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Systematic Review and Meta-analysis of the Impact of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) on Cytological Diagnosis and Thyroid Cancer Prevalence

Darin Ruanpeng [1] · Wisit Cheungpasitporn [2] · Charat Thongprayoon [3] · James V. Hennessey [4] · Rupendra T. Shrestha [1]

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Abstract

A re-named diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) likely impacts the prevalence of thyroid cancer and risk of malignancy in populations based on the established Bethesda System of Reporting Thyroid Cytopathology (TBSRTC). This study was done to investigate the prevalence and cytological distribution of NIFTP. PRISMA guided systematic review was done from a database search of Pubmed, EMBASE, and Medline using the search terms "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", "non-invasive follicular variant of papillary carcinoma", "niftp", and "Bethesda" until November 2018. Original articles with surgically proven diagnoses of NIFTP using strict NIFTP criteria were included. Twenty-nine studies with 1563 cases of NIFTP were included. The pooled prevalence of NIFTP in cases which would be classified previously as the follicular variant of papillary thyroid cancer (FVPTC) and papillary thyroid cancer (PTC) were 43.5% (95% CI 33.5–54.0%) and 4.4% (95% CI 2.0–9.0%) respectively. The pooled TBSRTC distribution of cases diagnosed as NIFTP was: from the non-diagnostic category 3.6% (95% CI 2.4–5.3%), benign 10.0% (95% CI 7.2–13.6%), AUS/FLUS 34.2% (95% CI 28.2–40.8%), FN/SFN 22.7% (95% CI 17.2–29.4%), suspicious for malignancy 22.4% (95% CI 17.7–27.9%), and malignant 7.5% (95% CI 4.2–12.9%). While a significant reduction in FVPTC prevalence is anticipated, a modest reduction of PTC prevalence is also expected with adoption of the NIFTP terminology that would be distributed mainly among lesions classified as indeterminate thyroid nodules. Further studies are needed to identify unique clinical characteristics of these lesions preoperatively.

Keywords NIFTP · Non-invasive follicular thyroid neoplasm with papillary-like nuclear features · Cytology

Introduction

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features or NIFTP is a subgroup of low risk encapsulated follicular variant papillary thyroid cancer which utilizes a strict diagnostic criterion (Table 1) to identify clinically low-risk papillary thyroid cancer. This is an initial step towards addressing the concern for overdiagnosis and overtreatment of such tumors that pose significant emotional and financial risks to patients impacted by this diagnosis [2–6]. The reported prevalence of follicular variant of papillary thyroid cancer (FVPTC) varies between 22 and 43% of all papillary thyroid

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✉ Rupendra T. Shrestha
shres053@umn.edu

Wisit Cheungpasitporn
wcheungpasitporn@gmail.com

Charat Thongprayoon
charat.thongprayoon@gmail.com

James V. Hennessey
Jhenness@bidmc.harvard.edu

[1] Department of Medicine, University Minnesota, 516 Delaware St SE, Minneapolis, MN 55455, USA

[2] Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

[3] Department of Medicine, Mayo Clinic, Rochester, MN 55455, USA

[4] Department of Endocrinology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, GZ-6 02215, MA, USA

Table 1 Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) criteria according to Nikiforov et al. [1]

	Criteria
1	Encapsulation or clear demarcation
2	Nuclear score 2–3
3	No vascular or capsular invasion
4	No tumor necrosis
5	No high mitotic activity (< 3/HPF)
6	Follicular growth pattern with: < 1% Papillae (criteria modified in 2018 to no well-formed papillae) No psammoma bodies < 30% solid/trabecular/insular growth pattern

