Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Selection criteria for study cohorts and case contribution

In May 2014, the working group pathologists were invited to contribute cases to the study that they diagnosed as encapsulated FVPTC based on the following accepted criteria: (i) encapsulated or well-circumscribed nodule, (ii) follicular growth pattern with no well-formed papillae, and (iii) nuclear features of PTC. Two study groups were formed. Group 1 included non-invasive EFVPTC that would fit the following selection criteria:

- tumor size >1 cm
- no vascular or capsular invasion on adequate tumor sampling, i.e. reasonable confidence that entire tumor capsule was examined
- no other invasive tumors in the gland except single small microcarcinoma
- no RAI treatment
- at least 10 years of follow-up.

Group 2 included encapsulated FVPTC with vascular invasion and/or tumor capsule invasion and at least 1 year of follow-up. Shorter follow-up as compared to Group 1 was accepted as some of these tumors would demonstrate tumor recurrence or distant spread earlier than 10 years after surgery.

Contribution of potential EFVPTC cases to the study

Contributors	Process of Case Selection	Group 1	Group 2
Dr. Fulvio Basolo, University of Pisa, Italy	Reviewed H&E slides for patients treated at the Department of Surgery, University of Pisa in 2000-13 and diagnosed as FVPTC with vascular and/or capsular invasion; follow-up data obtained from the Department of Endocrinology, University of Pisa		64 cases
Dr. Lester Thompson, Southern California Permanente Medical Group, Woodland Hills Medical Center, USA	Reviewed records of all 721 patients surgically treated for thyroid disease in 2002 at the hospitals of Southern California Permanente Medical Group to select cases based on the current criteria for EFVPTC	41 cases	3 cases
Dr. Ronald Ghossein, Memorial Sloan-Kettering Cancer Center, USA	Cases of thyroid carcinoma from 1981-2003 were reviewed microscopically to select those that were circumscribed/ encapsulated FVPTC without or with capsular and/or vascular invasion at Memorial Sloan-Kettering Cancer Center and had appropriate follow-up	20 cases	11 cases
Dr. Giovanni Tallini, University of Bologna, Italy	Reviewed all slides of tumors >1cm in size registered as follicular adenoma in the Maggiore Hospital pathology database from 1995-2010 and selected cases revised to encapsulated FVPTC with longest follow up available	26 cases	
Dr. Zubair Baloch, University of Pennsylvania, USA	Computerized search and review of cases from 1997-98 diagnosed as PTC for cases that were encapsulated with ~100% follicle formation and >10 year follow up	11 cases	4 cases
Dr. Justine Barletta, Brigham and Women's Hospital; Harvard Medical School, USA	Reviewed resection specimens with tumors >1cm in size diagnosed as FVPTC or follicular adenomas from 1991-2004 with ≥ 10 year follow up and selected non-	20 cases	

	invasive, non-infiltrative cases		
Dr. Bruce Wenig, Mount Sinai Beth Israel, USA	Computerized search of pathology information system for FVPTC from 2007-2014 followed by review of reports and glass slides to select cases that meet the criteria.		11 cases
Drs. Yuri Nikiforov/Raja Seethala, University of Pittsburgh, USA	Pathology reports of surgical thyroid specimens with benign and malignant thyroid nodules from 1995-1998 were selected and glass slides from the Department of Pathology, University of Pittsburgh reviewed to select cases that meet the criteria	20 cases	
Dr. Thomas Giordano, University of Michigan, USA	Searched records and glass slide reviewed for cases diagnosed as FV PTC at the Department of Pathology, University of Michigan from 1995-2010		7 cases
Dr. Abir Al Ghuzlan, Institut Gustave Roussy, France	Reviewed reports of cases diagnosed as PTC from 2008-2012 and slides diagnosed as minimally invasive follicular carcinoma for a 10 year period. Cases that met the criteria of FVPTC/ EFVPTC and >1 y follow-up were selected		11 cases
Dr. Venancio Alves, University of São Paulo School of Medicine, Brazil	Patients that underwent a complete thyroidectomy at Hospital Oswaldo Cruz, São Paulo with diagnosis of PTC from 2010-2014 were reviewed		5 cases
Dr. Kennichi Kakudo, Nara Hospital, Kindai University, Japan	Examined pathology reports and reviewed H&E sections from patients surgically treated at Yamashita Clinic in 2012		9 cases
Dr. Elham Khanafshar, University of California San Francisco, USA	Searched Department of Pathology database for FVPTC cases diagnosed in 2008-2013, reviewed H&E sections for FVPTC cases with vascular and/or capsular invasion that had >1 year follow up		5 cases
TOTAL:		**138 cases**	**130 cases**

Initial and subsequent histologic reviews and group discussions

The Working group pathologists were allotted 5 weeks to review the scanned slides and provide their diagnoses choosing from the following list of common histopathologic entities: Hyperplastic Nodule; Follicular Adenoma; Follicular Thyroid Carcinoma; Encapsulated Follicular Variant of Papillary Thyroid Carcinoma; Infiltrative Follicular Variant of Papillary Thyroid Carcinoma; and Classic Papillary Thyroid Carcinoma. Criteria suggested for diagnostic categories for the initial pathology review of study cases are as follows:

Hyperplastic Nodule (HN) – A well demarcated but not necessarily encapsulated proliferation of follicles of heterogeneous size and shape. Papillary infoldings with interspersed follicles were acceptable and the nuclear features were insufficient to participant's threshold for the diagnosis of papillary carcinoma.

Follicular Adenoma (FA) – A follicular patterned encapsulated/non-infiltrative neoplasm, often microfollicular and distinct from the surrounding thyroid but with insufficient nuclear features to meet the participant's threshold for the diagnosis of papillary carcinoma.

Follicular Thyroid Carcinoma (FTC) – A follicular patterned encapsulated neoplasm that showed tumoral capsular or angioinvasion but with insufficient nuclear features to meet the participant's threshold for the diagnosis of papillary carcinoma.

