Editorial

A rose by any name surely does smell just as sweetly: The controversy over revised nomenclature for encapsulated follicular variant papillary carcinoma

Leonard Wartofsky
MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington, DC, USA

An article published online on April 14, 2016, in *JAMA Oncology*[1] proposed that "a paradigm shift to reduce overtreatment of indolent tumors" is to be created by changing the name of encapsulated follicular variant papillary thyroid carcinoma (EFVPTC) to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). This revised nomenclature essentially reclassifies these tumors from the current status as "low risk" or "very low risk" cancers to being not cancers at all. The article has been viewed some 80,000 times online and has created quite a stir in endocrine and endocrine surgery circles, and even was highlighted in the *New York Times* where the lay public was advised that they may have been overtreated for a tumor that was not cancer.

The article derived from deliberations of a panel of two endocrinologists, one thyroid surgeon, and 24 pathologists from seven countries, with the conclusions based on follow-up outcome data on a comparison of 109 noninvasive EFVPTC patients and 101 invasive EFVPTC patients from 13 sites in five countries. All 109 of the noninvasive patients were alive with no evidence of disease after 10–26 years of follow-up (even though none had received 131-I ablation and 67/109 had only lobectomy) whereas adverse events such as biochemical or structural recurrences or death were seen in 12 of the 101 patients with invasive EFVPTC.

Historically, EFVPTC accounts for 10–20% of all thyroid cancers, with a frequency increasing two- to threefold over the past several decades, and largely accounts for the universally observed increasing frequency of thyroid cancer worldwide. Approximately half of all FVPTCs are of the encapsulated, noninvasive type, and typically show a low risk of recurrence. The nuclear features of these tumors are very similar to those of classic PTC with nuclear pseudoinclusions, crowding of nuclei, clear nuclei, and nuclear grooves. Yet they tend to have a follicular growth pattern rather than a papillary growth pattern and do not contain psammoma bodies. On a molecular basis, they may demonstrate RAS mutations but not the $BRAF^{V600E}$ mutation seen in the invasive tumors. Truly invasive tumors are likely to show intratumoral fibrosis, tumor necrosis, >3 mitoses/hpf, and possibly some discrete areas of poorly differentiated carcinoma. The authors, having observed the generally indolent behavior of the encapsulated noninvasive variant, have thus proposed that they be classified as nonmalignant. This reclassification could have profound effects on how patients with these tumors will be treated and we have to ask whether the data presented and the conclusions reached may be premature.

Indeed, there are patients seen and described in whom the biologic behavior of these tumors was not uniformly benign. In some series,[2, 3] up to one-third of the tumors showed invasiveness with one patient even recurring after 11 years. Of the 61 cases reported by Liu et al. (2), three patients had lymph node metastases; although with strict pathologic criteria for truly noninvasive

Address for Correspondence:
Dr. Leonard Wartofsky,MD, MACP, MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington D.C., USA.
Email: Leonard.Wartofsky@Medstar.net

Access this article online

Website: www.intern-med.com

DOI: 10.1515/jtim-2016-0023

Quick Response Code:

encapsulated tumors, there were no recurrences or adverse events even in the 31 patients treated by only lobectomy. In the series by Chan *et al.*[4], 27/107 patients had positive lymph node metastases and one had distant metastases. Finnerty et al.[5] have warned that encapsulated well-circumscribed FVPTC tumors may still have a notable incidence of lymph node metastases. Only 1/62 patients reported by Vivero et al.[6] had a recurrence, and two of the co-authors of the JAMA report previously have described a patient with distant metastases[7]. Conceivably, with attention to more rigorous pathologic criteria and complete examination of the tumor capsule, these cases with poor outcomes might have been reclassified as invasive initially.

It is curious that given such an extremely common tumor that the reclassification proposed is based on so few data, i.e., 109 and 101 patients from 13 sites in five different countries. We can ask how complete the follow-up data were as collected by pathologists, who unlike clinical endocrinologists, are not the physicians who follow these patients. The statistical analysis seems complex for a retrospective analysis with no power calculation, no blinding or independent validation, and such a relatively small number of adverse events. Moreover, we were puzzled for some time over the significance of the RAS mutations in these tumors[8,9]in regard to long-term significance as to whether the mutation suggests a premalignant state, and if longer term follow-up would be valuable to so determine. Indeed, Gupta et al.[10] recommended total thyroidectomy for these tumors, even while recognizing that lymph node and distant metastases are infrequent. Finally, an important mechanism for collection and collation of cancer outcome data is through national and international databases and one might ask whether these tumors will be lost to follow-up if not designated as "cancers" and we would thus be deprived of the long-term outcome data.

Will this reclassification actually change the management of these tumors? The American Thyroid Association (ATA) risk stratification system[11]classifies "low-risk tumors" as having all microscopic tumor resected, no local or distant metastases, no vascular or locoregional invasion, no aggressive histologic variant (e.g., tall cell, columnar, hobnail, insular), and no isotope uptake outside of the thyroid bed should radioiodine be administered. These "NIFTP" tumors readily fall into this low-risk category, and as such the ATA Guidelines suggest that lobectomy or lobectomy and isthmusectomy should suffice as surgical treatment without need for total thyroidectomy and its inherent greater surgical risk. Thus, a thyroid nodule with an indeterminate cytopathology (AUS, FLUS) or even one that is definitely PTC but only 1 cm or less, would not demand total thyroidectomy, and lobectomy alone would suffice according to the current ATA Guidelines. The arguments raised for these EFVPTC tumors are similar to those for papillary microcarcinoma, and the guidelines also allow for not administering radioiodine for ablation of these low-risk tumors.

