

Implementing noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) may potentially impact the risk of malignancy for thyroid nodules categorized as AUS/FLUS and FN/SFN

Running title:

Risk of malignancy in AUS/FLUS and FN/SFN

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Abstract

Background: Noninvasive encapsulated follicular variant of papillary thyroid carcinoma (PTC) has recently been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Implementation of the new terminology may alter the implied risk of malignancy (ROM) across the six categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). **Methods:** The study cohort consisted of thyroid fine needle aspiration (FNA) cases which were assessed between January 2011 and June 2016 and led to surgical resections. For each case, patient demographics as well as cytologic and corresponding histologic diagnoses were recorded. The surgical specimens diagnosed as follicular variant of PTC (FVPTC) were re-reviewed to identify cases that met the diagnostic criteria for NIFTP. The ROM with and without exclusion of NIFTP from malignant categorization, as well as the relative change in ROM were calculated for individual categories of TBSRTC. **Results:** A total of 908 FNA cases with surgical follow-up were retrieved and PTC was identified in 252 (27.8%) surgical specimens. Twenty-nine of 252 (11.5%) were initially classified as FVPTC, of which 17 (6.7%) were reclassified as NIFTP. The cytologic interpretations for the majority of NIFTP cases were atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS, n=8) or follicular neoplasm/suspicious for neoplasm/(FN/SFN, n=4). Excluding NIFTP from malignant categorization resulted in a relative decrease in ROM in AUS/FLUS (25.8%) and FN/SFN (22.3%) categories. **Conclusion:** Our institutional data demonstrates that eliminating NIFTP from malignant categorization may result in a reduction of the implied ROM for AUS/FLUS and FN/SFN categories.

Key words: noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); risk of malignancy (ROM); atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); follicular neoplasm/suspicious for follicular neoplasm (SFN/FN); papillary thyroid carcinoma.

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid worldwide. After conventional PTC, follicular variant PTC (FVPTC) is considered the most common variant of PTC. Jung, et al. studied the demographic, clinical, pathologic, and molecular characteristics of PTCs diagnosed at the University of Pittsburgh for the period from 1974 to 2009 and demonstrated an increased incidence of FVPTC, including both encapsulated and infiltrative subtypes, represented approximately 25% of all diagnosed PTCs. Furthermore, the study noted a sharp increase in detected RAS mutations in PTCs, particularly in tumors with follicular growth patterns.(1)

Recently, the Endocrine Pathology Society working group conducted a retrospective study of noninvasive encapsulated FVPTC with the aim of assessing clinical outcomes, refining diagnostic criteria, and developing a new terminology that appropriately reflects the biological and clinical characteristics of this entity. Based on its very low risk of adverse outcomes, the working group concluded that noninvasive encapsulated FVPTC should be reclassified as “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)”, eliminating the term carcinoma from the entity.(2)

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has been widely accepted as a standard reporting system for assessing fine needle aspiration (FNA) of thyroid. TBSRTC consists of six categories, including non-diagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SFM) and malignant. An implied risk of malignancy (ROM) has been assessed and estimated for each of the six categories.(3)

TBSRTC has been implemented in our clinical practice since January 2011. In comparison to the pre-TBSRTC period, the adoption of TBSRTC in our institution resulted in a reduced surgical rate, particularly for the benign and AUS/FLUS categories. However, the ROM for each of the six categories did not differ significantly between the pre- and post-TBSRTC periods. The rate of histology-proven malignancy after implementation of TBSRTC was 3.5%, 17.9%, 27.8%, 75.0%, and 98.0% for benign, AUS/FLUS, FN/SFN, SFM, and malignant categories, respectively. These values fall into or close to the ranges of the ROM estimated by TBSRTC (0%–3% for benign, 5%–15% for AUS/FLUS, 15%–30% for FN/SFN, 60%–75% for SFM, and 97%–99% for malignant).(4)

The current study was conducted to investigate if implementing NIFTP (formerly termed as non-invasive encapsulated FVPTC) terminology and excluding it from malignant categorization may alter the ROM across the six categories of TBSRTC.

Material and Methods

The retrospective study was approved by the Institutional Review Board (IRB) of the University of Michigan. The study cohort consisted of all thyroid FNA cases which were assessed between

January 2011 and June 2016, and were subsequently treated with surgical interventions.

Endocrinologists, radiologists, and surgeons performed palpation- or ultrasound-guided FNAs with or without cytopathologist-assisted rapid on-site evaluation (ROSE). Three to six passes were collected for each FNA specimen. For FNAs aided with ROSE, two conventional smears were made for each pass. One smear was air-dried and stained with Diff-Quik protocol to be evaluated immediately for specimen adequacy while the other smear was fixed with Sprayfix™ and later stained with Papanicolaou stain. The needle was then rinsed in Cytolyt solution for a ThinPrep and/or a cell block. For FNAs without ROSE, all passes were submitted in Cytolyt solution from which a ThinPrep and a cell block slide were prepared. All FNA specimens were interpreted using TBSRTC.

For each case, age and gender of the patient, size and location of the nodule, cytologic interpretation, and corresponding histologic diagnosis were retrieved and recorded. The histology slides from the surgical specimens originally diagnosed as FVPTC were re-reviewed by one surgical pathologist (AS) to identify cases that met the diagnostic criteria for NIFTP. Briefly, diagnostic criteria for NIFTP include 1) encapsulation or clear demarcation, 2) follicular growth pattern (<1% papillae, no psammoma bodies, 30% solid/trabecular/insular growth pattern), 3) nuclear score 2-3, 4) no vascular or capsular invasion, 5) no tumor necrosis and 6) no high mitotic activity. Each case was assessed using the detailed inclusion and exclusion criteria. Both FVPTC with Hurthle cell changes and microcarcinoma (less than 1 cm) were excluded. Based on the follow-up histologic diagnosis, the ROM with and without exclusion of NIFTP from malignant categorization, as well as the relative change in ROM were calculated for each of TBSRTC categories as follows :

ROM = number of cases with histology-proven malignancy/total number of cases

Relative change in ROM = $100\% \times [(\text{ROM with NIFTP} - \text{ROM without NIFTP}) / \text{ROM with NIFTP}]$

Z score calculation for two population proportions was used to compare the ROM with versus without the exclusion of NIFTP from malignant categorization for each of TBSRTC categories. A p-value less than 0.05 was considered to be statistically significant.