Papillary Thyroid Carcinoma, Encapsulated Follicular Variant (EFVPTC) – A follicular patterned encapsulated or well demarcated neoplasm with adequate nuclear features to meet the participant's threshold for the diagnosis of papillary carcinoma. This was considered the diagnostic category for retention of a case in both groups 1 and 2. Accordingly, for the initial exercise, participants were instructed to classify both encapsulated lesions with and without tumor capsular invasion and/or angioinvasion as EFVPTC.

Papillary Thyroid Carcinoma, Infiltrative Follicular Variant (IFVPTC) – An unencapsulated/partially encapsulated frankly infiltrative follicular patterned lesion with adequate nuclear features to meet the participant's threshold for the diagnosis of papillary carcinoma.

Papillary Thyroid Carcinoma, Classical (CPTC) - A neoplasm with papillary growth pattern and adequate, typically overt nuclear features for the diagnosis of papillary carcinoma.

Diagnoses rendered by 24 pathologists were tabulated and the initial findings were presented at the initiation of an 8 week series of weekly teleconference sessions aimed at refining groups 1 and 2. This process involved re-review of both scanned slides and still images from selected cases to achieve consensus for major and minor diagnostic criteria for encapsulated FVPTC and eliminate those that did not meet these criteria.

Revision of Nomenclature

Two weeks prior to the Face-to-Face Conference in Boston on March 20-21, 2015, all working group members were asked to provide their top choices for terminology revision for non-invasive encapsulated FVPTC. The proposed terms were collated and grouped according to broad themes including: no change, using "in-situ" or "non-invasive" terminology, elimination of the term "papillary," and elimination of the term "cancer." At the Conference, the previous literature, and data from the current study were summarized. Clinical, patient, pathologic (historic), and psychological perspectives were also provided on the impact of revision of nomenclature. The top 5 leading considerations for the new terminology were then listed and an initial vote was performed. A second vote between the two top candidates was performed and a majority vote was taken as the consensus terminology.

Schedule of teleconferences and face to face conference

Phase I (Pre-Boston Conference)

Teleconference Dates/ Times	Topics for Discussion	Participants
January 27, 2015	Overview of the project, introductory discussion	All working group members
February 3, 2015	Review of cases, histopathologic criteria	Pathologists
February 10, 2015	Review of cases, histopathologic criteria	Pathologists
February 17, 2015	Review of cases, histopathologic criteria	Pathologists
February 24, 2015	Review of cases, histopathologic criteria	Pathologists
March 3, 2015	Summary of data, discussion of new tumor name	All working group members
March 10, 2015	Discussion of new tumor name	All working group members

Phase II (Face-to-Face Conference in Boston, MA)

Conference Dates/ Times	Topics for Discussion	Participants

March 20, 2015	Summary of existing knowledge. Summary and discussion of data set. Consensus on diagnostic criteria.	All working group members
March 21, 2015	Discussion and acceptance of new tumor name	All working group members

Phase III (Post-conference)

Teleconference Dates/ Times	**Topics for Discussion**	**Participants**
April 14, 2015	Manuscript writing	Manuscript writing committee*
May 7, 2015	Manuscript writing	Manuscript writing committee
May 26, 2015	Manuscript writing	All working group members
June 23, 2015	Manuscript writing	Manuscript writing committee and clinicians
August 6, 2015	Manuscript writing	Manuscript writing committee
August 15, 2015	Manuscript editing	Manuscript writing committee
September15, 2015	Manuscript editing	All working group members

