

Cytology suspicious for or indicative of PTC is associated with younger age, male sex, and solitary versus multiple nodularity

Rago T, Fiore E, Scutari M, Santini F, Di Coscio G, Romani R, Piaggi P, Ugolini C, Basolo F, Miccoli P, Pinchera A, Vitti P. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. *Eur J Endocrinol* 2010;162:763-70.

SUMMARY

BACKGROUND

Thyroid nodular disease is common, especially in iodine-deficient areas, whereas the incidence of thyroid cancer, while steadily increasing in the past three decades, is relatively low, comprising approximately 1% of all new malignancies. The risk is quite low that a solitary thyroid nodule or multiple nodules within a goiter harbor clinically evident malignancies. Still, the risk of malignancy is higher in patients who have thyroid surgery for compressive symptoms, hyperthyroidism, or Graves' disease, during which occult thyroid cancers are often discovered by serendipity. Fine-needle aspiration biopsy (FNAB) of thyroid nodules has become the main source of distinguishing malignant from benign nodules. While FNAB has reduced surgical intervention by 25% and has increased the yield of cancer in surgical specimens to more than 30%, approximately 20 to 25% of FNAB cytology specimens are nondiagnostic or indeterminate, and a few (5%) have false positive or false negative cytology results. Thus, some patients still may undergo unnecessary surgery on the basis of FNAB. The objective of this study was to evaluate the risk of papillary thyroid carcinoma (PTC) in FNAB cytology in a cohort of 34,120 patients.

SUBJECTS AND METHODS

Thyroid-Function Tests

Serum free thyroxine (FT₄), free triiodothyronine (FT₃), antithyroglobulin antibodies (anti-TgAb; normal TgAb, <30 U/ml), antithyroid peroxidase antibodies (anti-TPOAb) (normal, <10 U/ml) were measured by immunoenzyme assays. In addition, serum thyrotropin (TSH), and TSH-receptor antibodies (TRAbs), normal ≤2 UI/L) were measured. Serum calcitonin was measured by Immunoradiometric IRMA (normal values, <10 ng/ml).

Patients

From 1997 through 2004, a total of 34,266 patients had FNAB performed in the Department of Endocrinology at the University of Pisa. Of this group, 27,826 (81%) were women, with a mean (±SD) age of 48±23 years (range, 13 to 76); 6440 were men (19%), with a mean age of 50±17 years (range, 13 to 80). The diagnosis of thyroid disease was established on the basis of clinical, ultrasound (US), and laboratory criteria as follows: multinodular goiter (MNG; n = 19,923); enlarged thyroid with multiple nodules on US and thyroid scintiscan; solitary nodules (SN; n = 13,549); single nodule in an enlarged thyroid or isolated nodule in a thyroid of normal volume; nodular Graves' disease (GD; n = 286); and nodular Hashimoto's thyroiditis (HT; n = 508). The diagnosis of nodular GD was made by standard criteria, including active or treated hyperthyroidism, goiter with a diffuse hypoechoic thyroiditis pattern on US, ophthalmopathy and positive serum anti-TRAbs or TPOAbs. Nodular HT was

diagnosed with a diffuse hypoechoic thyroiditis pattern on US and high TgAb levels, with or without TPOAbs.

FNAB was performed on all scintigraphically cold nodules, either solitary or in MNGs when the tumor was >1 cm, and in those <1 cm in the presence of clinical signs with or without ultrasound suspicious for malignancy. Thyroid surgery was advised for all patients with cytology suspicious or positive for carcinoma and in most patients with indeterminate cytology. Surgery was also advised for patients with thyroid nodules showing benign or nondiagnostic cytology with symptoms of compression or with nodules that were ultrasonographically suspicious for malignancy.

A comparison between cytologic and histologic findings was possible in 3406 nodules from 3004 patients who comprise the study cohort.

FNAB Cytology

FNAB was performed under ultrasound guidance, using a 23-gauge needle, usually with multiple passes. Cystic or mixed lesions had multiple needle passes in different parts of the nodule, and the sediment was completely aspirated and examined. The aspiration was repeated if the cytology was macroscopically insufficient or on immediate microscopic examination without staining. The sample was considered adequate if the aspirate had at least five or six well-defined and well-preserved groups of follicular epithelial cells, with each group containing at least 10 cells.