cancer (PTC) cases, and about 45,000 cases of potential NIFTP are expected to be diagnosed annually worldwide [1]. Following the application of NIFTP terminology, if a portion of thyroid carcinoma is considered to be a tumor with low potential of metastatic spread, the overall malignancy risk of a thyroid nodule as well as their distribution in each of the Bethesda System of Reporting Thyroid Cytopathology (TBSRTC) category is expected to be lower than prior estimates. Initial studies on noninvasive FVPTC showed that when a portion of these tumors were considered nonmalignant, significant clinical outcome risk reduction was noted not only in the categories of atypia of uncertain significance (AUS), follicular neoplasm (FN) and the suspicious for malignancy (SUS) category but also in the benign and non-diagnostic cytological categories thereby reducing false negative malignancy rates [7–9]. Several studies have attempted to estimate the impact on clinically relevant malignancy prevalence in populations evaluated and the subsequent predictive impact of the various TBSRTC categories following the introduction of the NIFTP diagnostic criteria. The results of these studies show a wide fluctuation of prevalence of NIFTP within lesions considered diagnostic of PTC [10–12]. Similarly, the prevalence of NIFTP within tumors considered FVPTC has also been reported to vary widely [13, 14]. The current systematic review and meta-analysis were performed to investigate prevalence of NIFTP in FVPTC and PTC and assess the distribution of tumors eventually considered NIFTP according to the current criteria of TBSRTC.

Research Design and Methods

Search Strategy

The systematic review was done according to PRISMA-guided systematic searches of the PubMed database, MEDLINE, and EMBASE from inception to November 2018. The search terms were "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", "non-invasive follicular variant of papillary carcinoma", "niftp", and "Bethesda" as described in Data S1. The search methodology is described in detail in Fig. S1. Investigator (D.R. and R.T.S.) independently performed this literature review. References of selected retrieved articles were also manually reviewed.

Study Selection

The inclusion criteria were as follows: (1) surgically proven NIFTP confirmed by NIFTP criteria adhering to those defined by Nikiforov et al. [1] and for cytological distribution analysis; (2) cytology obtained from fine needle aspiration from the proven histology in the Bethesda System for Reporting Thyroid Cytopathology [15]. Eligibility was independently determined by each investigator noted above. We excluded non-English literature, duplicate reports, poster presentations, reports without fine needle aspiration data, reports that did not consider NIFTP as a unique category, and reports without original data.

The quality of each included study was assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool.

Data Collection Process and Data Items

Information was extracted independently by two investigators (D.R and R.T.S) in a standardized form including last name of the first author, type of study, country of origin, year of publication, years of study, characteristics of study cohort, number of NIFTP cases, number of FVPTC cases, number of PTC cases, and cytology classifications in the various TBSRTC categories. Data were cross-checked, and discrepancies were mutually resolved.

Statistical Analysis

The data analysis was completed using the comprehensive meta-analysis software (version 3.3.070; Biostat Inc., Englewood, New Jersey, USA). Adjusted point estimates of prevalence of NIFTP and cytological distribution of NIFTP from each study were combined using the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance [16]. Given the likelihood of between-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were applied to determine the between-study heterogeneity. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity [17]. The presence of publication bias was evaluated via funnel plots and Egger test [18].

Results

The search methodology and literature review are outlined in Fig. S1 and Table S1. The literature review process yielded 108 potentially relevant studies (48 articles from EMBASE, 14 articles from MEDLINE, and 46 articles from Pubmed). After exclusion of 27 duplicates, 16 studies without full-text availability and 22 studies with no histologic data or incomplete TBSRCT data; leaving 43 studies for full-length article review. Of these 43 studies, 14 were excluded for various reasons (twelve did not follow strict criteria for NIFTP [1], one excluded NIFTP from results, and one reported core needle biopsy results), leaving 29 studies for review including 22 studies for TBSRTC distribution (1030 NIFTP), 19 studies for NIFTP prevalence in FVPTC (808 NIFTP) [10–14, 19–32], 9 studies for FVPTC within PTC [10, 11, 13, 19–21, 23, 24, 32], and 11 studies (568 NIFTP) for prevalence in PTC. [10, 11, 13, 19–21, 23, 24, 32–34]. The detailed characteristics and quality assessment of the included studies are shown in Tables 2 and 3.

The pooled prevalence of NIFTP in FVPTC and PTC were 43.5% (95% CI 33.5–54.0%) and 4.4% (95% CI 2.0–9.0%) respectively. The pooled prevalence of FVPTC in PTC was 15.4% (95% CI 7.4–29.2%). The forest plot of this overall analysis is shown in Figs. 1, 2, 3.

