEFVPTC, papillary carcinoma, EFVPTC.*

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INTRODUCTION:

The incidence of thyroid cancers has increased up to 3 times over the past few decades, in particular, the most common histologic type called papillary thyroid carcinoma [PTC].[1–7] If the latter trend continues, it is predicted that by 2030 it will be the fourth most common cancer among both genders worldwide.[8] In Saudi Arabia, thyroid cancer is the second most common cancer in females following breast cancer.[7]

Encapsulated follicular variant of papillary thyroid carcinoma [EFV-PTC] is a common subtype of PTC. It is architecturally similar to follicular thyroid neoplasms, however, it displays nuclear features of PTC. Based on capsular and vascular invasion they are further divided into non-invasive and invasive subtypes [NIEFV-PTC] and [IEFV-PTC], respectively.[9]

Follow-up studies of patients with NIEFV-PTC demonstrated a very low-risk of recurrence or metastases despite being treated by either surgery alone or in combination with radioactive iodine ablation.[10–16] In 2016, a group of international experts in thyroid cancer proposed that NIEFV-PTC be reclassified as a non-malignant thyroid neoplasm and to use the term: "Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features [NIFTP]" instead. This reclassification was based on characteristic clinical, morphological, and molecular features.[10] The purpose of our study was to evaluate the clinicopathological characteristics and management of NIEFV-PTC among patients attending a tertiary care institute in Saudi Arabia.

MATERIAL AND METHODS:

After obtaining institutional ethical research board approval, we retrieved 309 cases of thyroid gland malignancies from the Pathology archives at King Abdulaziz Medical City, Jeddah, Saudi Arabia, from January 2011 to December 2015. The pathology reports were retrospectively reviewed and a total of 248 cases were included and categorized as follows: classical papillary thyroid carcinoma [C-PTC] [n=179, 72%], NIEFV-PTC [n=44, 18%], and IEFV-PTC [n=25, 10%]. Other variant of PTC, incidental papillary microcarinoma [≤1 cm] and other types of thyroid malignancies [eg, follicular, medullary, anaplastic, and lymphoma] were excluded.

The diagnostic criteria used for diagnosis of these tumors were based on the 2004 WHO/IARC Classification of Endocrine Tumors.[17] All Histopathology related diagnostic materials and slides were examined with an Olympus BX53 microscope [U-DO model, Olympus, Waltham, MA] by a board certified pathologists and all thyroid specimens were adequately sampled with a mean of 13.4 blocks submitted per specimen. This study focuses on NIEFV-PTC; however, we evaluated C-PTC and IEFV-PTC for comparison.

Pathological data obtained were according to the following variables: maximum tumor size in cm, architectural pattern of growth, focality and laterality, tumor encapsulation, capsular invasion [defined as; complete transgression of` the capsule], vascular invasion [presence of endothelialized tumor within the capsular or extra-capsular vessels with or without fibrin thrombus], perinural invasion, extra-thyroidal extension into perithyroidal soft tissue stroma, margin status, and pathological [TNM] tumor staging.

The patient's records were reviewed for the following variables: gender, age at diagnosis, treatment, and follow up, which was based on patient's history, clinical examination, significant elevation in serum thyroglobulin, and radiological findings.

For statistical analysis, IBM SPSS 22 [SPSS Inc., Chicago, Il, USA] was used. Chi-square and one-way ANOVA tests were used to delineate statistical association between categories and means, respectively. Level of significance was determined at $p< 0.05$.

RESULTS:

The mean age for all 248 cases was 42-years-old [range: 8–87 years], majority of which were females [n= 204] with a male-to-female ratio of 1:4.6. Table 1 lists the clinical and pathological features of NIEFV-PTC, IEFV-PTC, and C-PTC. Using one-way ANOVA, it was found that the difference between mean age and maximum tumor size of the study groups was significant [P=0.001] and [P=0.001] respectively. Post hoc analysis showed that NIEFV-PTCs affected younger age group [mean=35 years ±13] than IEFV-PTCs [P=0.046] and C-PTCs [P=0.003], where IEFV-PTCs and C-PTCs presented in similar age group. NIEFV-PTCs had larger maximum tumor size than C-PTCs [P=0.013], but no difference was found between the size of NIEFV-PTCs and IEFV-PTCs. NIEFV-PTCs tended to be unilateral [P=0.001] and unifocal [P=0.028] compared to IEVFV-PTC and C-PTC. Histologically, all NIEFV-PTCs were characterized by a well-formed tumor capsule, with no capsular or vascular invasion and absence of extrathyroidal extension, perinural invasion, and positive margins. Lymph node and distant metastases were not identified.