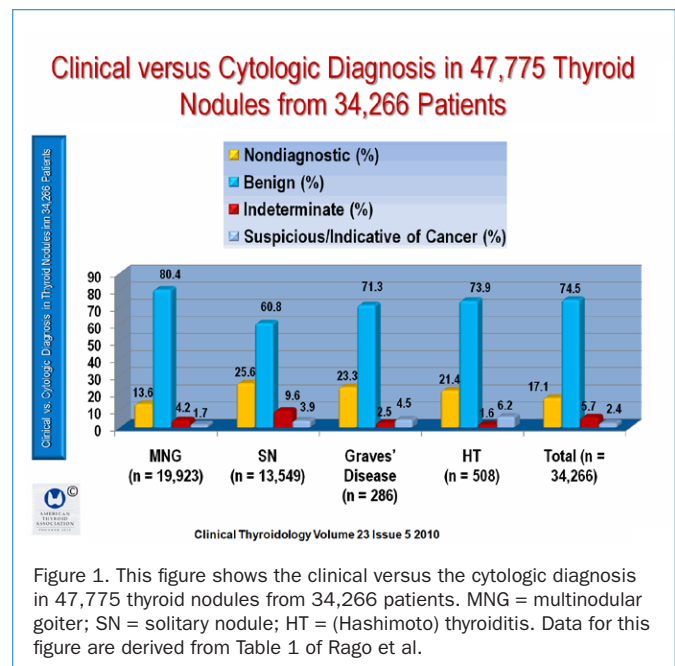


Figure 1. This figure shows the clinical versus the cytologic diagnosis in 47,775 thyroid nodules from 34,266 patients. MNG = multinodular goiter; SN = solitary nodule; HT = (Hashimoto) thyroiditis. Data for this figure are derived from Table 1 of Rago et al.

The cytology was considered adequate according to the British Thyroid Association as follows: (i) nondiagnostic; (ii) nonneoplastic (benign or negative for malignancy); (iii) follicular; (iv) suspicious for malignancy; and (v) indicative of malignancy.

Histopathologic Diagnosis

The histopathologic diagnosis was made blindly by two independent pathologists who were unaware of the cytologic result and according to the World Health Organization guidelines. Discordant diagnoses were reconciled by joint reexamination of each case. The histologic diagnosis of a microcarcinoma <1 cm was classified as a benign tumor.

RESULTS

FNAB Cytology in 47,775 Nodules from 34,266 Patients. (Figure 1)

The overall results of FNAB cytology in 47,775 nodules from 34,266 patients is shown in Figure 1. In all, 74.5% of the nodules were cytologically benign, 5.7% were indeterminate, 2.4% were suspicious for carcinoma, and 17.1% were nondiagnostic. The accuracy of cytology was evaluated by comparing the FNAB results with the histology results from surgery.

Comparison of FNAB Cytology and Surgical Histology Results (Figure 2)

Figure 2 shows the comparative results of cytology and histology in 3406 nodules from 3004 patients who had thyroidectomy. All nodules with cytology indicative of carcinoma (n = 504) were confirmed as malignant on the basis of the tumor histology; however, 11 of 391 nodules with an FNAB suspicious for malignancy were benign based on histology. Eight had a nodular goiter, three of which had extensive necrotic features; two had Hashimoto's thyroiditis, one with a 2-mm PTC and one with pseudopapillary organization based on cytology that was suspicious for or indicative of thyroid cancer on the basis of histology.

Of 1295 nodules with benign cytology, 1271 (98.2%) were confirmed as benign hyperplastic nodules or adenomas, whereas 24 of 1295 (1.8%) were found to be malignant on the basis of histology; 23 were PTC, and of these, 19 were follicular variants, 4 were classic variants, and 1 was a minimally invasive follicular carcinoma. Among these 24 patients, 13 had thyroidectomy on the basis of a single isolated nodule, and 11 with MNG had surgery based the size of the nodules in 18, and was performed on the basis of clinical echographic patterns suspicious for malignancy in 5 patients and for toxic MNG in 1.