The pooled TBSRTC distribution of reported NIFTP cases were as follows: B1, non-diagnostic category 3.6% (95% CI 2.4–5.3%), B2, benign 10.0% (95% CI 7.2–13.6%), B3, AUS/FLUS 34.2% (95% CI 28.2–40.8%), B4, FN/SFN 22.7% (95% CI 17.2–29.4%), B5, suspicious for malignancy 22.4% (95% CI 17.7–27.9%) and B6, malignant 7.5% (95% CI 4.2–12.9%). The distribution summary is outlined in Fig. 4. The forest plot of overall analysis is shown in Fig. S2–7. The highest number of reported NIFTP cases was reported within the B3, AUS/FLUS category.

Evaluation for Publication Bias

We assessed publication bias of pooled prevalence of NIFTP in FVPTC, NIFTP in PTC, and FVPTC in PTC and found no publication bias as assessed by the funnel plots (Fig. S8–10 and Egger's regression asymmetry test with $p = 0.19$, 0.39, and 0.10 for prevalence of NIFTP in FVPTC, prevalence of NIFTP in PTC and prevalence of FVPTC in PTC, respectively.

Discussion

The prevalence of FVPTC diagnoses among PTC cases varies widely from 3 to 41% [10, 11, 19]. Similarly, the prevalence of NIFTP found among FVPTC cases varies ranging from 16 to 80% [14, 30]. Our analysis of studies that followed the strict published criteria of NIFTP showed a pooled prevalence of NIFTP within FVPTC to be 43.5% indicating a significant lowering of the prevalence of clinically significant FVPTC after the NIFTP category was introduced. Therefore, as NIFTP use becomes more widespread, and if this is considered a separate and nonmalignant entity, the prevalence of remaining FVPTC on histological sample will decline significantly. On the other hand, the remaining diagnoses of PTC after the exclusion of NIFTP is expected to have higher risk histological features and lower rates of American thyroid association (ATA) low-risk PTC [11]. The overall impact of NIFTP terminology depends on prevalence of FVPTC within the general category of PTC which was found to be close to 15% with a pooled prevalence of NIFTP within PTC of 4.4%.

Our study indicates a lower than anticipated prevalence of FVPTC within PTC and a modest decline of significant malignancy rate within PTC (4.4%) indicating that overall impact may be lower than initially anticipated. Several studies have noted the rising prevalence of FVPTC. In a large study by Jung et al., about 1 out of 4 resected PTC were subclassified as FVPTC and the incidence of this designation rose over the study period of 1974–2009 with significant rise of microcarcinomas [43]. Similarly, in a multicenter study, noninvasive FVPTC accounted for about 23% of total surgically proven PTC [21]. However, in a study by Hirokawa et al., only 284 FVPTC were detected after evaluating 10,076 cases of PTC with results in a calculated prevalence of 2.8% [10]. Similarly, in a study by Kim et al., the prevalence of FVPTC within PTC was lower (5%), and more than half of the FVPTC reported were microcarcinomas [24]. Therefore, the prevalence of FVPTC and therefore NIFTP would be lower if microcarcinomas are excluded. Another explanation for such differences could be interobserver variation in the diagnosis of encapsulated FVPTC itself leading to a difference in malignancy rates [44]. The diagnostic criteria for noninvasive encapsulated FVPTC proposed in a study by Nikiforov et al. required agreement among 50% of the pathologists [1]. This clearly may have an impact on this diagnosis when dual confirmation of the histopathologic diagnosis is not routine. Geographical variation has been considered to be a factor in lower prevalence rates in studies conducted in Asian countries, but a recent Canadian study has also shown a lower prevalence rate of 2.1% [33]. In this report by Parente et al., only 2.1% of PTC met the criteria for NIFTP. Nonetheless, a true variation in prevalence of FVPTC among different population remains a possibility.