Table 1: Clinical and pathological features of C-PTCs, NIEFV-PTCs, and IEFV-PTCs among the studied patients

Feature	C-PTC [n=179], n[%]	NIEFV-PTC [n=44], n[%]	IEFV-PTC [n=25], n[%]	P
Mean Age ± SD [years]	43±15	35±13	44±14	P=0.004[a]
Gender				
- **Female**	142 [79.3]	40 [90.9]	22 [88]	
- **Male**	37[20.7]	4 [9.1]	3 [12]	
Average tumor size ± SD [in cm]	2.55 ± 1.77	3.41 ± 1.88	3.71 ± 1.95	P=0.001[a]
Focality				
- **Unifocal**	113 [63.1]	37 [83.7]	16 [64]	P=0.028[b]
- **Multifocal**	66 [36.9]	7 [16.3]	9 [36]	
Laterality				
- **Unilateral**	134 [74.9]	44 [100]	19[88]	P=0.001[b]
- **Bilateral**	45 [25.1]	0	6 [12]	
Encapsulation				
- **Complete**	25 [14]	44 [100]	25 [100]	
- **Partial**	12 [6.7]	0	0	
- **Absent**	142 [79.3]	0	0	
Invasion				
- **Capsular**	17 [10]	0	25 [100]	
- **Vascular**	34 [19]	0	7 [28]	
- **Perinural**	8 [4.5]	0	1 [4]	
Extra-thyroidal extension	44 [24.7]	0	2 [8]	
- **Present**	135 [75.3]	44 [100]	23 [92]	
- **Absent**				
Margin status				
- **Positive**	42 [23.5]	0	3 [12]	
- **Negative**	137 [76.5]	44 [100]	22 [88]	

Abbreviations: C-PTC, classic Papillary carcinoma; NIEFV-PTC, non-invasive encapsulated folli5ular variant of papillary thyroid carcinoma; IEFV-PTC, invasive encapsulated follicular variant of papillary thyroid carcinoma.
[a] one-way ANOVA test
[b] Chi-square test
Level of significance was determined at $p< 0.05$.

Tumor staging and treatment of NIEFV-PTC cases are summarized in table 2. Post-operative radioactive active iodine ablation was administered for 67% of C-PTCs, 68% of IEFV-PTCs, 56.8% of NIEFV-PTCs with a mean dose of 127.7 ±59.6 mCi, 108.7 ±44.3 mCi, 92.8 ±25.4 mCi, respectively. A median follow-up of 24 months was available for 227 [91.5%] patients. None of NIEFV-PTC cases demonstrated any evidence of disease recurrence, regardless of treatment status by radioactive iodine therapy. However, eight cases of C-PTCs and one of the IEFV-PTCs had an evidence of disease recurrence or metastasis.

Table 2: TNM tumor staging and treatment of NIEFV-PTC

	NIEFV-PTC [n=44], n[%]
Tumor T stage	
- **pT1a**	3 [6.8]
- **pT1p**	11 [25]
- **pT2**	19 [43]
- **pT3**	11 [25]
Tumor N stage	
- **Nx**	31 [70.5]
- **N0**	13 [29.5]
Tumor M stage	
- **M0**	44 [100]
Thyroid surgery	
- **Lobectomy**	1 [2.3]
- **Total thyroidectomy**	24 [54.5]
- **Completion thyroidectomy**	19 [43.2]
Received RAI therapy	25 [56.8]
Mean dose of RAI therapy ± SD [mCi] [Range]	92.8 ± 25.4 [30-150]

Abbreviations: NIEFV-PTC, non-invasive encapsulated follicular variant of papillary thyroid carcinoma; RAI, radioactive iodine; mCi, millicurie