A non-aggressive treatment approach is supported by studies such as reported by Schvartz *et al.*[12] of 1298 low-risk patients with differentiated thyroid carcinoma in whom overall survival was no different from those who received radioiodine ablation than in those treated by surgery alone. Similarly, Kim *et al.*[13] found radioiodine ablation to offer no significant difference in survival in 704 microcarcinoma patients of low to intermediate risk after follow-up for five years. We have tended to attribute the excellent outcome data seen with papillary microcarcinomata to our surgical management, whereas it is possible that the behavior of these tumors might be quite indolent even without surgery. This, in fact, has been shown by a report[14] of 570 patients with biopsy proven PTC demonstrating good outcomes without thyroidectomy after up to 15 years of follow-up. Similarly, Ito *et al.*[15] exercised nonoperative management on 340 patients with adverse outcomes (lymph nodes; increase in tumor size) seen in only 6% at 5 years and 16% at 10 years, with 109/340 ultimately undergoing surgery and no patients showing recurrences. In a subsequent study[16] of1235 patients with papillary microcarcinoma, Ito *et al.* observed a greater rate of progression (8.9%) in younger patients < age 40 than the rate (1.6%) in patients >age 60.

The authors of the *JAMA Oncology* article aver that their reclassification will benefit more than 45,000 patients worldwide by reducing the psychological burden of a cancer diagnosis, and by reducing medical and surgical overtreatment and cost. There clearly will be benefits that patients may derive from this reclassification, but I believe that we will need to have well-controlled longer term studies to confirm and validate the recommendation. Conceivably, tumors called FVPTC by pathologists in the past may not strictly conform to the diagnosis of "non-invasive" EFVPTC or NIFTP because a complete examination of the capsule and description of the other criteria were lacking. So it is not at all clear that patients have been previously overtreated with too much surgery and/or too much radioactive iodine. Indeed, this name change may not change management significantly at all because low-volume clinical practitioners are unlikely to be aware of it, while the more experienced thyroid clinicians at major medical centers are already following the less aggressive therapy advocated in our guidelines, and will be sufficiently aware to recognize patient outliers with the less common malignancies that require more intensive therapy and/or follow up. Perhaps ultrasonographic features of these tumors may identify which ones will have more aggressive behavior and thereby guide subsequent

therapy[17].Nevertheless, although the reclassification is far from groundbreaking, it will serve as a very useful tool in getting us to continue to rethink the management of small thyroid cancers with typically indolent behavior. But as most eloquently stated several centuries ago, "What's in a name? that which we call a rose by any other name would smell as sweet"[18]and therefore perhaps "a rose is a rose is a rose"[19].

Conflict of Interest

None declared.

REFERENCES

1. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, *et al*. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: A paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016 Apr 14. doi: 10.1001/jamaoncol.2016.0386. [Epub ahead of print]
2. Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, *et al*. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer 2006; 107:1255-64.
3. Piana S, Frasoldati A, Di Felice E, Gardini G, Tallini G, Rosai J. Encapsulated well-differentiated follicular-patterned thyroid carfcinomas do not play a significant role in the fatality rates from thyroid carcinoma. Am J Surg Pathol 2010;34:868-72.
4. Chan JKC. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002; 117:16-8.
5. Finnerty BM, Kleiman DA, Scognamiglio T, Arinbiova A, Beninato T, Fahey TJ 3rd, et al. Navigating the management of follicular variant papillary thyroid carcinoma subtypes: a classic PTC comparison. Ann Surg Oncol 2015; 22:1200-6.
6. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid 2013;23:273-9.
7. Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. Mod Pathol 2000;13:861-5.
8. Nikiforova MN, Nikiforov YE. Molecular diagnostics and predictors in thyroid cancer. Thyroid 2009; 19:1351-61.
9. Zhu Z, Gandhi M, Nikiforova MN, Fischer AH, Nikiforov YE. Molecular profile and clinical-pathologic features of the follicular variant of papillary thyroid carcinoma. Am J Clin Path 2003;120:71-7.
10. Gupta N, Dasyam AK, Carty Se, Nikiforova MN, Ohori NP, Armstrong M, *et al*. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular pattern cancers. J Clin Endocrinol Metab 2013; 98:E914-22.
11. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al*. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.
12. Swartz C, Bonnetain F, Dabakuyo S, Gauthier M, Cueff A, Fieffé S, *et al*. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. J Clin Endocrinol Metab 2012;97:1526-35.
13. Kim HJ, Kim Nk, Choi JH, Kim SW, Jin SM, Suh S, *et al*. Radioactive iodine ablation does not prevent recurrences in patients with papillary thyroid microcarcinoma. Clin Endocrinol 2013; 78:614-20.
14. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 2010; 34:1222-31.
15. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, *et al*. An observation trial for papillary microcarcinomain Japanese patients. World J Surg 2010; 34:28-35.
16. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 2014;24:27-34.
17. Rhee SJ, Hahn SY, Ko ES, Ryu JW, Ko EY, Shin JH. Follicular variant of papillary thyroid carcinoma: Distinct biologic behavior based on ultrasonographic features. Thyroid 2014; 4:683-8.
18. Shakespeare, William. Romeo and Juliet, Act II, Scene II, 1594-95.
19. Stein, Gertrude. In the poem "Sacred Emily" (1913). Geography and Plays, 1922.

How to cite this article: Wartofsky L. A rose by any name surely does smell just as sweetly: The controversy over revised nomenclature for encapsulated follicular variant papillary carcinoma. J Transl Intern Med 2016; 4: 55-7.