Long-term follow-up data is also lacking in most of the included studies, but when available utilizing initial criteria, no evidence of structural disease was detected in the follow-up period ranging from 2 to 15 years. [20, 24, 30, 35]. Although the majority of examined NIFTP cases possess *RAS* mutations

Table 2 Study characteristics

	Bychkov [12]	**Rosario** [35]	**Mahajan** [26]	**Maletta** [36]	**Bizzarro** [22]	
Country	Thailand, India, Korea, Taiwan, and Japan	Brazil	India	Italy	Italy	
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	
Year publication	2018	2016	2018	2016	2016	
Study period	2010–2017	–	2015–2017	–	2013–2016	
Study cohort	All lobectomy/thyroidectomy	All NIFTP diagnosis	Case reported histology as FVPTC or NIFTP	–	NIFTP and I-FVPTC	
NIFTP criteria use	Yes	Yes	Yes	Yes	Yes	
NIFTP size		> 1 cm	No size cutoff		0.6–5.4 cm	
NIFTP number	59	129 (126 available cytology)	23	96	37	
NIFTP TBSRTC	59	126	23	96	37	
ND	6	1	0	0	0	
Benign	11	10	0	0	0	
AUS/FLUS	13	25	14	14	5	
FN/SFN	19	53	8	54	15	
SUS	7	32	1	26	13	
Malignancy	3	5	0	2	4	
Total PTC	–	–	–	–	–	
Total FVPTC	107	–	51	–	61	
	Hirokawa [10]	**Hahn** [30]	**Kim** [24]	**Lee** [13]	**Brandler** [37]	
Country	Japan	Korea	Korea	Korea	USA	
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	
Year publication	2017	2017	2018	2017	2017	
Study period	2007–2016	2008–2014	2014–2016	2010–2014	2013–2016	
Study cohort	All PTC	FVPTC > 0.5 cm	All PTC	779 patients who underwent thyroidectomy for thyroid nodules	NIFTP, PTC, FA	
NIFTP criteria use	Yes	Yes	Yes	Unclear	Yes	
NIFTP size	0.4–5.0 cm	> 0.5 cm		0.4–3.0 cm		
NIFTP number	54	35	73	21	56	
NIFTP TBSRTC	41	35	59	21	56	
ND	2	2	1	0	0	
Benign	2	5	10	2	6	
AUS/FLUS	5	9	21	12	21	
FN/SFN	1	2	3	0	15	
SUS	4	10	12	4	10	
Malignancy	27	7	12	3	4	
Total PTC	10076	–	2853	769	–	
Total FVPTC	284	208	175	126	–	
	Kiernan [25]	**Li** [20]	**Strickland** [32]	**Chandler** [27]	**Song** [38]	**Zhao** [28]
Country	USA	USA	USA	USA	USA	USA
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
	2018	2017	2018	2017	2017	2017

Table 2 (continued)

Year publication						
Study period	2009–2016	2011–2016	2010–2012	2012–2016	2016–2017	2000–2011
Surgical follow-up	All surgery	All surgery	All surgery	FVPTC	All NIFTP	FVPTC
NIFTP criteria use	Yes	Yes	Yes	Yes	Unclear	Yes
NIFTP size	No size cutoff	0.8–4.0 cm	No size cutoff	0.4–6.5 cm	1–7 cm	
NIFTP number	17	17	31	51	87	50
NIFTP TBSRTC	17	17	31	51	72	50
ND	0	0	0	1	0	3
Benign	1	3	0	7	5	2
AUS/FLUS	5	8	8	18	29	14
FN/SFN	2	4	2	14	27	13
SUS	7	1	21	11	6	9
Malignancy	2	1	0	0	5	9
Total PTC	–	252	50	–	–	–
Total FVPTC	37	29	50	93	–	97
	Lastra [39]	**Mito** [40]	**Lindeman** [41]	**Mao** [23]	**Jiang** [42]	**Kim** [24]
Country	USA	USA	USA	USA	USA	Korea
Study design	R	R	Retrospective	R	R	R
Year publication	2018	2017	2018	2018	2016	2018
Study Period	2016–2017	2016	2016–2017	2010–2016	2012–2016	2012–2014
Surgical follow-up			Lobectomy/thyroidectomy	Thyroidectomy	FVPTC	FNA
NIFTP criteria use	Yes	Unclear	Yes	Yes	Yes	Yes
NIFTP size		No size cutoff				
NIFTP number	119	29	26	32	8	25
NIFTP TBSRTC	119	29	26	32	8	25
ND	1	0	0	1	0	1
Benign	7	1	2	10	0	5
AUS/FLUS	51	14	13	11	7	14
FN/SFN	37	5	4	6	1	2
SUS	19	8	6	3	0	3
Malignancy	4	1	1	1	0	0
Total PTC	–	–	–	454	–	1700
Total FVPTC	–	–	–	181	–	132
	Jaconi [19]	**Wong** [11]	**Lau** [14]	**Yang** [29]	**Point du Jour** [31]	
Country	Italy	USA	USA	USA	USA	
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	
Year publication	2017	2017	2018	2017	2018	
Study period		2010–2012	2013–2016	21 years	2014–2015	
Study cohort	First 200 histological diagnoses of thyroid	Database of thyroid	All adult cases of	All archival material from ultrasound-guided		

