

## Inadequate Cytology of Thyroid Nodules. Repeat It or Live With It

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“The specimen is inadequate for diagnosis” after ultrasound (US) guided fine needle aspiration (FNA) of a thyroid nodule is a phrase all thyroid surgeons and physicians are uncomfortable with. In most cases, repeating the biopsy within the next 6 months seems to be the obvious next step. However, what if your hospital is performing 6000 biopsies a year, and 1500 (25%!) were reported as inadequate? Assuming a constant referral rate, the following year the number of biopsies would have increased to 7500. One can see why the article of Yoon et al. in this issue of *Annals of Surgical Oncology* becomes so relevant in their setting.<sup>1</sup> In their article, the authors report that “in thyroid nodules with inadequate cytology, malignancy rates of mainly cystic nodules showing no suspicious US features were significantly lower than those with suspicious features present.” They conclude that “follow-up ultrasound (US) can be considered over repeat aspiration if there were no suspicious US features present,” especially in mainly cystic thyroid nodules.

The authors should be congratulated on this comprehensive study for several reasons. The authors state that their current study is the first report on malignancy rate after inadequate cytology of thyroid nodules based on US features. Secondly, the number of FNAs is impressive: 6178 in just 1 year. Lastly, this is a timely and important issue as thyroid nodules are extremely common.<sup>2</sup> As with all well-performed studies, this paper will generate many points for discussion, a few of which are summarized in this editorial.

The inadequacy rate in this study seems a little high (22%). Yes, it is true that the reported rate of inadequacy is 2–25%, as the authors mentioned.<sup>3–8</sup> However, the highest rates are from times when biopsies were done by palpation without ultrasound localization.<sup>3,7,8</sup> Hence, the high proportion of malignant vs benign (25 vs 75%) in the current study may be biased. Also, a sizable number of nodules with inadequate cytology (42%) were excluded for lack of further evaluation. Additional patient biopsies (28%) were excluded because of small size, decreasing size, or highly cystic characteristics on the original US, another reason for a biased result.

US imaging characteristics included in this study were all the important ones. Unfortunately, color flow Doppler was not included. Yet the categorization of probably-benign or suspicious-malignant seems appropriate especially because only 1 feature of malignancy was enough for the distinction.

The technique used for FNA (23-gauge/aspirator) was somewhat different from the most commonly used (25-gauge plain or Inrad needles) techniques and could have also affected the results.

The lack of onsite cytology assessment, however, is clearly the most important handicap. US-guided FNA biopsy and on-site assessment of cytology improves the adequacy rate of FNA biopsy. In the study of Redman et al., thyroid FNA biopsy specimens were obtained with and without ultrasound guidance and with or without on-site cytology assessment.<sup>9</sup> Only 4% of the specimens were inadequate for diagnosis. With US guidance, even fewer of the cytology specimens (3%) were inadequate, compared with a 7% rate when US was not used ( $P = .003$ ). The mean number of needle punctures necessary for an adequate specimen was  $3.8 \pm 0.06$  (median 3.0; range 1–11) and was different among various types of doctors, ranging

from  $3.2 \pm 0.07$  to  $5.4 \pm 0.12$  ( $P = .001$ ). The fewest number of needle passes required to achieve an adequate specimen were accomplished by university endocrinologists and cytologists working together (radiologists alone in Yoon et al. study<sup>1</sup>). Stepwise regression analysis showed that onsite assessment of cytology, US-guided FNA biopsy, and cystic nature of the nodule ( $P < .0001$  for all) correlated with adequacy of the specimen. US-guided FNA with on-site evaluation of cytology specimens substantially increased the adequacy of cytology specimens and decreased the number of required needle passes, which ultimately reduced diagnostic errors, thus raising the question as to whether this should eventually become the standard of care. This is a goal we all should strive to achieve.

Moreover, it is now established that for exclusion of cancer in a thyroid with multiple nodules larger than 10 mm, up to 4 nodules should be considered for FNA. Sonographic characteristics can be used to prioritize nodules for FNA based on their individual risk of cancer but not to less than 4.<sup>10</sup> This is another major handicap of the accompanying study.<sup>1</sup> Yoon et al. mostly biopsy single dominant nodules. For comparison, our institution (the University of Wisconsin Thyroid Multidisciplinary Clinic) is a large referral site for thyroid diseases in the Midwest. Since we use the standard of care described (endocrinologists with on-site cytopathology support) our inadequacy rate is less than 2.5%.<sup>11</sup> This low rate is even more remarkable when you factor in the multiple nodule diagnostic approach we systematically follow.<sup>10</sup>

We believe this paper is important because of the size of the database used; however, as the authors point out there are several limitations to this retrospective study. Aside from those noted previously, selection bias may have also been the cause of the relatively high malignancy rate (25.4%) of nodules with inadequate cytology. Yet, this goes against their conclusion of not pursuing repeat FNAs even of cystic nodules (5.3% malignancy rate).

In conclusion, thyroid FNA is the most important diagnostic study for patients with thyroid nodules, optimizing the management for patients with thyroid cancer.<sup>12</sup> For nodules with inadequate cytology, the best option is clearly on-site cytopathology assessment. More passes during the same visit are the most efficient and cost-

effective solution. Short of that, repeating the FNA within 6–12 months is still reasonable. We believe that at this time leaving the possibility of malignancy to a sonographic characterization is too high of a risk, regardless of the number of biopsies your institution may have to perform. Although thyroid ultrasound is a critical tool for the assessment of thyroid nodules, imaging findings alone are not sufficient to rule out malignancy, thereby emphasizing the importance of cytological or pathological assessment of thyroid nodules.

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