*ZB, RG, VL, GR, RRS, YEN

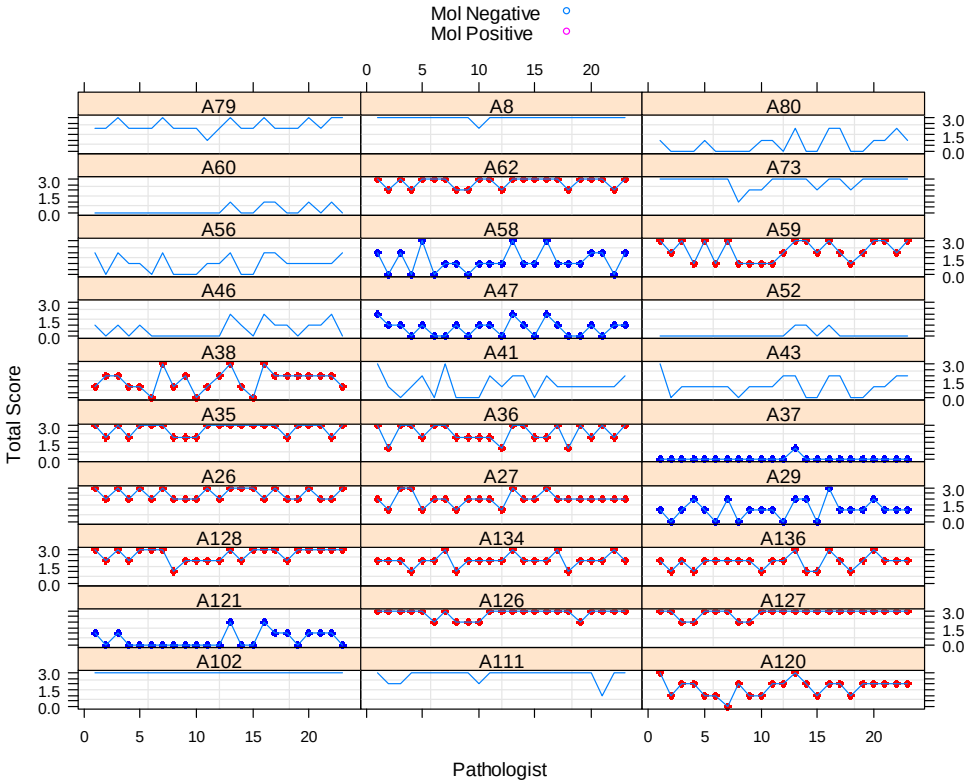
eResults

Performance of the Nuclear Scoring System

Training set

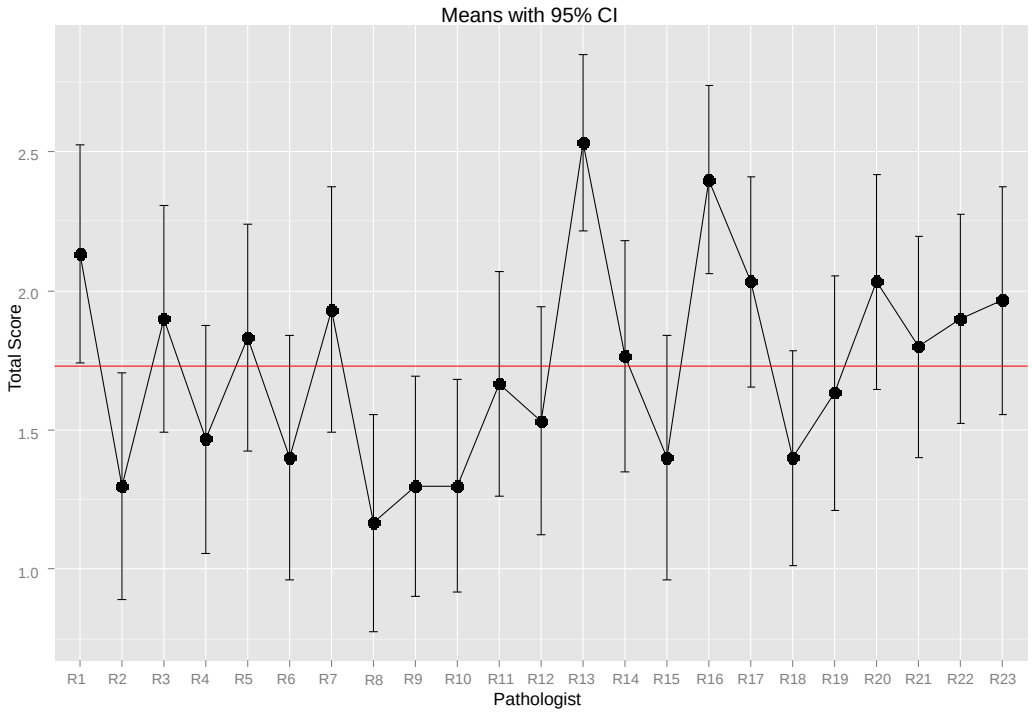
The training set consisted of 30 cases initially submitted to Group 1, including 13 mutation-positive, 5 mutation-negative, and 12 not tested. The latter were not used for classification. The cases were reviewed and scored by 23 pathologists. Overall, mutation-negative cases were more consistently scored lower than mutation-positive cases.

Distribution of scores rendered by 23 pathologists and molecular status of cases in the training set. Each line connects all pathologists' scores for a single case. Lines without dots represent the 12 cases without molecular diagnoses that were excluded from classification. Pathologists are arbitrarily numbered on the x axis



Performance of individual pathologists as compared to the average score is shown below.

Mean case score with 95% confidence interval by individual pathologist for cases in the training set. The red horizontal line is the grand mean across all cases and all pathologists.



Using molecular status as the reference standard, the most accurate classification was achieved when score 0-1 was used to identify mutation-negative and score 2-3 mutation-positive lesions.

		Molecular Status		
	Most Accurate Cutoff	Positive	Negative	
Classification Based on Total Score	2,3	270	23	293
	0,1	42	97	139
		312	130	432

Using the established cutoff, the three-point scoring system demonstrated the following performance in predicting molecular alterations in the training set:

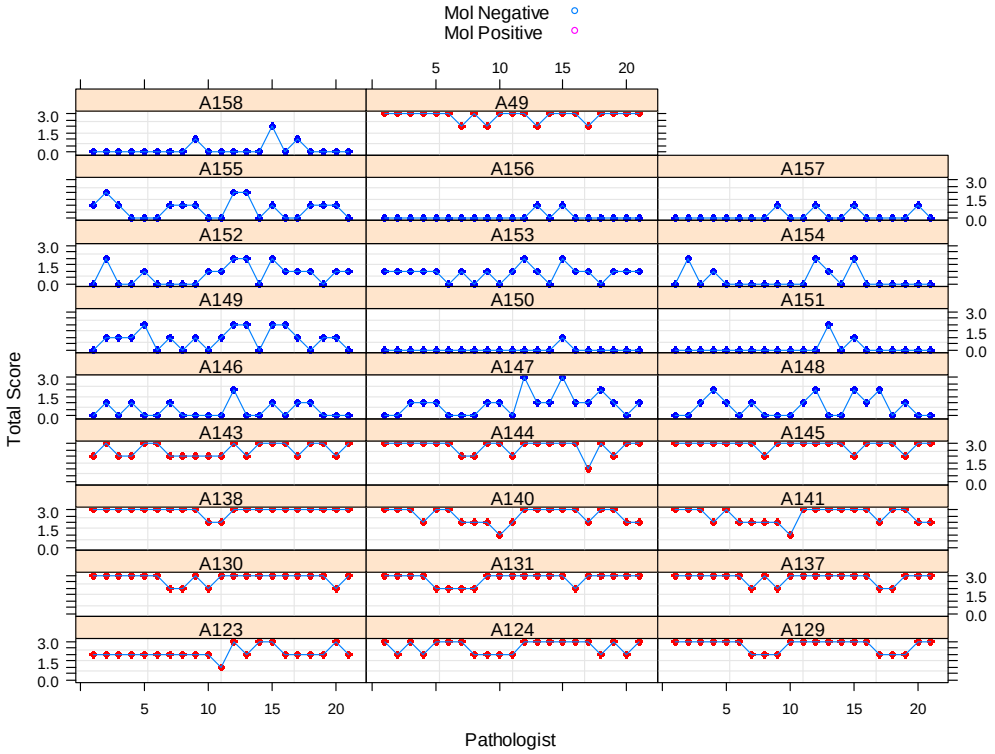
- Sensitivity - 86.5% (82.7% - 90.3%)
- Specificity - 80.8% (73.8% - 87.9%)
- PPV - 92.2% (89.1% - 95.2%)
- NPV - 69.8% (62.2% - 77.4%)
- Classification Accuracy - 85.0% (82.8% - 90.3%)

Validation set

Validation set included 26 new cases, all with the known mutational status (13 mutation positive, 13 mutation negative). These cases were reviewed and scored by 22 pathologists who were blind to the molecular diagnosis. Similar to the training set, mutation-negative cases were more consistently scored lower than mutation-positive cases.

