Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance

Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, Untch B, Ganly I, Shaha AR, Shah JP, Pace M, Li D, Bach A, Lin O, Whiting A, Ghossein R, Landa I, Sabra M, Boucai L, Fish S, Morris LGT. JAMA Otolaryngol Head Neck Surg. 2017;143(10):1015-1020.

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In Brief

There has been a significant increase in the incidence of papillary thyroid cancer (PTC) over the past several decades, largely due to the increased incidental detection of small, subclinical PTCs.1 Since the majority of these microcarcinomas have indolent behavior and will not result in significant growth, symptoms, or death if left untreated,2 the American Thyroid Association (ATA) guidelines currently endorse active surveillance as an alternative to thyroidectomy in select patients with low-risk tumors.3

The present study by Tuttle et al4 seeks to determine not only the probability of growth, but also the rate and magnitude of growth of low-risk PTCs in a cohort of 291 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) who were prospectively followed with active surveillance. They defined low-risk PTCs as any nodule ≤1.5 cm with suspicious ultrasound features classified as Bethesda category V or VI by fine needle aspiration biopsy review by thyroid cytopathologists at MSKCC. Nodules with extrathyroidal extension, local invasion, or regional/distant metastasis were excluded. Patients were followed with serial ultrasounds every 6 months for 2 years, then annually. Tumor dimensions, volume, and doubling time were compared to baseline measurements. Any nodule displaying tumor growth >3 mm over baseline or evidence of extrathyroidal extension or regional/distant metastasis was recommended to undergo surgery.

Among the 291 patients, 80% had tumors ≤1.0 cm and 20% were 1.1-1.5 cm in maximal dimension. Over a median follow-up of 25 months (range: 6-166 months), 11 patients (3.8%) demonstrated tumor diameter growth >3 mm with a cumulative incidence of 2.5% at 2 years and 12.1% at 5 years. The cumulative incidence of volume increase >50% was 11.5% at 2 years and 24.8% at 5 years. Tumors with >50% increase in volume demonstrated a classic exponential growth pattern (median doubling time 2.2 years; range: 0.5-4.8 years). Among the 11 tumors with growth >3 mm, all demonstrated a volume increase >50% that preceded the >3 mm increase in tumor diameter (median 8.2 months; range: 3-46 months). Younger age and high-risk category were independently associated with likelihood of tumor growth. To date, 10 patients have undergone thyroidectomy (5 for increase in size, 5 due to personal preference). None of the 10 thyroidectomy specimens had adverse features; no patient underwent radioactive iodine treatment or had evidence of residual or recurrent disease over a mean follow-up of 7 months (range: 3-32 months). The authors conclude that active surveillance is an effective strategy in patients with PTCs ≤1.5 cm without suspicious features with a low likelihood of growth (10-15% during the first 5 years). Since tumor growth follows

predictable growth kinetics, serial tumor volume measurements may be beneficial in deciding when to continue active surveillance or surgery.

Critique

This study from Tuttle et al. begins to define the growth kinetics associated with small papillary thyroid cancers and corroborates the results of previous studies of active surveillance in Japan demonstrating a low risk of growth and adverse outcomes. This study adds several points of consideration compared to the Japanese studies. First, increase in 3-dimensional growth >50% occurred prior to growth of ≥3 mm in largest diameter, which may offer an earlier and potentially more sensitive marker. Second, this study included patients with PTCs <1 cm as well as 1-1.5 cm with no difference in results, suggesting that active surveillance rather than biopsy and resection may be appropriate for all nodules ≤1.5 cm. Additional data are needed to confirm these findings.

The current American Thyroid Association (ATA) guidelines3 do not recommend biopsy of nodules <1 cm. Although Tuttle et al. do not discuss why all lesions were biopsied in their study, the article does lend support for the ATA's recommendations that nodules <1cm, even with radiographically suspicious features, can be monitored. Ito et al.2 suggest biopsy of nodules that are being considered for active surveillance so that patients can have an accurate diagnosis. This may prevent them from seeking a second opinion elsewhere that can lead to unnecessary surgery, and may make them more likely to follow up appropriately given a diagnosis of cancer. Studies are needed to determine whether biopsy confirmation of cancer is a valuable component of active surveillance.

This study has several limitations. The authors rely on a highly skilled multidisciplinary team, including cytopathologists and radiologists, to carry out this active surveillance protocol, which may limit the generalizability of the results. In addition, the long and generally favorable natural history of thyroid cancer is such that a median follow-up period of 25 months overall and mean postoperative follow up of only 7.3 months may be insufficient to truly determine the long-term impact of active surveillance on disease progression and survival. However, their results mirrored those of Ito et al2 who demonstrated no difference in recurrence or survival after 10 years of follow-up using the same active surveillance protocol.

Future Directions

As the incidence of thyroid cancer continues to increase, the most appropriate treatment strategy will need to change to avoid both under- and overtreatment. This article provides additional evidence in support of considering an active surveillance strategy for low-risk PTCs. Future investigations should continue to define the patient population that is most appropriate for surveillance. Additionally, the duration and impact of surveillance still needs to be determined, as a period of prolonged surveillance may lead to increased patient anxiety, decreased quality of life, and increased cost.5 Finally, as Tuttle and colleagues suggest, further studies are needed to define the significance of mild growth and to further refine the threshold for treatment.

References:

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Additional High Yield Reading:

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