Of 969 nodules with indeterminate cytology, 283 (29.3%) were malignant based on the histology; 240 were PTCs (164 follicular variants, 66 classic, 2 oxyphilic, and 8 tall-cell variants), 28 were minimally invasive follicular carcinomas, and 10 were poorly differentiated Hürthle-cell carcinomas. In all, 70.7% (686 of 969) of the nodules with indeterminate cytology were benign, of which 159 were hyperplastic nodules, 520 were adenomas, and 7 were benign nodules in HT.

Of 247 nodules with nondiagnostic cytology obtained from patients who had thyroidectomy on the basis of nodule size, or for clinical ultrasound findings suggesting malignancy, 82 (33%) were malignant—63 PTCs, 12 medullary carcinomas, 3

follicular carcinomas, 2 Hürthle-cell carcinoma sand 2 poorly differentiated carcinomas—and 165 (67%) were benign based on the histology (Figure 2).

When indeterminate cytology results were considered as negative for neoplasm, the FNAB cytology had a sensitivity of 69%, a specificity of 99%, and an accuracy of 88%. If indeterminate results were included among the positive results for neoplasm, the sensitivity increased to 92%, while specificity was 67% and accuracy was 76%. Foci of PTC were occasionally found on a histologic examination in 222 of 3004 patients and were not included among malignant lesions under study.

Clinical Features Associated with PTC on FNAB (Figure 3)

Patients were classified according to the following cytologic results: (i) nondiagnostic (7126 patients), (ii) benign nodular thyroid disease (BNTD; 23,587 patients), (iii) indeterminate (2506 patients), (iv) suspicious for or indicative of carcinoma (1047 patients) (Figure 3). Patients with MNG were assigned to one of the diagnostic classifications according to the following criteria: BNTD, if all nodules were diagnostic for benign lesion; cancer, if they had at least one nodule with this cytology; indeterminate, if they had at least one nodule with this cytology and none with carcinoma; and nondiagnostic, if they had one or more nodules with this cytology and none with carcinoma or indeterminate cytology. In the cancer group, 901 patients had cytology suspicious for or indicative of PTC and 146 had other types of neoplasia, including 53 medullary carcinomas, 26 poorly differentiated carcinomas, 1 Hürthle-cell carcinoma, and 66 lymphomas or metastases of nonthyroidal neoplasia. To establish risk factors for PTC based on cytology, various clinical parameters of the patients with PTC (n = 901) were reviewed in comparison with all the other diagnostic classes taken together (n = 33,219).

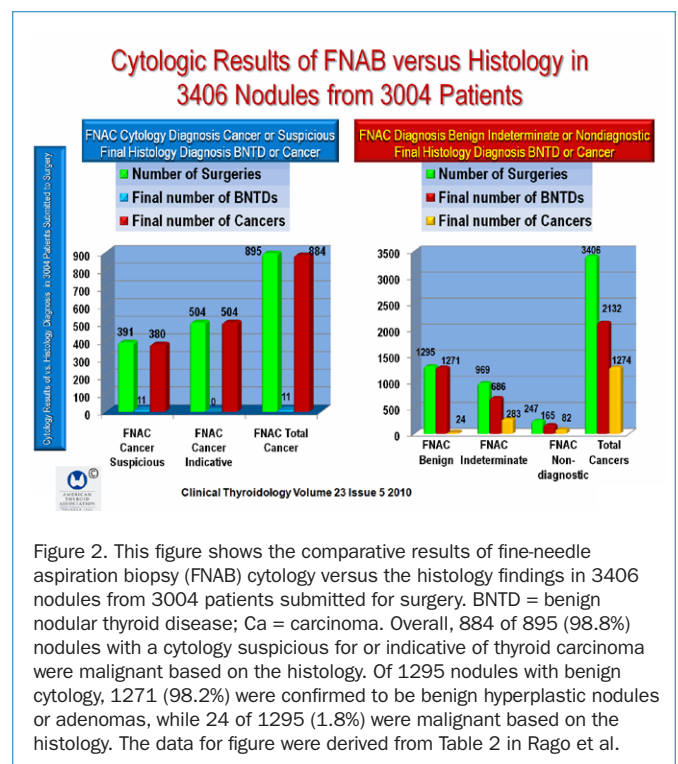


Figure 2. This figure shows the comparative results of fine-needle aspiration biopsy (FNAB) cytology versus the histology findings in 3406 nodules from 3004 patients submitted for surgery. BNTD = benign nodular thyroid disease; Ca = carcinoma. Overall, 884 of 895 (98.8%) nodules with a cytology suspicious for or indicative of thyroid carcinoma were malignant based on the histology. Of 1295 nodules with benign cytology, 1271 (98.2%) were confirmed to be benign hyperplastic nodules or adenomas, while 24 of 1295 (1.8%) were malignant based on the histology. The data for figure were derived from Table 2 in Rago et al.