Table 2 (continued)

	specimens	resection specimens	thyroid FNAs with subsequent surgical resection	FNA biopsies	Tumors diagnosed as FVPTC
NIFTP criteria use	Yes	Unclear	Yes	Yes	Yes
NIFTP size	No size cutoff	No size cutoff		0.6–7.4 cm	No size cutoff
NIFTP number	14	94	87	72	17
NIFTP TBSRTC	NA	NA	NA	NA	NA
ND					
Benign					
AUS/FLUS					
FN/SFN					
SUS					
Malignancy					
Total PTC	51	348	–	–	–
Total FVPTC	21	132	108	179	50
	Parente [33]	**Cho** [34]			
Country	Canada	Korea			
Study design	Retrospective	Retrospective			
Year publication	2018	2017			
Study period	2004–2013	2008–2014			
Study cohort	All pathological reports with slides for FVPTC review	All thyroidectomy			
NIFTP criteria use	Yes	Yes			
NIFTP size					
NIFTP number	102	105			
NIFTP TBSRTC	–	–			
ND					
Benign					
AUS/FLUS					
FN/SFN					
SUS					
Malignancy					
Total PTC	4790	6269			
Total FVPTC	–	–			

Table 3 Studies quality assessment

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1. Bychkov [12]	L	U	L	L	L	L	L
2. Rosario [35]	L	U	L	L	L	L	L
3. Mahajan [26]	L	L	L	L	L	L	L
4. Maletta [36]	U	L	L	U	L	L	L
5. Bizzarro [22]	L	U	L	L	L	L	L
6. Hirokawa [10]	L	H	L	H	L	L	L
7. Hahn [30]	H	H	L	L	L	L	L
8. Kim [24]	L	L	L	L	L	L	L
9. Lee [13]	L	U	H	L	L	L	L
10. Brandler [37]	L	L	L	L	L	L	L
11. Kiernan [25]	L	L	L	L	L	L	L
12. Li [20]	L	H	L	L	L	L	L
13. Strickland [32]	L	L	L	L	L	L	L
14. Chandler [27]	L	L	L	L	L	L	L
15. Song [38]	L	L	L	L	L	L	L
16. Zhao [28]	L	U	L	L	L	L	L
17. Lastra [39]	L	H	L	L	L	L	L
18. Mito [40]	H	L	U	U	U	L	L
19. Lindeman [41]	L	L	L	L	L	L	L
20. Mao [23]	L	L	L	L	L	L	L
21. Jiang [42]	H	L	L	L	L	L	L
22. Kim [24]	H	H	L	L	L	L	L
23. Jaconi [19]	L	L	L	L	L	L	L
24. Wong [11]	L	H	L	L	L	L	L
25. Lau [14]	L	H	L	L	L	L	L
26. Yang [29]	H	H	L	H	L	L	L
27. Point du Jour [31]	L	L	L	L	L	L	L
28. Parente [33]	L	U	L	L	L	L	L
29. Cho [34]	L	L	L	U	L	L	L