Results

A total of 908 FNA cases with surgical follow-up were retrieved. The corresponding surgical specimens revealed malignant neoplasms in 278 (30.6%) cases, among which were 252 PTCs, representing 27.8% of the total cohort. The remaining malignant neoplasms included 10 follicular cell carcinomas, 10 medullary thyroid carcinomas, 5 anaplastic thyroid carcinomas, and 1 poorly differentiated thyroid carcinoma. Among the histology-proven PTC cases, 61.1% (154/252) and 13.5% (34/252) were cytologically interpreted as positive and suspicious for PTC, respectively, on prior cytologic specimens. The remaining PTC cases were classified as AUS/FLUS (11.1%), benign (5.5%), FN/SFN (4.8%) and non-diagnostic (4%) on prior cytologic specimens (Table 1).

As can be seen in Table 2, 29 (11.5%) out of 252 PTC cases were initially diagnosed as FVPTC. Re-review of these surgical specimens confirmed 17 (6.7%) cases of noninvasive encapsulated FVPTC, now reclassified as NIFTP. The majority of these cases were classified as AUS/FLUS (47.1%) and FN/SFN (23.5%) on the pre-operative cytologic specimens, while only two (11.8%) were interpreted as SFM or malignant. Three (17.6%) of these cases were interpreted as a benign nodule on cytology. On re-review of cytologic material, the various degrees of

architectural atypia were appreciated while nuclear features of conventional PTC were absent or subtle in most of NIFTP cases (Figure 1).

The 17 cases that were reclassified as NIFTP revealed female predominance, with a female to male ratio of 16:1. The ages of patients ranged from 15 to 72 years old. The size of the thyroid nodules ranged from 0.8 cm to 4.0 cm. Unifocal disease was detected in 14 cases, while the remaining 3 had multifocal disease. Hemithyroidectomy and total thyroidectomy was performed in 13 and 4 cases, respectively. Total thyroidectomies were performed for multifocal disease involving both lobes (2 cases) or a pre-operative cytologic diagnosis was SFM (1 case) or malignant (1 case). None of patients received radioactive iodine therapy. All patients have remained disease free during the follow-up period of up to six years.

Table 3 compares the ROM calculated when NIFTP was excluded from malignant categorization with the ROM when NIFTP was considered a malignancy. When NIFTP was excluded from malignant categorization, the ROM decreased across all diagnostic categories. The relative decrease in ROM was most pronounced in the AUS/FLUS (25.8%) and FN/SFN (22.3%) categories. The relative decrease in ROMs was subtle in both SFM (2.8%) and malignant (0.6%) categories. Regardless, the p-values (0.42 to 1.0) did not reach statistical significance for any of the TBSRTC categories.

Discussions

The potential alteration of the ROM across the six categories of TBSRTC as a result of excluding NIFTP from malignant categorization has become one of the major concerns raised among pathologists, as well as endocrinologists and surgeons who treat patients with thyroid nodules. It

is important to stress that the current study is one of a few studies following the landmark publication on NIFTP from Endocrine Pathology Society working group. During the re-review of the FVPTC surgical specimens in the current study, detailed inclusion and exclusion criteria outlined in the landmark manuscript were utilized as a guideline to identify the cases that fulfilled the criteria for NIFTP.⁽²⁾ The current study demonstrates that histology-proven NIFTP represented 6.7% (n=17) of 252 cases that were previously classified as PTC. The majority of the NIFTP cases on surgical resections were interpreted as AUS/FLUS (47.1%) and FN/SFN (23.5%) on pre-operative cytology specimens. When NIFTP was not considered malignant, there was a notable relative decrease in ROM for both categories (25.8% and 22.3%). However, the difference in ROMs failed to reach statistical significance due to the limited cohort of NIFTP. It is noteworthy to mention that the patients with NIFTP were less likely to be overtreated at our institution as thyroid nodules with a cytologic diagnosis of AUS/FLUS or FN/SFN are commonly managed by hemithyroidectomy rather than total thyroidectomy.

Table 4 compares our data with the published data of other studies on the relative decrease in ROMs across the categories of TBSRTC after excluding noninvasive FVPTC from malignant categorization. Briefly, Strickland, et al. studied 655 patients who underwent FNA and subsequent surgical resection in a single institution. PTC was identified in 304 (46.4%) patients including 85 patients with noninvasive FVPTC, accounting for 23.7% of all PTC cases. Excluding noninvasive FVPTC from malignant categorization resulted in the most significant relative decrease in ROM (nearly 50%) in the SFM category. Their findings are quite remarkable as these patients were treated with a total or near total thyroidectomy rather than hemithyroidectomy.⁽⁵⁾ Faquin, et al. studied 756 cases of histology-proven PTCs in institutions in the United States and Europe, of which 173 (22.8%) were classified as noninvasive FVPTC.

Most of the cases classified as noninvasive FVPTC were interpreted as AUS/FLUS (31.2%), FN/SFN (26.6%) or SFM (24.3%) on pre-operative cytology. In this study, the relative decrease in ROM was most pronounced in FN/SFN category (45.5%) followed by AUS/FLUS category (43.6%) and SFM category (28.3%).⁽⁶⁾ Similarly, a single-institution study by Canberk, et al also showed the most significant relative decrease in ROM in the FN/SFN category (66.0%).⁽⁷⁾ Recently, Layfield, et al analyzed their own institutional data along with these three aforementioned studies using a meta-analysis method. They found that re-categorization of noninvasive FVPTC or NIFTP as benign entities showed the greatest reduction in ROM in SFM and AUS/FLUS categories.⁽⁸⁾ Two of these aforementioned studies (Strickland, et al and Faquin, et al) showed a higher percentage of PTC among all surgically treated cases (41.4% and 46.4%) than our institution (27.8%). In addition, our data revealed a lower proportion (6.7%) of NIFTP among all PTCs compared to rate of diagnosis of noninvasive FVPTC in the aforementioned studies led by Strickland, Faquin and Cranbrek (23.7% , 22.8% and 27.5%, respectively). However, these three studies were conducted prior to the publication of the diagnostic criteria for NIFTP by the Endocrine Pathology Society working group. Thus, it remains unknown how many of the cases reclassified as benign in these studies actually met the current criteria for NIFTP and how application of the criteria would affect the study outcomes. It is important to be aware of variations among different institutions with regard to prevalence of PTC and NIFTP, as well as diagnostic thresholds for assessing cytologic and/or histologic specimens for each diagnostic category. It is crucial for pathologists, endocrinologists, and surgeons to have a clear understanding of practice patterns in their own institutions in order to provide management appropriate to patients with NIFTP and to avoid overtreatment, i.e. total or near total thyroidectomy.