PTC was significantly more frequent in SN (446 of 13,549 [3.3%]) than in MNG (411 of 19,923 [2%], $P < 0.0001$), and was significantly higher in men (209 of 6382 [3.27%]) as compared with women (648 of 26,945 [2.4%], $P < 0.0001$) in both men with SN (111 of 2820 [3.9%]) and women with SN (335 of 10,644 [3.1%], $P = 0.03$) and in MNG (men: 98 of 3562 [2.7%]; women: 313 of 16,301 [1.9%]; $P = 0.001$) (Figure 4).

The prevalence of PTC in patients with nodular GD (31 of 508 [6.1%]) was higher than that found in SN ($P = 0.003$), but not in GD ($P = 0.2$). The frequency of PTC was higher in men than in women, both in Graves' disease (44 of 55 [7.3%] vs. 9 of 231 [3.9%], $P = 0.27$) and in Hashimoto's thyroiditis (4 of 48 [8.3%] vs. 27 of 460 [5.8%], $P = 0.49$) (Figure 1). The age distribution of PTC was higher in younger patients ($P < 0.0001$) (Figure 2). The mean age of patients with PTC (43 ± 14 years) was significantly lower than that of patients with BNTD (48.8 ± 15.7 , $P = 0.0001$) (Figure 4).

Multiple Logistic-Regression Analysis

The probability of malignancy in FNAB cytology in six index patients, which was assessed by a formula devised by the authors, showed that of the 4 index men, 3 had solitary nodules and 1 had MNG, and of the 2 women, 1 had solitary nodule and 1 had multinodular goiter. The TSH levels in the 4 men were individually 4,2,6 and 1.9 IUm/L as compared with 8.0, and 0.5 IUm/L in the 2 index patients who were women, and the percent risk of malignancy on FNAB was 35, 15.2, 2,11.5, and 7.5% in men, and 21 and 3.4% in women. Men thus had higher

TSH levels and were at greater risk of having malignant tumors in solitary nodules as compared with women.

Using sex, age and the type of nodularity (solitary and multinodularity) in a multiple regression analysis, PTC cytology was found to be inversely related to age (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.964 to 0.974; $P < 0.0001$), and was positively associated with male gender (OR, 1.440; 95% CI, 1.231 to 1.683, $P < 0.000$, and with single nodules, as compared with MNG, (OR = 0.626, 95%CI, 0.547 to 0.717, $P < 0.0001$).

Risk for PTC on FNAB According to Clinical Parameters and TSH Levels

There was an association with risk for PTC in 10,182 patients with nonautoimmune nodular thyroid disease who were not taking methimazole or levothyroxine. These 10,182 patients are also included in the present series of patients, together with an additional 1734 who satisfied the same conditions with a mean TSH of 76 ± 0.93 IUm/L; median, 0.5 IUm/L (range, 0.005 to 9.9 IUm/L).

CONCLUSION

Cytology suspicious for or indicative of PTC is associated with younger age, male sex, and solitary versus multiple nodularity. These clinical parameters, together with serum TSH, may allow a formulation of an algorithm that could be usefully applied to predict the risk of PTC in individual patients when cytology does not provide a diagnostic result.