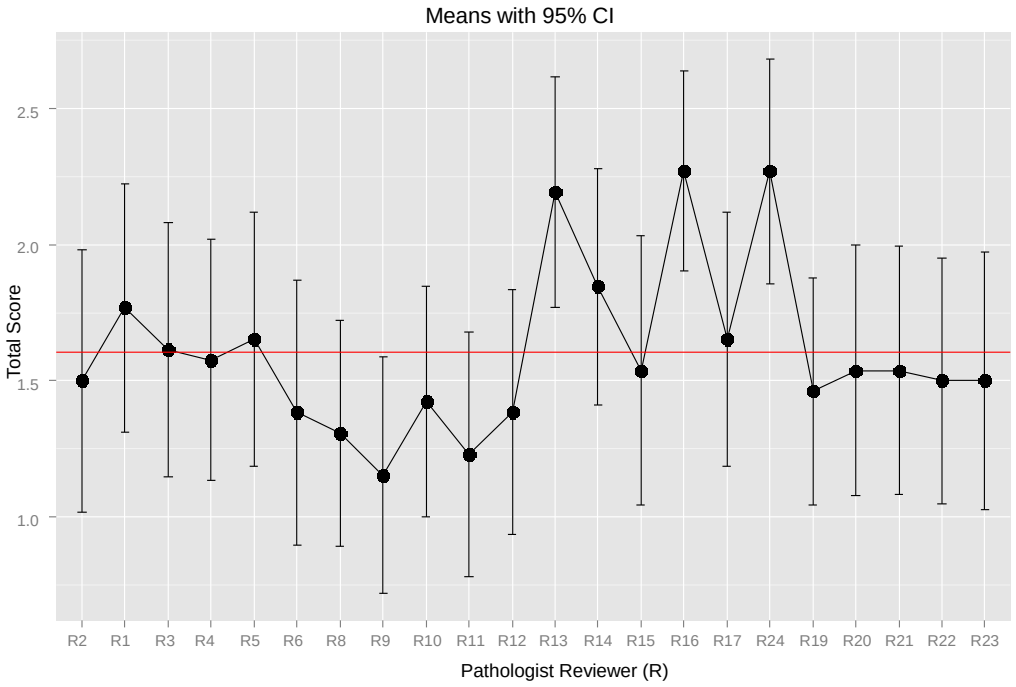
Distribution of scores rendered by 22 pathologists and molecular status of cases in the validation set.

Each line connects all pathologists' scores for a single case. Pathologists are arbitrarily numbered on the x axis.



Performance of individual pathologists as compared to the average score is shown below.

Mean case score with 95% confidence interval by individual pathologist for cases in the validation set.
The red horizontal line is the grand mean across all cases and all pathologists.



Out of the 22 pathologists, 19 had a 95% confidence interval of their mean scores overlap the average score for the entire group which was 1.6, whereas 3 pathologists had their scores consistently higher with respect to the overall mean.

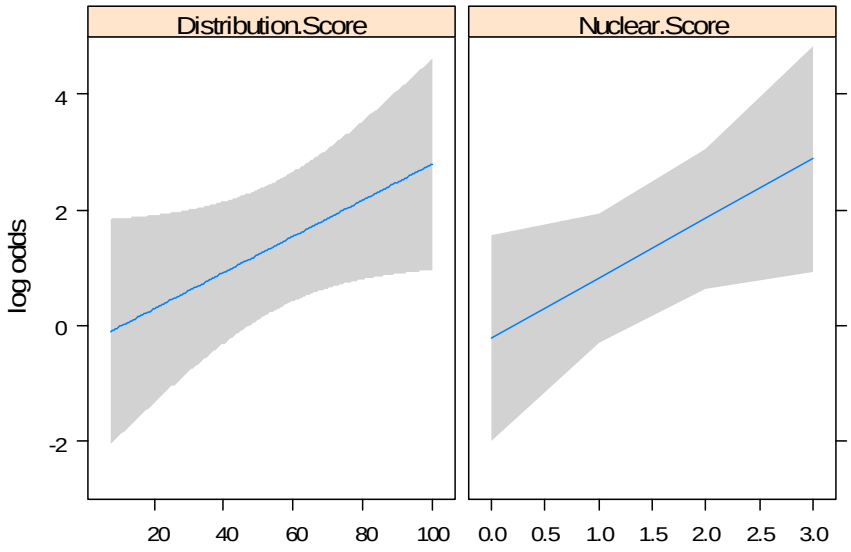
Using the cutoff established in the training set and mutational status as the reference standard, the three-point scoring system demonstrated the following performance in the validation set:

- Sensitivity - 98.6% (96.3% - 99.4%)
- Specificity - 90.1% (86.0% - 93.1%)
- PPV - 90.9% (87.1% - 93.7%)
- NPV - 98.4% (96.0% - 99.4%)
- Classification Accuracy – 94.3% (92.1% - 96.0%)

Distribution score

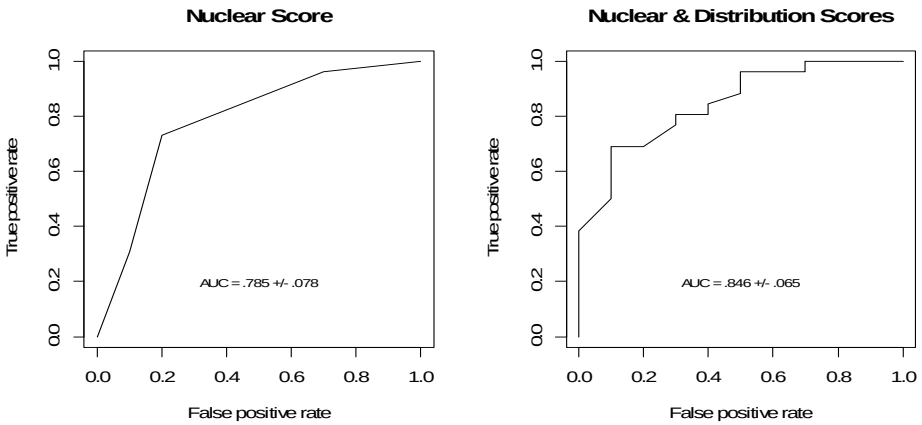
In addition to the level of expression of diagnostic nuclear features, EFVPTC are known to have either diffuse or multifocal presence of cells with the nuclear features of PTC. The possible contribution of the distribution score was assessed in a set of 30 cases used for the validation set that were reviewed by two pathologists (RRS, GT) who independently scored the distribution of the cells with nuclear features within the nodule. A logistic regression model for molecular diagnosis as a function of nuclear feature score and distribution was fitted. Analysis of the data showed that both the nuclear score (p=0.0506) and the distribution score (p=0.0632) were equally and independently informative for predicting mutational status in the 18 test cases.