Despite rendering pre-operative cytologic diagnoses of SFM or PTC in 2 of 17 NIFTP cases in the current study, most cases carried a preoperative diagnosis of AUS/FLUS or FN/SFN. While many of these cases lacked diagnostic features of conventional PTC, others displayed only subtle or focal cytologic atypia associated with PTC. Our findings are similar to another study by Ibrahim, et al, who studied 23 NIFTP cases. The pre-operative FNAs of these 23 cases were most commonly categorized into the AUS/FLUS category (61%), followed by FN/SFN (17%). One case (4%) was interpreted as suspicious for PTC, but none were interpreted as positive for PTC.(9) The phenomena that most NIFTP fall into AUS/FLUS and FN/SFN categories was also seen in a study containing 56 NIFTP cases by Brandler, et al.(10) Efforts to investigate if a definitive diagnosis of NIFTP may be established based on cytologic findings alone have been attempted. Bizzarro, et al. claimed that NIFTP showed a different microfollicular pattern, grooves, and nuclear size compared to follicular adenoma, invasive FVPTC, and conventional PTC while no definitive evidence of PTC was identified in NIFTP. They hoped that an algorithmic approach to follicular-patterned lesions would improve the diagnostic accuracy of NIFTP by FNA.(11) Maletta, et al. found that nuclear features (size, irregular contours, and chromatin clearing) seen in NIFTP did not differ significantly from those of invasive FVPTC, indicating that NIFTP cannot be reliably diagnosed preoperatively.(12) Given the lack of quantitative and qualitative cytologic atypia diagnostic of conventional PTC in NIFTP on cytologic specimens in our study and other studies, it's unlikely to be diagnosed as positive for PTC on cytology. However, it seems problematic to differentiate NIFTP from other entities with follicular growth pattern, i.e. follicular adenoma/carcinoma and invasive FVPTC. Overall, making a definitive diagnosis of NIFTP basen on cytologic evaluation alone is a great challenge.(10, 13, 14).

Over the past several years, molecular tests have been utilized as an adjunct to FNA cytology to further categorize the thyroid nodules with indeterminate cytologic diagnoses (AUS/FLUS, SFN, SFM) and each has its strengths and limitations.⁽¹⁵⁾ Several studies on molecular profiling of NIFTP have been published following the proposal of the new terminology. Accordingly, Paulson, et al. found that NIFTP accounted for more than half of RAS-mutant thyroid neoplasms.⁽¹⁶⁾ Molecular analysis performed on the surgical specimens of NIFTP and invasive FVPTC revealed that NIFTP was primarily associated with mutations in RAS while invasive FVPTC cases were associated with BRAFV600E or RAS mutations, indicating a lower likelihood of accurate distinction between NIFTP and invasive FVPTC by FNA due to the overlapping molecular profiles.⁽¹⁷⁾

In summary, our institutional data demonstrates that NIFTP is most likely categorized as AUS/FLUS or FN/SFN on pre-operative cytologic evaluation. Eliminating NIFTP from malignant categorization may result in a marked reduction of the implied ROM for AUS/FLUS and FN/SFN categories. It is important to have a clear understanding of practice patterns in one's own institution in order to provide management appropriate to patient with NIFTP and to avoid overtreatment.

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Legends

Figure 1. Cytologic categorization of histology-proven noninvasive FVPTC (NIFTP).

A and B. AUS/FLUS (Diff-Quik stain, 40x and Papnicouluo stain, 600x);

C and D. FN/SFN (Diff-Quik stain, 100x and Papnicouluo stain, 600x);

E and F. SFM (Diff-Quik stain, 100x and Papnicouluo stain, 400x);

G and H. PTC (Diff-Quik stain, 200x and Papnicouluo stain, 400x);

I and J. noninvasive FVPTC (NIFTP) (H&E 40x and 400x).

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Table 1. Cytologic-histologic correlation

TBSRTC category	Histologic			Diagnoses		Total
	Benign	FA	FCA	PTC	M (non-PTC)	
ND	83	18	1	10	0	112
Benign	238	17	1	14	0	270
AUS/FLUS	160	52	0	28	3	243
FN/SFN	21	29	6	12	0	68
SFM	6	2	0	34	1	43
Malignant	3	1	2	154	12	172
Total	511	119	10	252	16	908

ND: non-diagnostic; AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: follicular neoplasm/suspicious for follicular neoplasm; SFM: suspicious for malignancy; FA: follicular adenoma; FCA: follicular carcinoma; PTC: papillary thyroid carcinoma; M: malignant.