L: Low Risk of Bias
H: High Risk of Bias
U: Unclear

[45], the occasional presence of *BRAF* V600E has raised the possibility of inclusion of conventional PTC variants. Studies have shown that when all tumors with papillary structures were considered malignant, the remaining cases designated as NIFTP were devoid of *BRAF* V600E mutations [34, 36]. Reports have indicated an increased risk of adverse clinical outcomes with positive *BRAF* V600E included in the NIFTP category [36]. Further, Kim et al. [34] clearly demonstrated that the arbitrary 1% cutoff for papillary structure was misleading and could lead to inclusion of tumors with higher risk of recurrence. When all tumors with papillary structure were excluded, Parente et al. [33] demonstrated that none of the remaining tumors were classical variants, yet 6% of the tumors included in this series were shown to have malignant behavior. These observations highlight our limitations in detection of invasive growth in the histology sections that are examined despite complete submission of the tumors. Such observation could also indicate that NIFTP may include a spectrum of tumor biology with variable outcome despite histological homogeneity. Subsequently, experts in the field revisited this issue to address this concern by modifying the criteria to "no true papillary structures" rather than "<1% papillae" as diagnostic inclusion criteria [46]. With this change in force, a further reduction in prevalence of NIFTP can be expected [34], and the initial approximation of annual 45000 cases could well be an overestimation leading to an overall smaller impact in PTC diagnosis.

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Strickland et al.	0.620	0.480	0.743	1.680	0.093	31 / 50	5.14
Jaconi et al.	0.667	0.447	0.832	1.497	0.134	14 / 21	4.49
Li et al.	0.586	0.404	0.748	0.924	0.356	17 / 29	4.83
Wong et al.	0.712	0.629	0.783	4.711	0.000	94 / 132	5.43
Lee et al.	0.167	0.111	0.242	-6.733	0.000	21 / 126	5.30
Kim et al. (1)	0.417	0.346	0.491	-2.182	0.029	73 / 175	5.52
Hirokawa et al.	0.190	0.149	0.240	-9.583	0.000	54 / 284	5.52
Bychkov et al.	0.551	0.456	0.643	1.062	0.288	59 / 107	5.42
Bizzarro et al.	0.607	0.480	0.720	1.652	0.099	37 / 61	5.23
Mao et al.	0.177	0.128	0.239	-7.895	0.000	32 / 181	5.42
Kim et al. (2)	0.189	0.131	0.265	-6.545	0.000	25 / 132	5.35
Kiernan et al.	0.459	0.308	0.619	-0.493	0.622	17 / 37	5.01
Mahajan et al.	0.451	0.321	0.588	-0.699	0.485	23 / 51	5.17
Chandler et al.	0.548	0.447	0.646	0.932	0.351	51 / 93	5.39
Zhao et al.	0.515	0.417	0.613	0.305	0.761	50 / 97	5.40
Lau et al.	0.806	0.720	0.870	5.846	0.000	87 / 108	5.29
Yang et al.	0.402	0.333	0.476	-2.599	0.009	72 / 179	5.52
Hahn et al.	0.163	0.119	0.220	-8.707	0.000	34 / 208	5.44
Point du Jour et al.	0.340	0.223	0.480	-2.222	0.026	17 / 50	5.12
	0.435	0.335	0.540	-1.223	0.221		

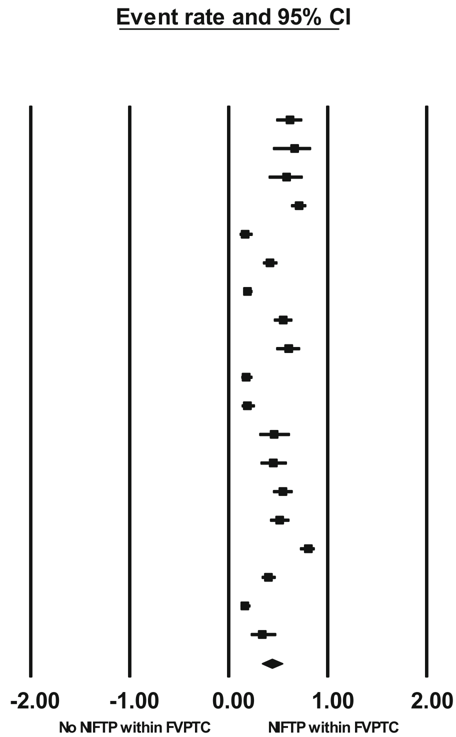


Fig. 1 Prevalence of NIFTP in FVPTC (Q 329.625, df 18, p 0, I^2 94.539). A diamond data marker depicts the overall rate from each included study (square data marker) and 95%CI.