Analysis of the distribution score. Effect of distribution score and nuclear score on log odds of a mutation-positive nodule status according to a logistic regression model.



However, the addition of the distribution score to the qualitative nuclear score resulted in a small, not statistically significant improvement of the accuracy of predicting the mutational status.

Analysis of the distribution score. Area under curve (AUC) analysis of nuclear score in isolation and in combination with distribution score.



Therefore, in order to avoid unnecessary increase in complexity of histopathological analysis, the distribution score was not included as a diagnostic feature of NIFTP.

eTable 1. Prevalence of encapsulated follicular variant of papillary thyroid carcinoma at different time intervals

Source	Setting/ Location	Time interval	Total number of PTC	FVPTC (% of all PTC)	EFVPTC (% of all PTC)
Chan KJ et al., *J Clin Endocrinol Metab* 99:E276-E285, 2014	University of Pittsburgh, PA, USA	1974-1992	186	8.1%	4.8%
		2009	230	25.2%	16.1%
Lupi et al., *J Clin Endocrinol Metab* 92:4085-4090, 2007	University of Pisa, Pisa, Italy	2006	500	22.8%	10.4%
R. Ghossein, *unpublished*	MSKCC, New York, USA	1977-1999	615	20.0%	14.3%
		2000-2003	303	27.7%	23.4%

PTC, papillary thyroid carcinoma; FVPTC, follicular variant of PTC; EFVPTC, encapsulated follicular variant of PTC

eTable 2. Results of molecular analysis of cases initially submitted to Group 1

	Cases		
Gene mutation	**Accepted to final Group 1**	**Excluded due to insufficient nuclear features**	**Excluded due to the presence of higher-grade exclusion criteria**
	n=27	*n=5*	*n=5*
*RAS**	8		2
NRAS	(5)		(1)
HRAS	(2)		(1)
KRAS	(1)		
BRAF K601E	1		
TERT			1
PPARG fusion	6		
ALK fusion			1
THADA fusion	6		
TOTAL MUTATION POSITIVE	**21 (78%)**	**0**	**4 (80%)**
TOTAL MUTATION NEGATIVE	**6 (22%)**	**5 (100%)**	**1 (20%)**

*Two cases had double mutations: *RAS* and *EIF1AX*

eTable 3. Summary of the results of the initial review of cases in Group 2

% of pathologists diagnosing EF VPTC	0%-9%	10%-19%	20%-29%	30%-39%	40%-49%	50%-59%	60%-69%	70%-79%	80%-89%	90%-99%
Number of cases (out of 130 total)	0	3	8	5	9	20	28	38	13	6
	25 (19%)					105 (81%)				

eTable 4. Details of follow-up for patients in Group 2 with adverse outcome

Study #	Age (years)	Sex	Type of Surgery	Tumor size (cm)	Capsular invasion	Vascular invasion	Other relevant features	Follow-up (years)	Findings on follow-up
B2	57	F	Total thyroidectomy	2.3	yes (3 foci)	yes (6 foci)	RAI given, bone metastasis at presentation	10.2	Dead of disease
B5	62	F	Total thyroidectomy	5.0	no	yes (8 foci)	RAI given, lung metastasis at presentation	15.1	Alive with disease
B8	66	M	Total thyroidectomy	5.0	yes (6 foci)	yes (8 foci)	RAI given, bone metastasis at presentation	2.9	Dead of disease
B69	63	F	Total Thyroidectomy	1.0	yes	no		2.6	lymph node recurrence, lung metastasis
B80	77	M	Total Thyroidectomy	3.5	yes	no		2	lung and bone metastases
B130	29	F	Lobectomy	2.0	yes	yes		2.6	lymph node metastasis, no recurrence
B58	53	F	Total Thyroidectomy	1.0	yes	no		7.2	persistent disease (residual)
B54	26	F	Total Thyroidectomy	1.5	yes	no		10.9	detectable serum Tg
B83	31	F	Total Thyroidectomy	2.7	yes	no		1	detectable serum Tg
B84	47	M	Total Thyroidectomy	1.6	yes	no		1.7	detectable serum Tg

B86	30	F	Total Thyroidectomy	2.5	yes	no		1	detectable serum Tg
B87	46	F	Total Thyroidectomy	0.6	yes	no		1	detectable serum Tg

M - Male; F - Female; Tg - thyroglobulin

eTable 5. Summary of cases used as a training set for three-point nuclear scoring scheme