Table 2. Distribution of histology-proven FVPTC across the diagnostic categories of TBSRTC

TBSRTC Category	All FVPTC	Noninvasive FVPTC (NIFTP)	Invasive FVPTC
ND	1	0	1
Benign	5	3	2
AUS/FLUS	11	8	3
FN/SFN	5	4	1
SFM	1	1	0
Malignant	6	1	5
Total	29	17	12

ND: non-diagnostic; AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: follicular neoplasm/suspicious for follicular neoplasm; SFM: suspicious for malignancy; FVPTC: follicular variant of papillary thyroid carcinoma; NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Table 3. Comparison of ROMs before and after excluding NIFTP from malignant categorization

TBSRTC Category	ROM (%) (before)	ROM (%) (after)	Absolute decrease in ROM (%)	Relative decrease in ROM(%)
ND	9.8	9.8	0	0
Benign	5.6	4.4	1.2	21.4
AUS/FLUS	12.8	9.5	3.3	25.8
FN/SFN	26.5	20.6	5.9	22.3
SFM	81.4	79.1	2.3	2.8
Malignant	97.7	97.1	0.6	0.6

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; ND: non-diagnostic; AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: follicular neoplasm/suspicious for follicular neoplasm; SFM: suspicious for malignancy;

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Table 4. Relative decrease in ROM at different institutions after excluding NIFTP from malignant categorization

Studies	Cases with surgical F/U (n)	Histology-proven PTC n (%)	cases classified as NIFTP	Relative decreases in ROM (%) across six categories					
				ND	Benign	AUS/FLUS	FN/SFN	SFM	M
Strickland	655	304 (46.4)	72 (23.7)	10	59	45	18	48	5
Faquin	1827	756 (41.4)	173(22.8)	5.5	37.6	43.6	45.5	28.3	3.3
Canberk	1886	341 (18.1)	94(27.5)	50	14	33	66	33	11.2
Layfield	315	-	-	0	33.6	13.2	11.3	20.5	12.8
Current	908	252 (27.8)	17 (6.7)	0	21.4	25.8	22.3	2.8	0.6

ROM: risk of malignancy; NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; ND: non-diagnostic;

AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: follicular

neoplasm/suspicious for follicular neoplasm; SFM: suspicious for malignancy; M: malignant.

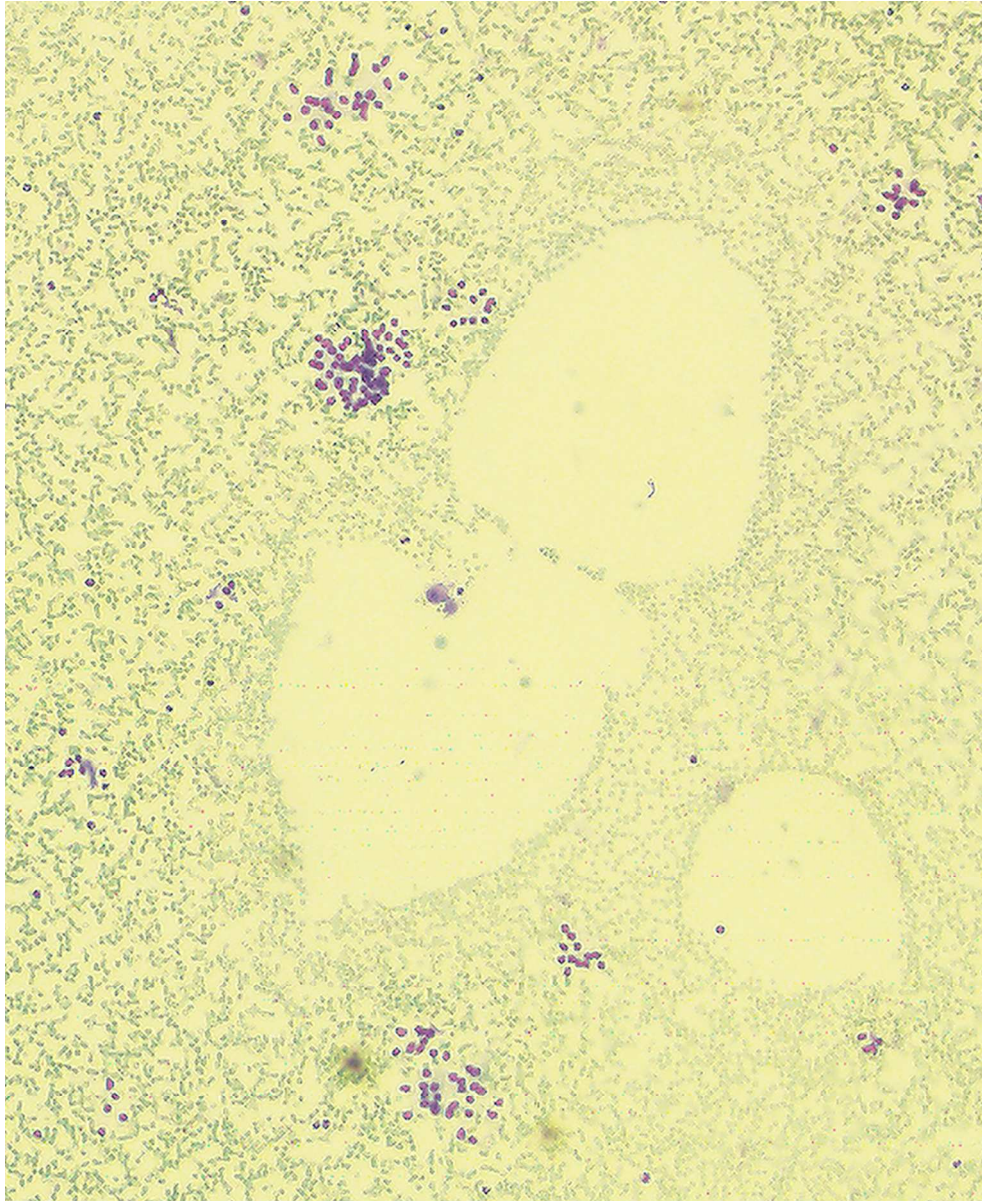
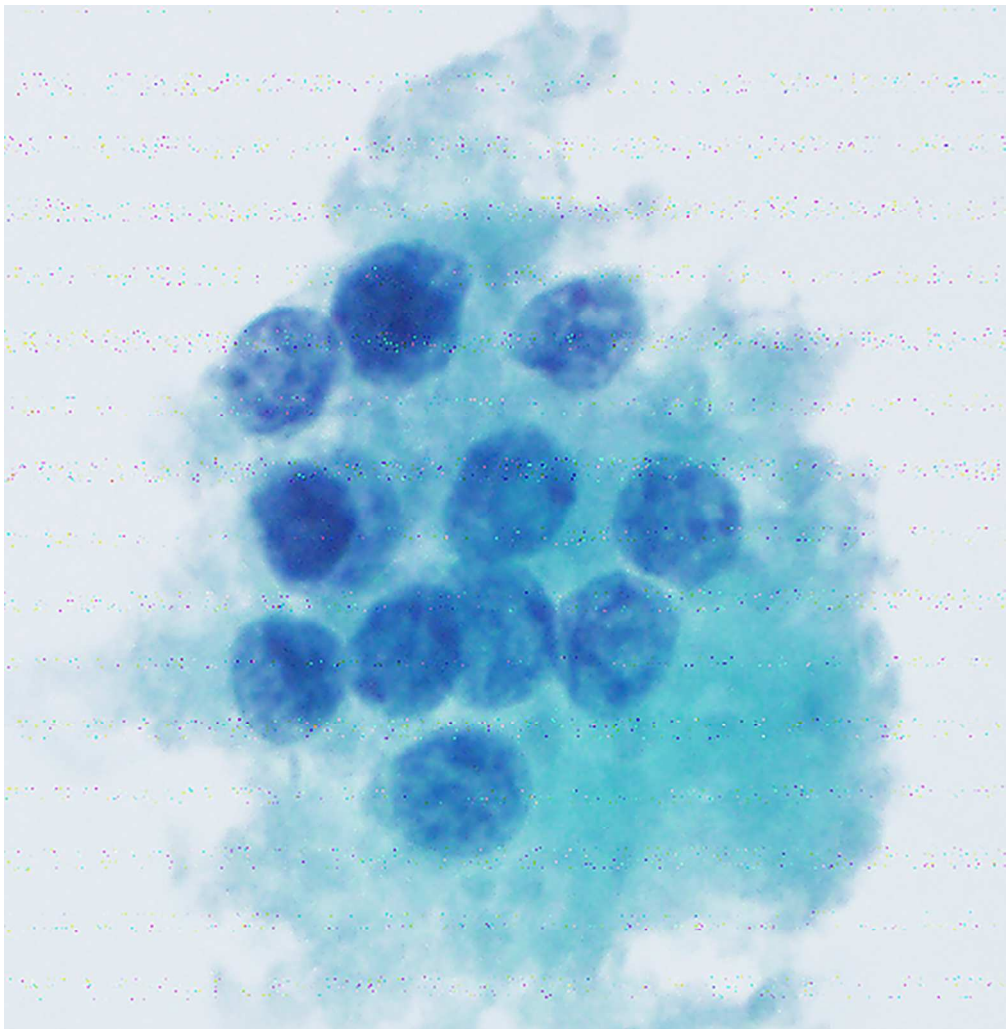