The overall predictive power of TBSRTC categories depends on the individual institution's observed distribution of FNA results across the cytologic categories and prevalence of malignancy in each designated diagnosis. This met-analysis showed that the vast majority of NIFTP cases reported across literature are identified in the B3 (AUS), B4 (FN), and B5 (SUS) TBSRTC categories with nearly a third of reported final diagnosis of NIFTP found within the AUS category followed by more than one in five each reported in FN and SUS categories. Among these studies, a

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Strickland et al.	0.102	0.073	0.141	-11.478	0.000	31 / 304	9.09
Jaconi et al.	0.275	0.170	0.412	-3.097	0.002	14 / 51	8.77
Li et al.	0.067	0.042	0.106	-10.457	0.000	17 / 252	8.95
Wong et al.	0.270	0.226	0.319	-8.234	0.000	94 / 348	9.20
Lee et al.	0.027	0.018	0.042	-16.148	0.000	21 / 769	9.02
Kim et al. (1)	0.026	0.020	0.032	-30.698	0.000	73 / 2853	9.20
Hirokawa et al.	0.005	0.004	0.007	-38.282	0.000	54 / 10076	9.18
Mao et al.	0.070	0.050	0.098	-14.067	0.000	32 / 454	9.10
Kim et al.(2)	0.015	0.010	0.022	-20.868	0.000	25 / 1700	9.06
Parente et al.	0.021	0.018	0.026	-38.245	0.000	102 / 4790	9.22
Cho et al.	0.017	0.014	0.020	-41.380	0.000	105 / 6269	9.22
	0.044	0.020	0.090	-7.746	0.000		

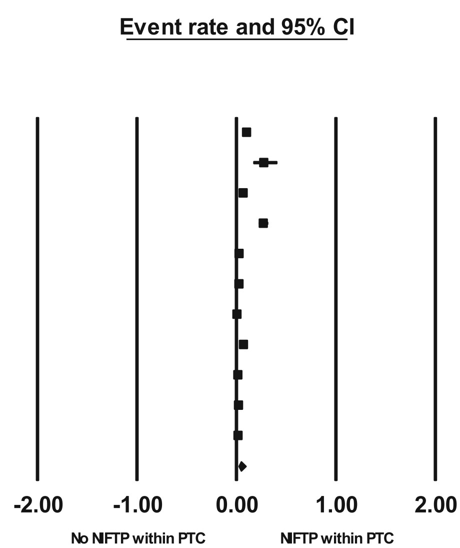


Fig. 2 Prevalence of NIFTP in PTC (Q 792.333, df 10, p 0, I^2 98.738). A diamond data marker depicts the overall rate from each included study (square data marker) and 95%CI.

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Strickland et al.	0.164	0.127	0.210	-10.505	0.000	50 / 304	11.09
Jaconi et al.	0.412	0.286	0.550	-1.254	0.210	21 / 51	10.71
Li et al.	0.115	0.081	0.161	-10.334	0.000	29 / 252	10.99
Wong et al.	0.379	0.330	0.431	-4.458	0.000	132 / 348	11.17
Lee et al.	0.164	0.139	0.192	-16.729	0.000	126 / 769	11.19
Kim et al. (1)	0.061	0.053	0.071	-34.964	0.000	175 / 2853	11.22
Hirokawa et al.	0.028	0.025	0.032	-58.816	0.000	284 / 10076	11.23
Mao et al.	0.399	0.355	0.444	-4.288	0.000	181 / 454	11.19
Kim et al.(2)	0.078	0.066	0.091	-27.307	0.000	132 / 1700	11.20
	0.154	0.074	0.292	-4.064	0.000		

