



Is There an Age Threshold for Active Surveillance in Highly Suspicious Subcentimeter Thyroid Nodules?

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Active surveillance (AS) for small papillary thyroid microcarcinomas (PTMCs), and even some small papillary carcinomas, is a reasonable alternative for many patients. There are a number of landmark papers with a much greater number of patients and with long enough follow-up to support this strategy in any patient who meets the criteria and does not have significant anxiety from surveillance. Current literature on AS shows that younger age is associated with an increased risk of disease progression over time, although no studies exist to define the recommended age cut-offs.^{1,2}

In this issue of *Annals of Surgical Oncology*, Zhuge and colleagues from the National Cancer Center in China aimed to identify the optimal age cut-off to predict progression of highly suspicious thyroid nodules ≤ 10 mm during AS.³ The group prospectively surveyed 779 consecutive patients diagnosed with subcentimeter thyroid nodules containing suspicious ultrasound characteristics, and performed a follow-up protocol once or twice a year with neck ultrasonography to assess the progression of disease. Disease progression was defined as an increase in nodule diameter of 3 mm or more, increase in nodule volume of 50% or more, novel appearance of highly suspicious nodules, or newly detected lymph node metastases or distant metastases. The study employed a statistical model that provided a structural breakpoint, highlighting the hazards of disease progression with age, and found this 'change-point' to be 30 years of age. In other words, the risk of disease progression rapidly decreased after patient age > 30 years. Furthermore, after stratifying by age,

the group found that nodule size was the only significant predictor of disease progression in patients aged < 30 years; and more specifically in nodule sizes larger than 6 mm, the hazards of disease progression was nearly eightfold compared with nodule size < 6 mm. In patients over 30 years of age, significant predictors of disease progression were multifocality and thyroiditis.

The investigation into an age change-point for AS in highly suspicious subcentimeter nodules is a worthwhile endeavor. Thyroid nodules are common, and suspicious subcentimeter nodules are not infrequently found incidentally on unrelated imaging. Ito et al. investigated arbitrary age parameters every 20 years (< 40 , 40–60, and > 60 years) in patients with PTMC, and highlighted that the youngest age group (< 40 years) had the largest percentage progression to clinical disease.¹ Miyauchi et al. demonstrated an age by decade-dependent decreased rate in disease progression for PTMCs in a much larger cohort of patients.⁴ Other international cohorts have also demonstrated 'older age' as a risk factor for progression, but no studies have produced a robust statistical analysis to accurately define an age cut-off.^{5,6} The present study attempts to do just that, and defines age of 30 years as the cut-off for when AS should be implemented with caution for PTMC.

Although the potential clinical utility of this work should be praised, the findings must also be taken with caution. One of the main study limitations is a small sample size in the clinically relevant group. Less than 10% of the total cohort was in the < 30 years age group ($N = 74$), and an even smaller number had clinically relevant 6–10 mm nodules (total sample size unknown). In the US, most nodules < 6 mm would not even be put under an official AS protocol and would thus not be deemed clinically relevant unless they presented with nodal metastases. Thus, the overlap of patient age < 30 years and subcentimeter nodule size > 6 mm

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creates a very small study size with an unknown robustness of statistical significance.

Additionally, given that the majority of small thyroid nodules are indolent in nature, the limited median follow-up of 20 months for this study's entire cohort is likely too short to draw meaningful conclusions on disease progression beyond the first 12–18 months.⁷ Moreover, the protocol for AS requires neck ultrasonography every 6 months until stability is documented, usually at 2 years, after which interval imaging is performed every year, and possibly less frequently as time goes on concurrent with annual thyroid function tests.^{2,8} Thyroid cancers are almost always slow growing, and patients whose tumors progress on an AS protocol have equivalent oncologic outcomes to those that had immediate surgical intervention.⁹ Therefore, as opposed to the author's statement that young patients should have more 'intense' surveillance, we feel that the current approach to AS should be maintained regardless of age. However, in our practice, we do discuss biopsy with possible surgical intervention for the youngest patients with clinically relevant PTMCs > 8–9 mm based on current literature, and thus look forward to an updated analysis with longer follow-up, and possibly a larger young patient population (age ≤ 30 years), of highly suspicious clinically relevant PTMCs 6–10 mm in size.

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