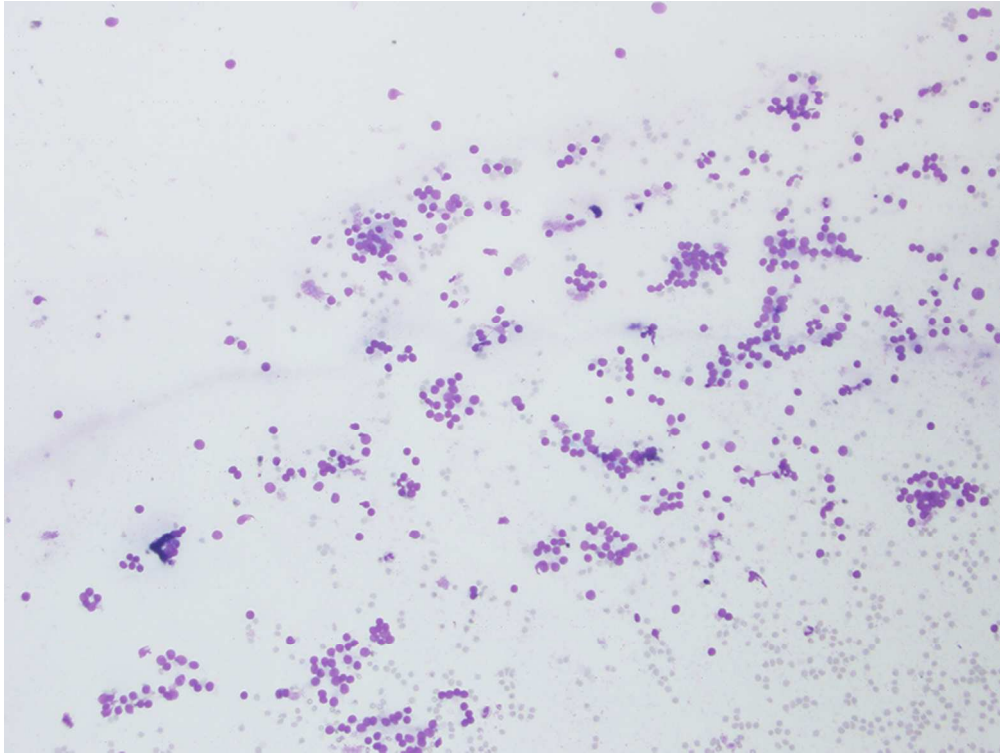
Figure 1. Cytologic categorization of histology-proven noninvasive FVPTC (NIFTP).
A and B. AUS/FLUS (Diff-Quik stain, 40x and Papnicouluo stain, 600x);
C and D. FN/SFN (Diff-Quik stain, 100x and Papnicouluo stain, 600x);
E and F. SFM (Diff-Quik stain, 100x and Papnicouluo stain, 400x);
G and H. PTC (Diff-Quik stain, 200x and Papnicouluo stain, 400x);
I and J. noninvasive FVPTC (NIFTP) (H&E 40x and 400x).