Case Number	Nuclear Score				Molecular results
	Nuclear size and shape (Mean)	Membrane irregularities (Mean)	Chromatin characteristics (Mean)	Total Score (Mean)	
A8	0.95	1.00	1.00	2.95	-
A26	0.95	0.55	0.95	2.45	*PAX8/PPARG*
A27	0.77	0.73	0.55	2.05	*HRAS*; *EIF1AX*
A29	0.32	0.64	0.14	1.09	NEG
A35	0.95	0.82	0.91	2.68	*NRAS*
A36	0.95	0.73	0.59	2.32	*PAX8/PPARG*
A37	0.09	0.00	0.00	0.09	NEG
A38	0.64	0.64	0.41	1.68	*NRAS*; *EIF1AX*
A41	0.64	0.36	0.09	1.09	-
A43	0.68	0.36	0.05	1.09	-
A46	0.41	0.18	0.05	0.64	-
A47	0.36	0.18	0.18	0.73	NEG
A52	0.00	0.14	0.00	0.14	-
A56	0.64	0.32	0.09	1.05	-
A58	0.45	0.36	0.55	1.32	NEG
A59	0.50	0.91	0.68	2.09	*THADA* fusion
A60	0.14	0.14	0.00	2.95	
A62	1.00	0.73	0.95	2.68	*HRAS*
A73	0.95	1.00	0.77	2.73	-
A79	0.95	0.86	0.50	2.32	-
A80	0.45	0.23	0.05	0.73	-
A102	1.00	1.00	1.00	3.00	-
A111	0.91	0.91	0.95	2.77	-
A120	0.91	0.09	0.68	1.68	*NRAS*
A121	0.41	0.14	0.00	0.55	NEG
A126	0.82	1.00	0.95	2.77	*THADA* fusion
A127	0.91	1.00	0.91	2.82	*PAX8/PPARG*
A128	0.95	0.82	0.82	2.59	*BRAF K601E*
A134	0.95	0.77	0.36	2.09	*PAX8/PPARG*
A136	1.00	0.27	0.68	1.95	*KRAS*

eTable 6. Summary of cases used as a validation set for three-point nuclear scoring scheme

Case Number	Nuclear Score				Molecular results
	Nuclear size and shape (Mean)	Membrane irregularities (Mean)	Chromatin characteristics (Mean)	Total Score (Mean)	
A49	0.91	1.00	0.91	2.82	*THADA* fusion
A157	0.14	0.09	0.05	0.27	NEG
A123	0.82	0.55	0.82	2.18	*PAX8/PPARG*
A124	1.00	0.64	0.95	2.59	*HRAS*
A152	0.14	0.18	0.50	0.82	NEG
A158	0.09	0.09	0.00	0.18	NEG
A145	1.00	0.86	1.00	2.86	*NRAS*
A129	0.82	0.95	0.91	2.68	*THADA* fusion
A153	0.77	0.14	0.00	0.91	NEG
A137	1.00	1.00	0.82	2.82	*PAX8/PPARG*
A138	1.00	0.91	1.00	2.91	*NRAS*
A151	0.05	0.09	0.05	0.18	NEG
A150	0.05	0.00	0.00	0.05	NEG
A140	1.00	0.73	0.77	2.50	*PAX8/PPARG*
A156	0.05	0.05	0.00	0.09	NEG
A141	0.86	0.68	0.95	2.50	*HRAS*
A155	0.18	0.50	0.09	0.77	NEG
A131	0.82	1.00	1.00	2.82	*ALK* fusion
A149	0.50	0.09	0.32	0.91	NEG
A143	1.00	0.50	1.00	2.50	*NRAS*
A154	0.23	0.23	0.09	0.55	NEG
A130	1.00	0.82	1.00	2.82	*THADA* fusion
A146	0.14	0.09	0.23	0.45	NEG
A147	0.45	0.27	0.27	1.00	NEG
A144	0.86	0.86	1.00	2.73	*NRAS*
A148	0.32	0.18	0.23	0.73	NEG

eTable 7. Estimation of worldwide incidence of NIFTP

Source	Parameter	Value	Result
Ferlay J. et al (2012)[1]	Total number of new cases of thyroid cancer worldwide	298,000	298,000
Aschebrook-Kilfoy B. et al. (2011) [2]	Percentage of papillary thyroid carcinoma (PTC) among all thyroid carcinomas	84%	250,320
Estimation based on unpublished data[3]	Percentage of encapsulate follicular variant of PTC with no invasion among all PTC	18.6%	**46,560**

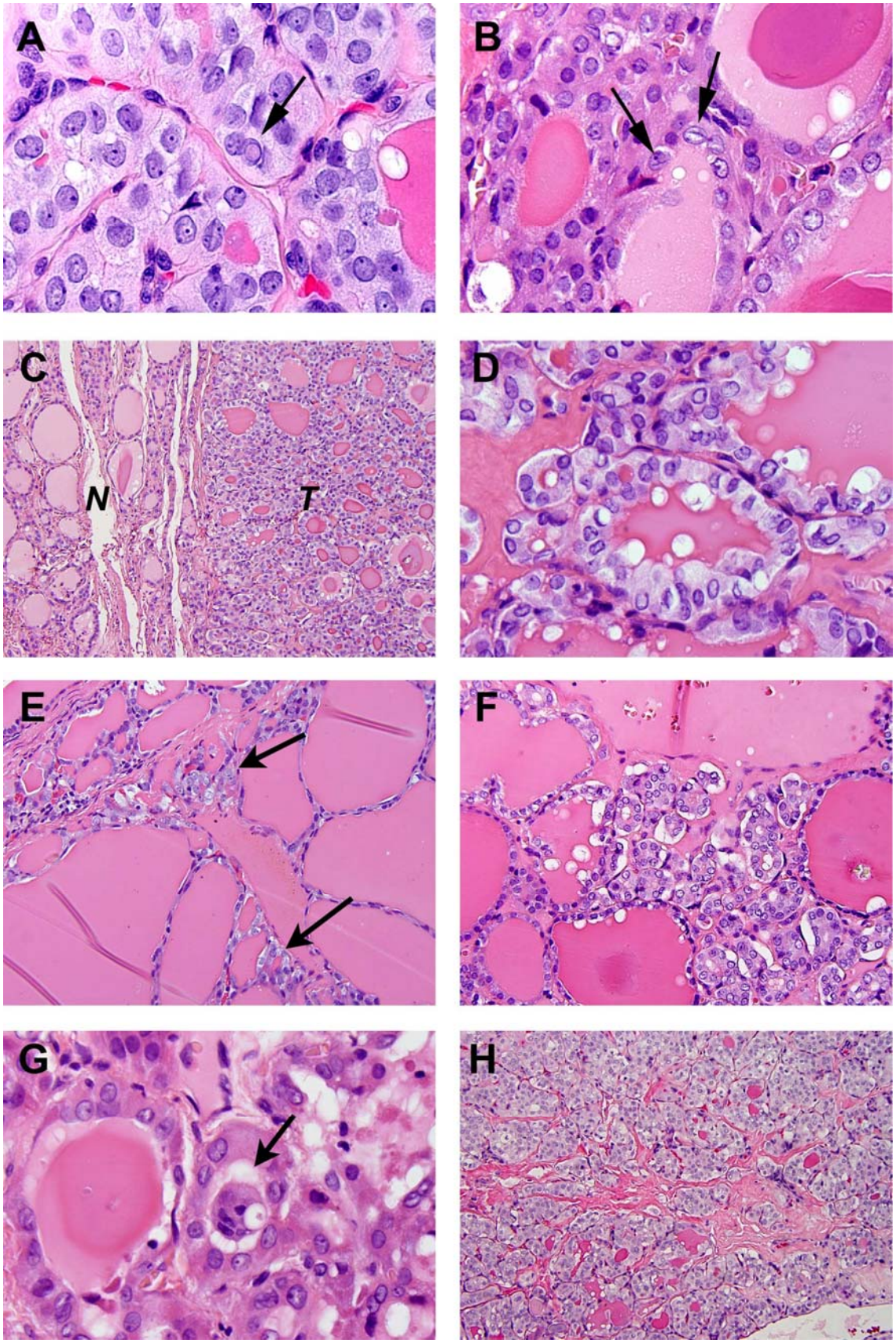
[1]Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.