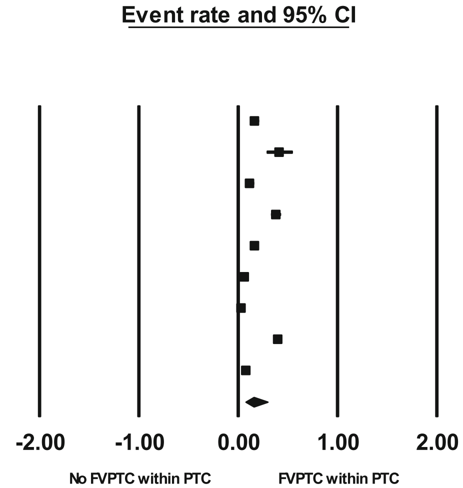
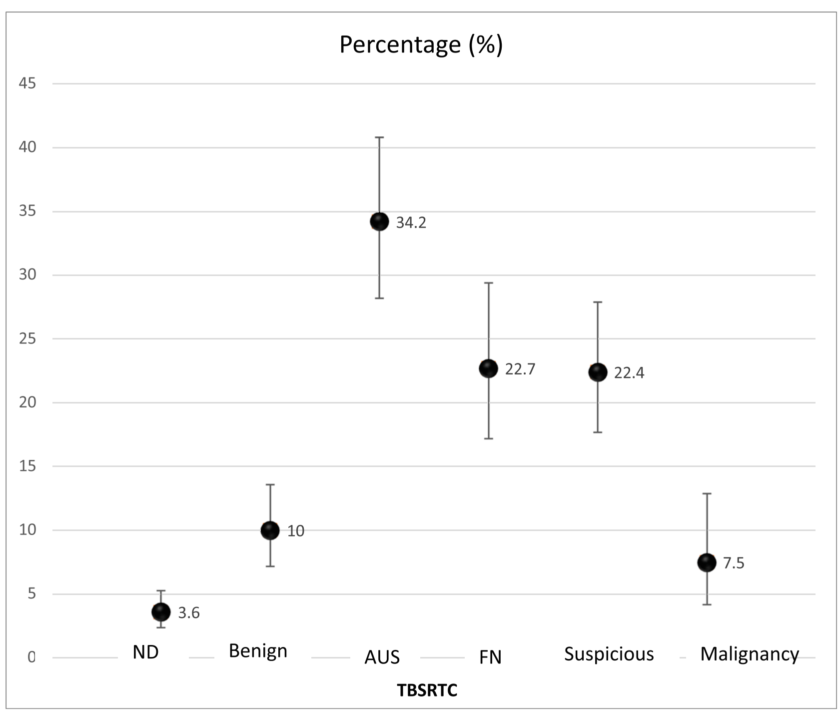


Fig. 3 Prevalence of FVPTC in PTC (Q 1226.618, df 8, p 0, I^2 99.348). A diamond data marker depicts the overall rate from each included study (square data marker) and 95%CI.

few have reported risk of clinically significant malignancy to be reduced across all TBSRTC categories. The greatest impact was seen in the B5 suspicious of malignancy category as a nearly 31–42% absolute risk reduction of malignancy is observed with the NIFTP reclassification [9, 14, 47]. This result is consistent with other publications estimating the impact of recategorization of noninvasive FVPTC [7–9]. At this time, preoperative identification of NIFTP cannot be achieved utilizing TBSRTC or cytological features. No cytomorphologic features have been identified that can reliably distinguish NIFTP from invasive or infiltrative FVPTC [19, 36, 48]. While some features such as nuclear folds [48] and presence of microfollicles along with nuclear features of PTC [37] have been identified associated with NIFTP, preoperative identification remains difficult even in tertiary care setting [40].

Our study was not without its limitations. Almost all studies we had analyzed were retrospective. Additionally, although strict diagnostic criteria were applied, the diagnosis of NIFTP was made after a pathology re-review in

Fig. 4 Percentage of NIFTP cytology in each TBSRTC



most studies. This could introduce a bias in these studies. Since NIFTP is a histological diagnosis, and not every thyroid FNA leads to a surgery; therefore, the FNA category distribution of NIFTP in the available literature does not represent a true estimate of disease prevalence. This limitation is unavoidable in the real-world clinical setting where only a portion of thyroid biopsies lead to surgery. The pooled prevalence in our study incorporates rates across different geographic settings with distinct populations and different disease prevalence rates. Finally, while several studies have not included size of the tumor, some have excluded microcarcinoma [35] which may have altered the malignancy rates.

In conclusion, nearly 44% of FVPTC were reclassified as NIFTP in the published literature when strict criteria of diagnosis were followed. Nearly 80% of NIFTP were diagnosed in the AUS, FN, and SUS cytology categories. While a significant reduction in the diagnosis of FVPTC prevalence is anticipated, a modest reduction of PTC prevalence is also observed with adoption of NIFTP terminology that again are be distributed mainly across AUS, FN, and SUS categories.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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