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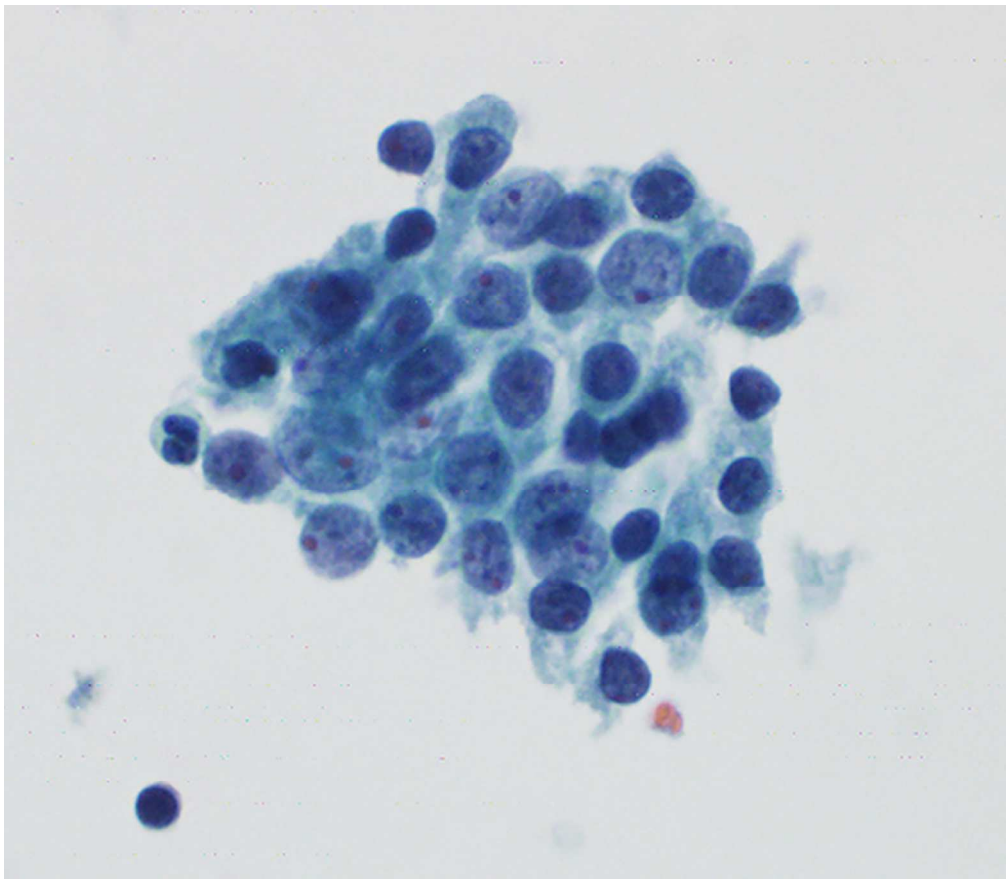
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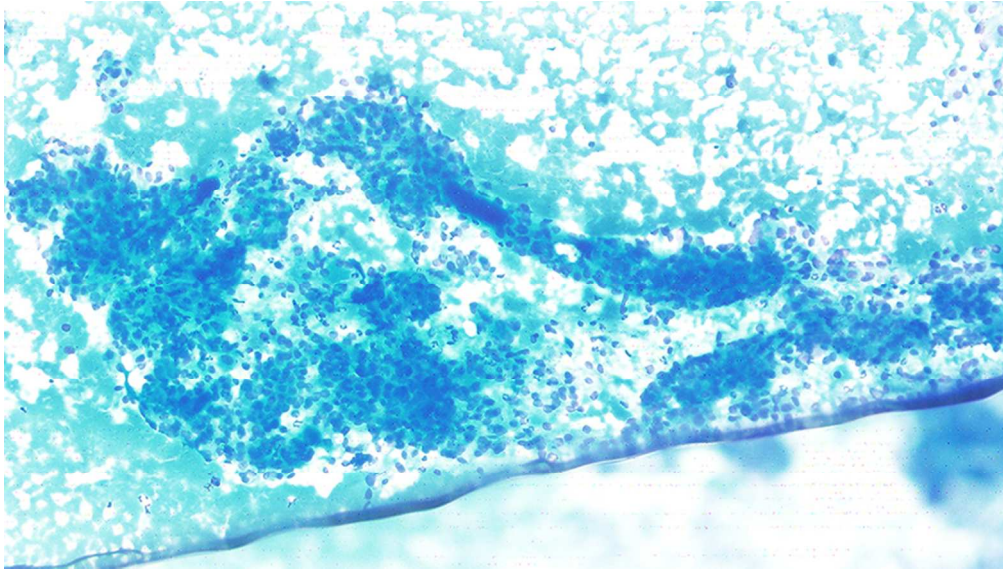
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