[2]SEER data (Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid Cancer Incidence Patterns in the United States by Histologic Type, 1992–2006. Thyroid. 2011 Feb;21(2):125-34).

[3]Estimation of the proportion of EFVPTC without invasion among all currently diagnosed PTC

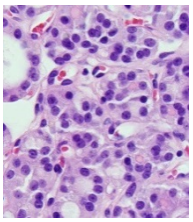
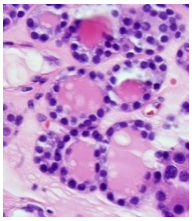
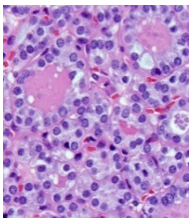
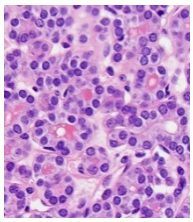
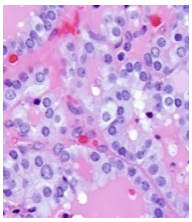
Source	Setting/ Location	Time interval	Total number of PTC	Analysis performed	FVPTC	EFVPTC	EFVPTC with no invasion
G. Tallini, *unpublished*	Bellaria Hospital, Bologna, Italy	2000-2015	523	Hospital database search	22.4%	20.7%	13.6%
M. Papotti, *unpublished*	San Luigi Hospital, Turin, Italy	2005-2014	409	Hospital database search	36%	36%	25%
F. Basolo, *unpublished*	Hospital of Pisa, Pisa, Italy	2000-2004	2197	Hospital database search	43.4%	22.7%	18.7%
R. Ghossein, *unpublished*	MSKCC, NY, USA	2000-2003	303	Pathology slide review	27.7%	23.4%	18.8%
							Mean – 18.6%

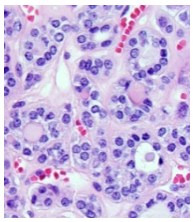
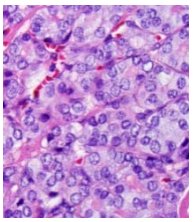
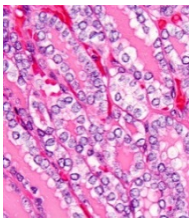
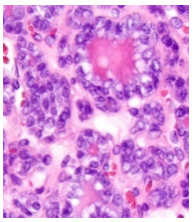
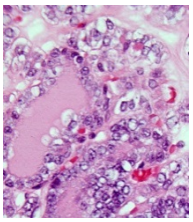
PTC, papillary thyroid carcinoma; FVPTC, follicular variant of PTC; EFVPTC, encapsulated follicular variant of PTC



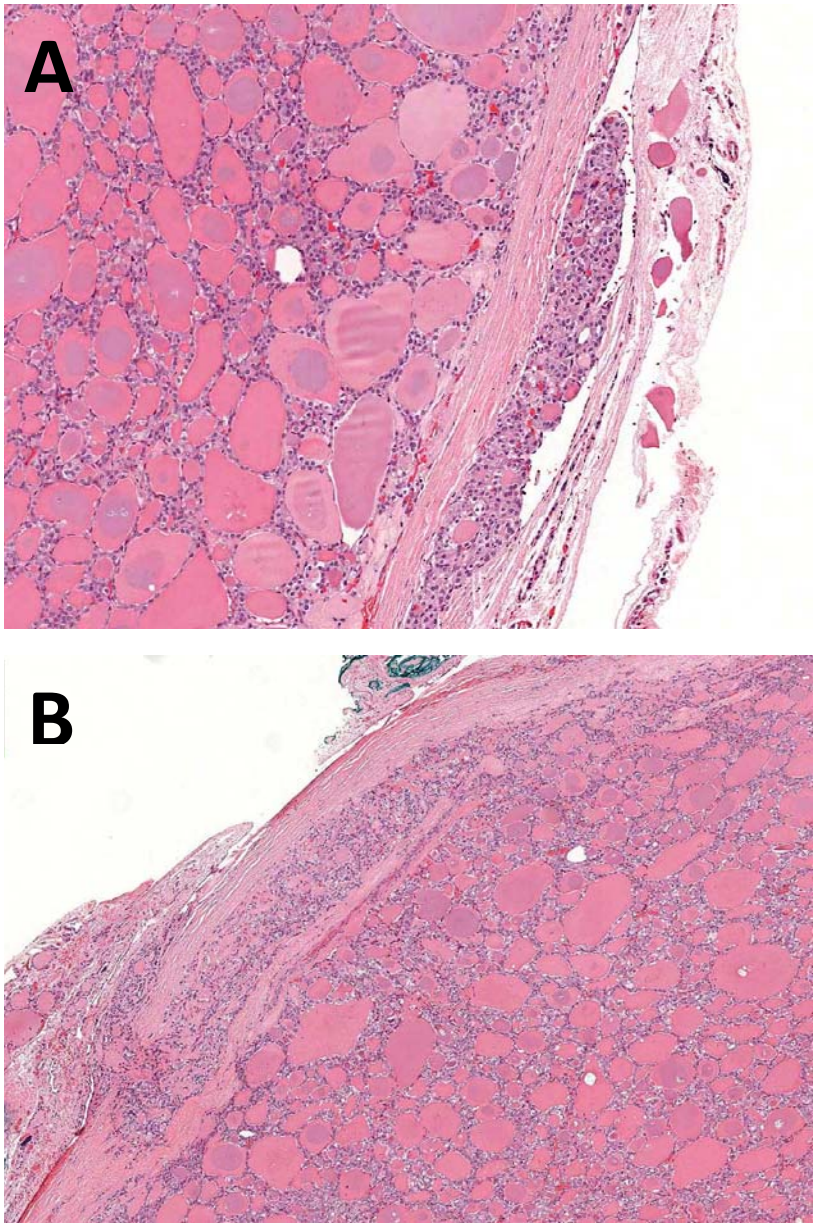
eFigure 1. Illustration of selected major and minor diagnostic features of EFVPTC used by majority of the working group pathologists.