DISCUSSION:

Papillary thyroid carcinomas account for 90% of all annually diagnosed thyroid malignancies with better prognostic outcome compared to other tumors.[2,6,17] Encapsulated follicular variant of papillary thyroid carcinoma [EFV-PTC], a challenging and controversial entity, is a common subtype of PTC with low malignant potential.[11,12,18] Its incidence has been reported to increase by 2 to 3 fold over the past few decades, representing 10% to 20% of all thyroid malignancies diagnosed in Europe and North America.[19,20] Morphologically, they are characterized by predominance of follicular architecture, follicular cells with nuclear changes resembling those in classical papillary thyroid carcinoma and a peripheral capsule. Based on capsular and/or vascular invasion, EFV-PTC can be either invasive or non-invasive.[9] Their molecular analysis showed a high prevalence of RAS mutations, which are frequent in follicular adenoma and follicular carcinoma.[21,22]

The recently emerging data reporting the benign behavior and the potential for over-treatment and costs of treatment for NIEFV-PTC has created, amongst other concerns, a major public concern.[23] Invasion rather than nuclear features of PTC was the major determinant of biological behaviour.[10–12,24] This has led to a paradigm shift in the classification, diagnosis, and management of these tumors. The harbinger of this shift was a proposal by an international panel of pathologists and clinicians who proposed to re-classify NIEFV-PTC as a non-malignant thyroid neoplasm and to use the term: "Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features [NIFTP]".[10] Based on the re-classification, NIFTP are best managed conservatively by surgery alone without radioactive iodine therapy.[9,11,12,18,25]

In keeping with recent studies that indicated the indolent behavior of NIEFV-PTC, none of our cases displayed vascular invasion, perinural invasion, extra-thyroidal extension, positive margins, lymph node or distant metastases. All our cases demonstrated no evidence of disease after a median follow up of 19 months, regardless of receiving radioactive iodine therapy. This outcome is consistent with previous studies that were able to follow up patients for a median follow up of more than 9.5 years.[10–12, 24]

The impact of the recent paradigm shift has major repercussions on the overall management of thyroid cancer. The obvious impact is on the pre-operative diagnosis of thyroid nodules by fine-needle-aspiration using The Bethesda System for Reporting Thyroid Cytology [TBSRT] criteria, particularly for criteria used for follicular-patterned lesions. Different

studies have demonstrated that the rate of definitive diagnosis of follicular variant of papillary thyroid carcinoma is low, ranging from 9.8% to 37.5%.[26–28] The main strength of TBSRT its ability to predict a risk of malignancy [ROM] for each of its diagnostic categories. This ROM would further assist in the management of patients with thyroid nodules in conjunction with clinical and radiological features. The NIEFV-PTC comprise a significant proportion of cases in the indeterminate category of the TBSRT, which include: atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, and suspicious for malignancy. Changing the diagnosis of NIEFV-PTC to NIFTP will likely decrease the ROM for these categories. Further, these changes may be reflected in further updates to the current TBSRTC.[29–31]

Furthermore, the rate of diagnosis of thyroid tumors may decrease and the management may experience a shift in surgical and medical options of treatment based on this new recommendation. When the NIEFV-PTC is viewed as a malignant neoplasm, staging would be performed according to malignant thyroid tumor protocols and treatment decisions would be based on this perspective. This may lead to over-treatment of these indolent tumors and major medical, surgical, psychological, financial, and medicolegal issues.[32–34]

Limitations to our study include that it is a retrospective study of patients treated in a tertiary care center, thus referral bias cannot be excluded. Larger nationwide and international studies based on data from tumor registries would be helpful to further establish local/regional guidelines for diagnosis and management of patient with NIFTP diagnosis. Our study further lacks molecular characterization of these tumors. Utilization of new molecular techniques could be helpful and may be considered in a future study.

In Conclusion, NIEFVPTC is an indolent thyroid tumor. The recent NIFTP nomenclature and re-classification of this tumor represent a paradigm shift. We recommend further studies involving larger-cohorts of patients, as well as, adoption of most recent guidelines in the diagnosis and management algorithms of patients with thyroid tumors to avoid potential over-treatment.

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