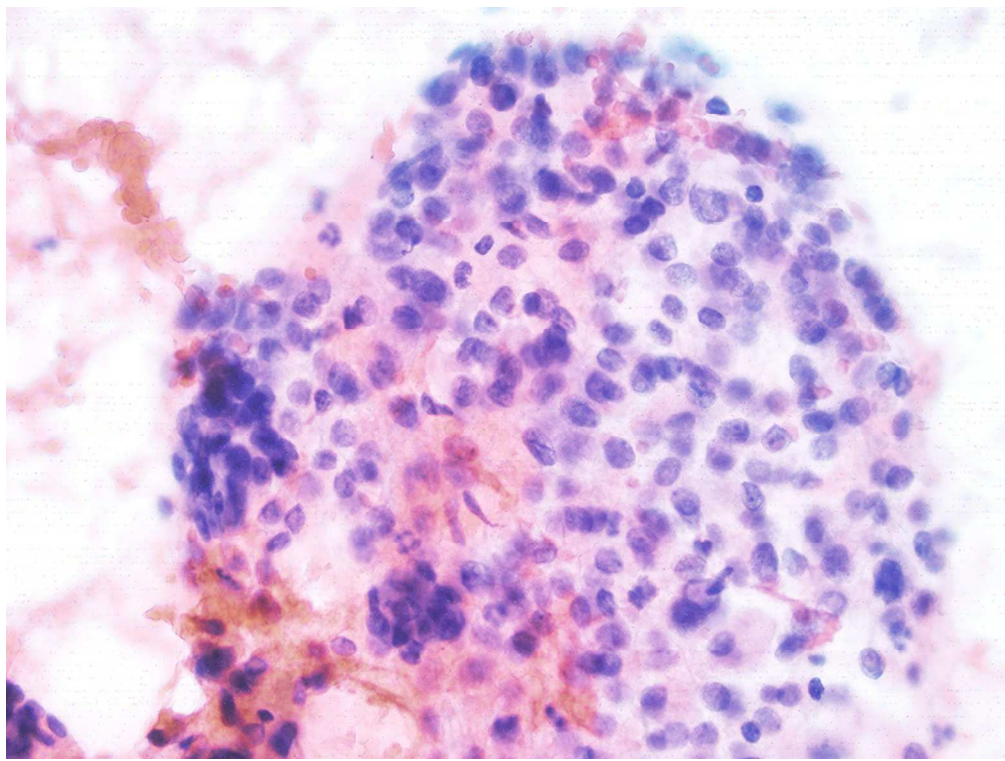
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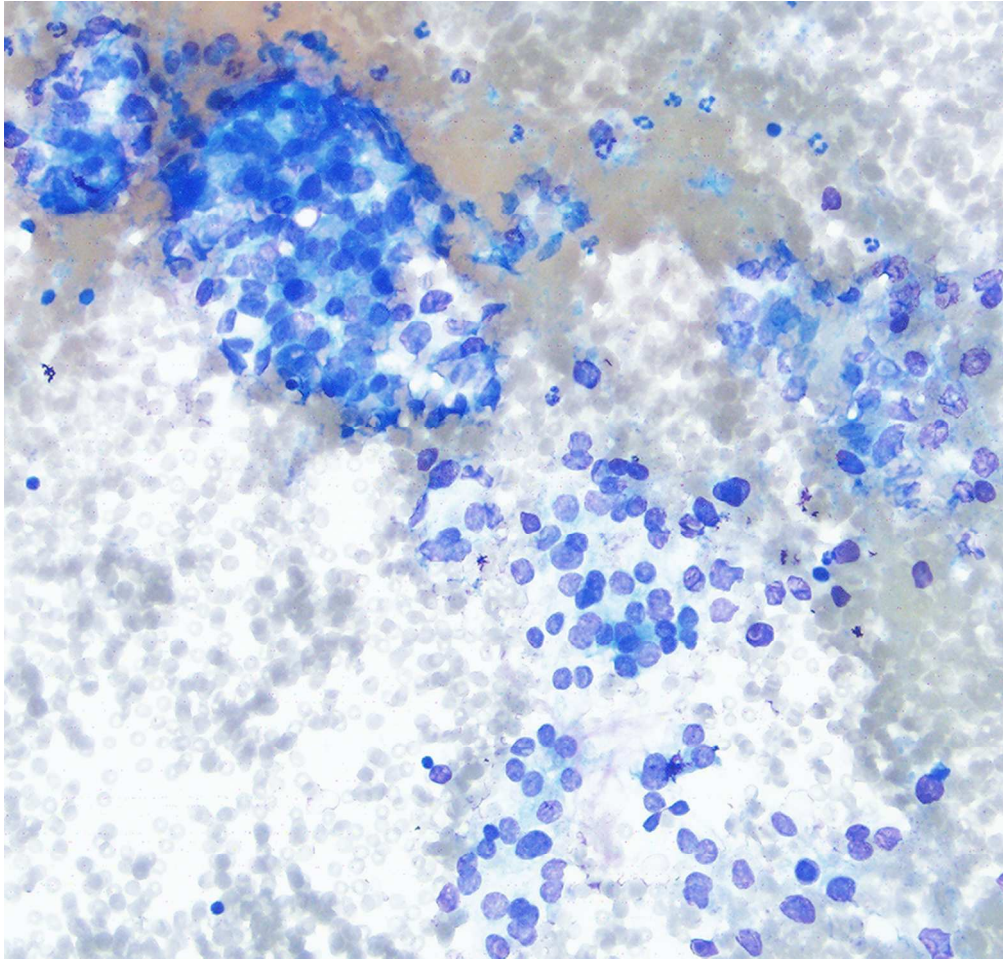
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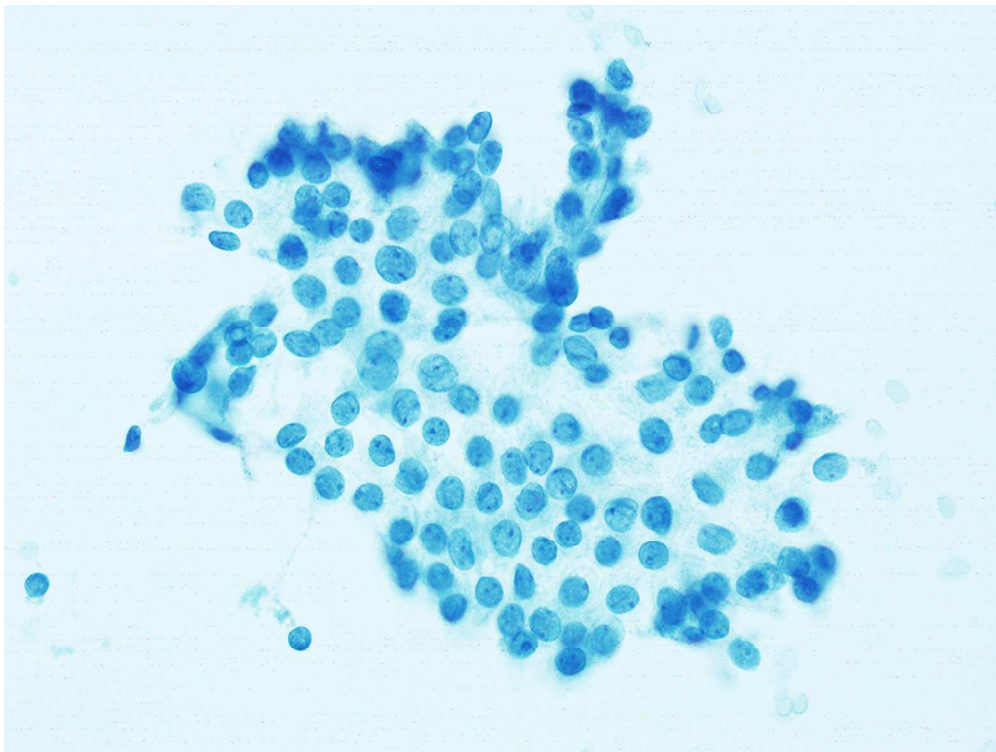