Major diagnostic features: **(A) –** Nuclear pseudoinclusion (arrow); **(B) –** Nuclear grooves (arrows). Minor diagnostic features: **(C) –** Dark colloid in the tumor follicles (*T*) as compared to the adjacent normal tissue follicles (*N*); **(D) –** Irregularly-shaped follicles with haphazard placement of follicular cell nuclei along the basement membrane of the follicle; **(E) –** "Sprinkling" of the follicles lined by cells showing the characteristic nuclear features of PTC (arrows) on the background of follicles with benign appearing cells; **(F) –** Follicles clefting from stroma; **(G) –** Multinucleated giant cells within follicles; **(H) –** Intratumoral fibrosis. **A**-**H** – H&E stain; **A,B,D,G -** - 400X; **C**,**H** – 100X; **E,F** – 200X.

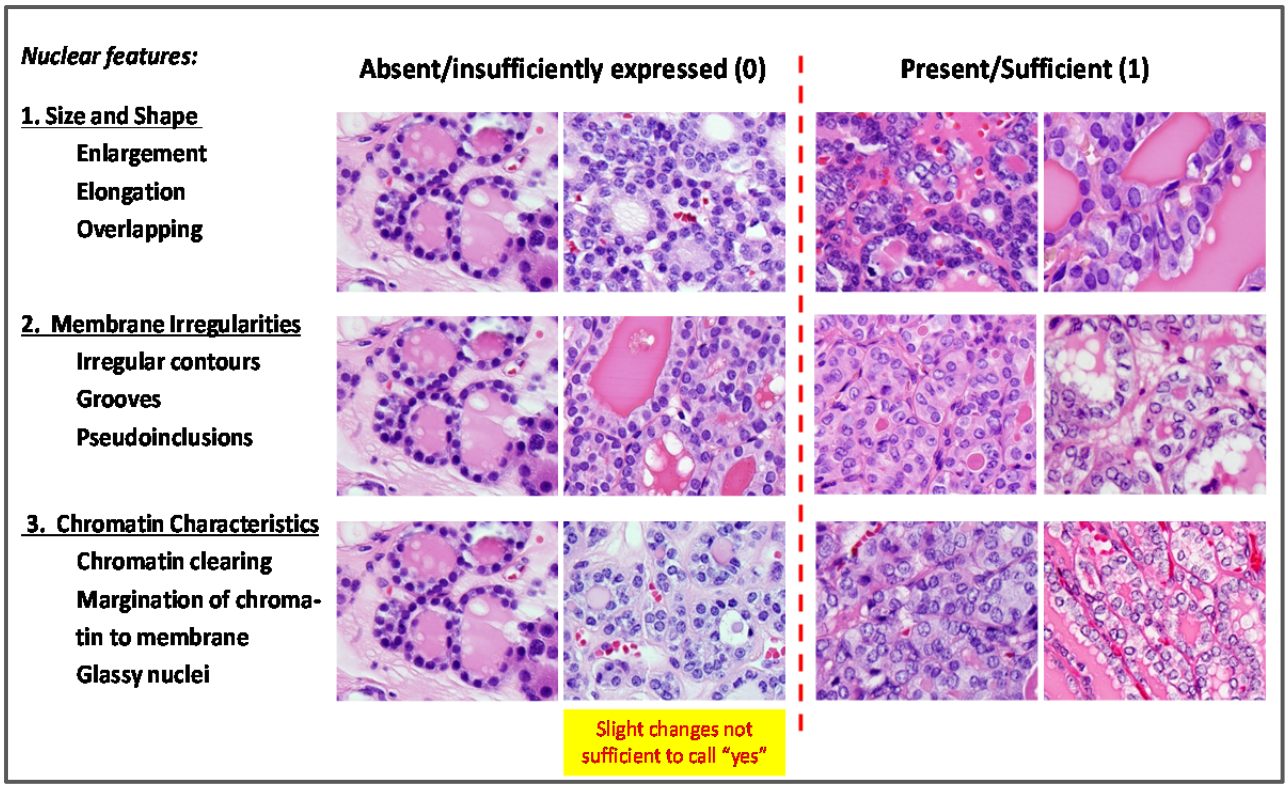
% of pathologists	0-9%	10-19%	20-29%	30-39%	40-49%
Number of cases (out of 138 total)	1	1	12	10	9
Representative image					

% of pathologists diagnosing	50-59%	60-69%	70-79%	80-89%	90-99%
Number of cases (out of 138 total)	15	34	29	19	8
Representative image					

eFigure 2. Results of initial review of cases in Group 1 by 24 pathologists and representative images of cases.



eFigure 3. Illustration of vascular (A) and capsular (B) invasion in a case from Group 2.



eFigure 4. Visual guide for scoring nuclear features using the three-point scoring scale.