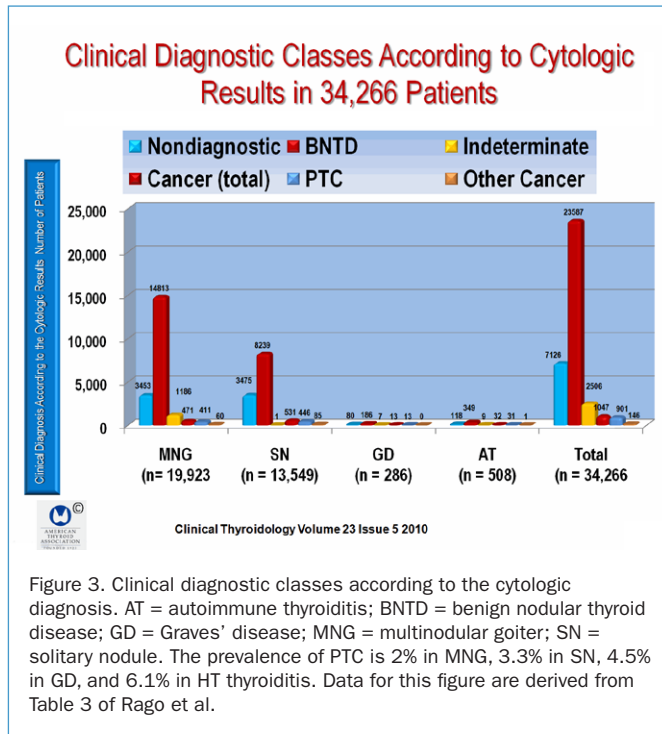


Figure 3. Clinical diagnostic classes according to the cytologic diagnosis. AT = autoimmune thyroiditis; BNTD = benign nodular thyroid disease; GD = Graves' disease; MNG = multinodular goiter; SN = solitary nodule. The prevalence of PTC is 2% in MNG, 3.3% in SN, 4.5% in GD, and 6.1% in HT thyroiditis. Data for this figure are derived from Table 3 of Rago et al.

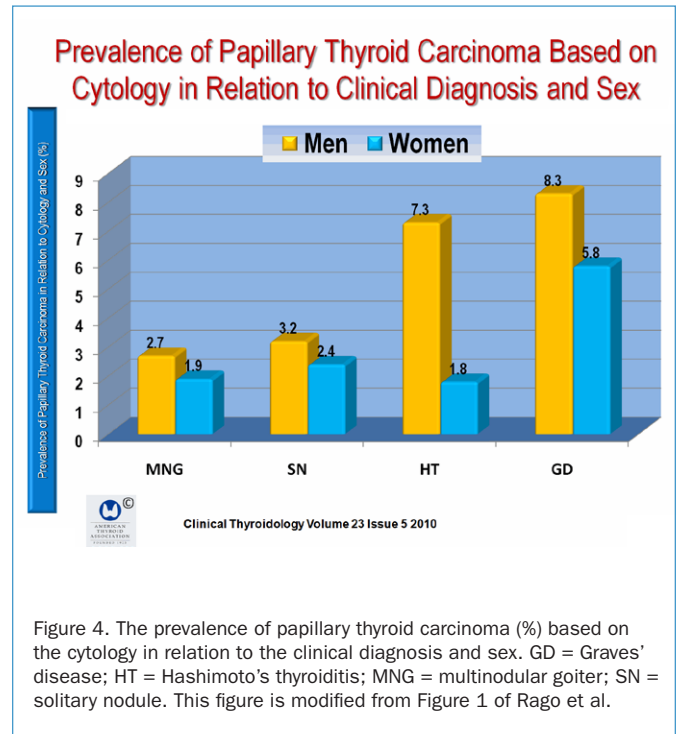


Figure 4. The prevalence of papillary thyroid carcinoma (%) based on the cytology in relation to the clinical diagnosis and sex. GD = Graves' disease; HT = Hashimoto's thyroiditis; MNG = multinodular goiter; SN = solitary nodule. This figure is modified from Figure 1 of Rago et al.

COMMENTARY

This is an important study from the group in the Pisa Departments of Endocrinology, Surgery, and Pathology. The study is one of the best to be published. The methodology is meticulously articulated, showing the considerable detail that underpins the findings in this study. The accuracy of FNAB in this article is quite high: 74.5% of the nodules were cytologically benign, 5.7% were indeterminate, 2.4% were suspicious for carcinoma, and 17.1% were nondiagnostic. This accuracy of FNAB cytology is among the most studies published, with a sensitivity of 92%, specificity of 67% and an overall accuracy of 76%, when indeterminate results were considered as positive for neoplasm. Cytology suspicious for or indicative of PTC was associated with younger age, male sex, and solitary versus multiple nodularity.