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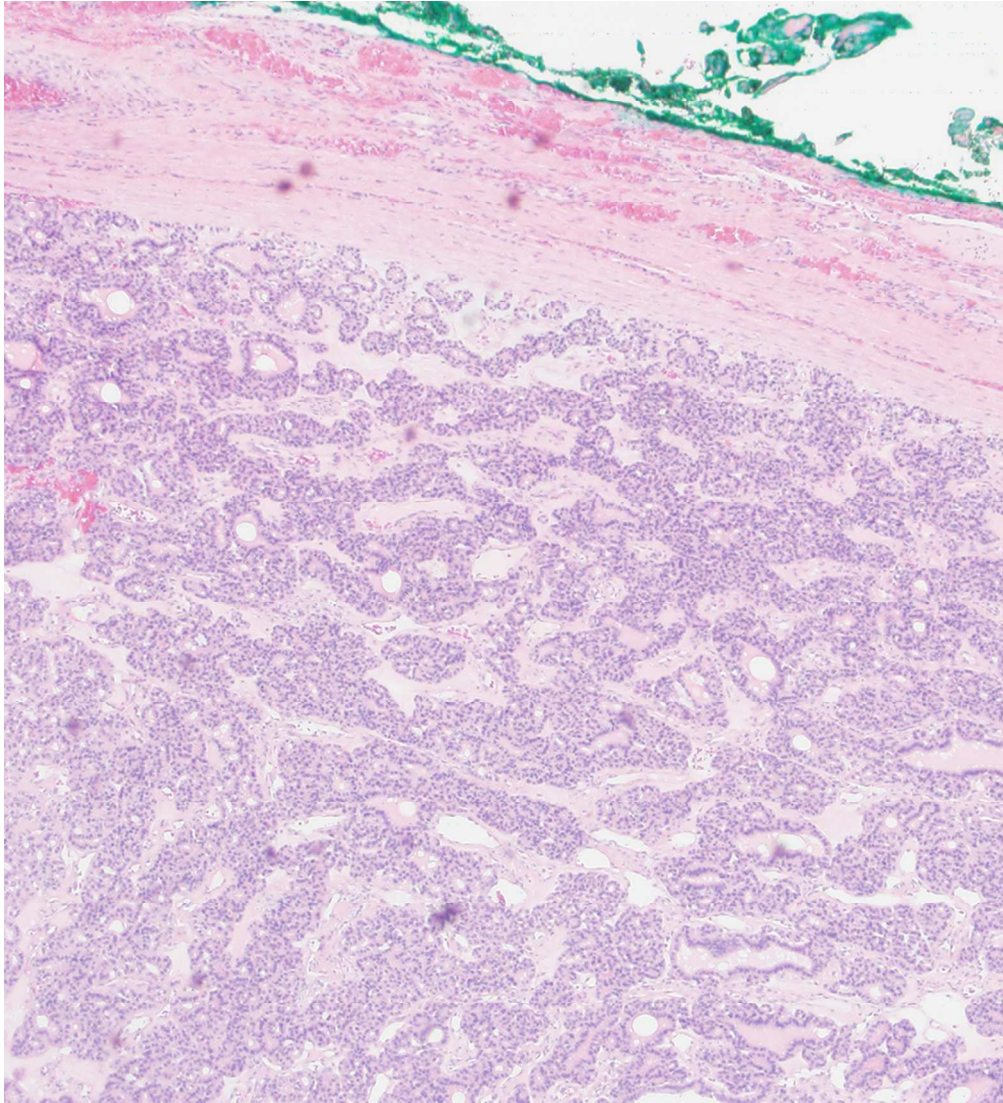
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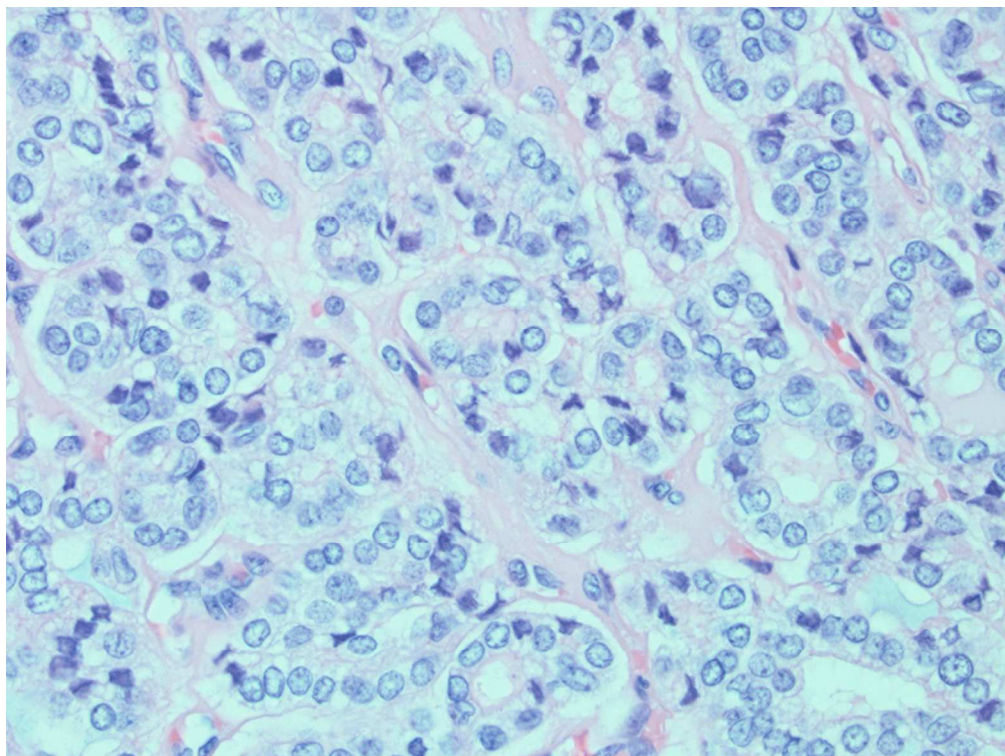
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