

Puzzle over active surveillance for micropapillary thyroid carcinoma

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Abstract: It is worth distinguishing between the two strategies of management for low risk micropapillary thyroid cancer (MPTC). Immediate therapy, whereas active surveillance (AS) entails delivering curative treatment on signs of disease progression. AS appears to reduce overtreatment in patients with low-risk MPTC without compromising cancer-specific survival at 10 years. Therefore, AS is an option for select patients who want to avoid the side-effects inherent to the different types of immediate treatment. However, inclusion criteria for AS and the most appropriate method of monitoring patients on AS have not yet been standardized.

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Active surveillance (AS) has emerged to address the concern for over-treatment of low-risk papillary microcarcinoma (PMC) (1,2). AS is distinct from previously proposed watchful waiting which was generally prescribed to patients with multiple comorbidities limiting more definitive treatments. These patients were treated with non-curative intent and only when symptoms developed. In contrast, AS "actively" follows the selected patients in efforts to intervene only at disease progression and thereby delaying the treatment-related complications. This treatment strategy may lead to the quality-of-life improvements.

Authors suggest AS as the preferred management option for low-risk PMC, that it may be offered to selected patients with favorable prognosis. In some parts of the world, AS has been embraced (2-5). In other countries, the majority of individuals with low-risk small thyroid cancer still receive upfront treatment with the increased chance of lesser extent surgery, and the application of minimally

invasive approaches, as well as no need for lifelong thyroid replacement therapy, a consistent follow-up, low-dose or no radioactive iodine therapy (RAI) administration and risk factor assessments (1,6,7).

The underutilization of AS in some Countries appears to be multifactorial, including both patient, physician factors and surgeon (1). This underutilization of AS is partly due to the general anxiety faced by the physicians and general population given the limited long-term evidence and universally accepted guidelines, different health care systems.

With conflicting reports, data and recommendations, it is often difficult for clinicians and patients to determine the optimal management plan for PMC.

Nevertheless, it is clear that not all Patients with newly diagnosed PMC need definitive treatment. An elderly patient with high comorbidity and a one-centimeter tumor deserves observation only. Indeed, the most effective

management of PMC requires selective treatment strategy reflecting the disease and patient characteristics (1).

An understanding of the oncologic, biology, functional outcomes, psychological and health-related quality-of-life for different treatment options is important for patients to make informed decisions. Use of AS for low-risk disease may continue to expand as an increasing body of literature supports its oncologic equivalence and functional advantages.

De facto, there are intrinsic questions about AS without precise answer available.

Who to include to AS?

While variations on the scheme exist, risk stratification schemes have been developed based on the post-treatment failure rates and its associations with the pretreatment Patient scores, fine needle aspiration (FNA), imaging features, and American Joint Committee on Cancer clinical stage, age to define the low-risk PMC (2-5).

For this low-risk population, at a minimum, AS should be discussed as an acceptable initial intervention along with other definitive therapies. The goal of AS is to identify and monitor this low-risk group and to intervene when necessary. Despite its indolent nature, low-risk PMC can develop local progression and distant metastasis years after diagnosis (2-5).

Given the current status of scarce AS guidelines with no uniformly accepted standard, further research is needed to reach a consensus on the AS inclusion criteria. Considering the indolent nature of low-risk PMC, an ideal inclusion criteria might incorporate the most Patients initially and later delineate whom to treat based on the evidence of disease progression. To this end, advances in imaging as well as various genetic tests and biomarkers are eagerly anticipated.

A low-risk scheme needs to be refined and develop for the eligibility criteria for AS. An AS eligibility criteria are attempted to predict clinically insignificant PMC with accuracy. A stringent criteria with low sensitivity and high specificity for identifying low-risk PMC on surgical specimen, imaging and patients demographic, increasing age, ethnicity and heredity. The anatomic location of PMC in the framework of AS has definitely been limited examined (1).

Nonetheless, the clinical implications of aggressive biologic features in the context of AS is not immediately clear. However, additional progress in genomics and

proteomics are likely necessary to identify this group.

How to follow?

Disease progression should be followed with strict protocols under an AS program. One of these principles combines serial imaging, nodule kinetics, clinical stage, grade and nodule volume (7). Ultrasound and clinical evaluation available today represent a limit. Fluctuations in nodule size may generate anxiety and uncertainty in both patients and physicians as this may indicate disease progression requiring intervention. Not uncommonly, however, it is also a mere biological variation (2-5).

The concept of thyroid nodule kinetics has been evolved (5). Studies have also identified pre-treatment thyroid-stimulating hormone (TSH) as a strong predictor (6). Although a standardized protocol does not yet exist, most institutions have incorporated the above findings to detect disease progression and to adequately select those in need for intervention. Perhaps, addition of new biomarkers may help improve the outcome of AS during the follow-up period.

When to treat and what the outcomes are following delayed intervention?

The triggers for intervention in patients on AS are not clearly defined yet. Different guidelines incorporate a varying combination of changes and increase in nodule size and volume kinetics and ratio, appearance of lymph node metastasis, clinical stage, biochemical (1-7). The efficacy and safety of such protocols still need to be confirmed. On the other hand, progression on clinical stage remains an absolute trigger for intervention in AS protocols (2). Differences in defining biological progression on biopsy results is essential, associated with time to intervention. Longer follow-up data is pending to further assess the long-term efficacy and safety of current AS protocols.

Over the last decade, there have been significant advances in the biology of PMC. New biomarkers are being investigated and new modalities are being developed to help distinguish indolent cancer from more aggressive forms (7). These novel biomarkers may be a valuable tool in counseling Patients considering AS. Multigene assays are currently under investigation with aims to overcome tumor heterogeneity in men with low-risk PMC. Examining genetic influences would help identify Patients with greater risk. Tumor genetics is already incorporated into the management guideline for breast cancer and is currently

being evaluated as a prognostic predictor in colon cancer. The multigene assays can aid to appropriately select and counsel these men considering AS as the treatment option in near future (7).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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