When indeterminate results were considered negative for neoplasm, the FNAB cytology demonstrated a sensitivity of 69%, a specificity of 99%, and an accuracy of 88%. A false negative cytologic result was found in 24 of 1295 patients (1.8%) in whom surgery was advised because of the size of the nodule in 18 cases, the presence of suspicious clinical ultrasound findings in 5 cases, and toxic MNG in 1 case. Twenty-three were PTCs, 19 of which were follicular variants of PTC, 4 were classic PTC variants, and one was a minimally invasive follicular carcinoma.

Nonetheless, indeterminate cytology continues to be a difficult problem (1). Although most aspirates provide diagnostic cytology, approximately 15 to 25% will be classified as indeterminate (often referred to as follicular neoplasm, suspicious for carcinoma, or atypical), in which case, abnormal cellular findings preclude interpretation of benignity. Although only a minority prove cancerous on final histopathology, in today's practice, patients with indeterminate aspirates are commonly referred for hemithyroidectomy or near-total thyroidectomy for indeterminate cytology. To avoid this dilemma, the use of molecular analysis of cytologic specimens is on the horizon, which is not only feasible, but has been shown to improve the diagnostic performance of traditional indeterminate cytology (2).

The other important problem with FNAB is cytology that is inadequate for diagnosis, which occurs in up to 20% of patients, a major problem that has been recognized for decades (3). FNAB samples, especially those from cystic nodules, continue to be inadequate for diagnosis even with the use of US-guided FNAB. This is extremely important, because when repeated FNAB attempts fail to provide adequate cytology, surgery has been recommended for this problem over the past decade (4, 5) because 5% or more of such nodules are malignant. The severity of this problem is underscored by a study by Yeh et al. (6) of 100 consecutive patients, which found that a single false negative FNAB result delayed surgical treatment by 28 months, sometimes despite clinical evidence suggesting malignancy. Subjects whose tumors were not detected by FNAB experienced delayed treatment, had higher rates of vascular and capsular

invasion, and were more likely to have persistent disease at follow-up (hazard ratio, 2.28).

In 2002, Alexander et al. (7) reported the results of an important study of inadequate FNAB cytology. The study comprised 1128 patients with 1458 nodules that were biopsied over a 6-year period. A total of 1269 aspirations in 950 patients were diagnostic, and 189 nodules in 178 patients were nondiagnostic. The study found that the cystic content of each nodule was the only significant independent predictor of nondiagnostic cytology ($P < 0.001$). The fraction of cytology specimens that were nondiagnostic increased as the cystic content became greater ($P < 0.001$ for trend). A diagnostic US-guided FNAB was obtained on the first repeat biopsy in 63% of nodules, which was inversely related to the increasing cystic content of each nodule ($P = 0.03$). One hundred nineteen patients with a total of 127 nodules returned for follow-up as advised, and malignancy was documented in 5% of the patients. The authors concluded that despite US-guided FNAB, a significant risk of initial nondiagnostic cytology remains, which was largely predicted by the cystic content of each nodule. The authors recommended repeat aspiration, which is often successful and should be the standard approach to such nodules, given their risk of malignancy.

Thus, despite US-guided cytology, nondiagnostic cytology remains a significant problem, which ranges widely from 5 to 10%, depending on the operator (7) and is largely due to the cystic content of a nodule. This may be improved by US-guided FNAB with on-site evaluation of cytologic specimens, which can substantially increase the adequacy of cytologic specimens and may decrease the number of needle passes required (8).

Rago et al. performed US-guided FNAB on all nodules, and in cystic or mixed lesions, the fluid was aspirated completely and the sediment was examined. The aspiration was repeated if the material was judged as insufficient macroscopically or at an immediate microscopic examination without staining.

It has recently been shown by a series of studies by Haymart et al. that higher serum TSH levels in patients with thyroid cancer not only occurs independent of age and correlates with extrathyroidal tumor extension (9), but is also associated with greater risks of differentiated thyroid cancer in nodular disease and with advanced tumor stage (10). The studies by Rago et al. have not only confirmed these observations, but found that cytology suspicious of or indicative of PTC was associated with younger age, male gender, and solitary nodules versus multiple nodularity, which together with serum TSH may provide information for an algorithm that might be used to predict the risk of PTC in individual patients when cytology does not provide a diagnostic result.

This study by Rago et al. is an important study that should be read in its entirety to appreciate the nuances of this article.

— Ernest L. Mazzaferri, MD, MACP

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