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EDITORIAL

Should patients with papillary microcarcinoma undergo radioiodine ablation?

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Introduction

Current management trends for patients with papillary thyroid microcarcinoma (PTMC) of <1 cm are based upon a predicted excellent outcome without radioiodine ablation. Guidelines suggest that post-surgical ablation is not necessary for such small tumors and rather that the patients may be followed by monitoring serum thyroglobulin and performing periodic neck ultrasonography [1]. In this issue of *Endocrine*, Gallicchio et al. [2] report on a retrospective 14-month follow up of 85 pT1 patients with PTMC who did receive ablation of whom 35 % were shown subsequently to have lymph node metastases on SPECT/CT. They suggest that perhaps we may have abandoned ablative therapy either prematurely or too broadly, and that the criteria for or against ablation of these PTMC patients need to be re-examined. Similar caution was raised recently by Malandrino et al. [3] from a survey of two cancer registries, one in Sicily and one in the USA, from which the same proportion, i.e., 35 % of patients, were noted to have two or more risk factors for recurrence that included lymph nodes, multifocality, younger age, and extrathyroidal extension. The significance of lymph node metastases lies in their association with future recurrence. This issue was recognized in the most recent ATA Guidelines [1] which while not advocating radioiodine ablation for small tumors or even multifocality, did leave the door open for ablation of those tumors with higher risk features such as lymph node metastases, local invasiveness, or aggressive histologies such as tall cell, insular, or columnar variants of PTC.

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It is conceivable that the selected cut-off size of 1 cm may be too arbitrary and can be further refined with better discrimination in regard to which PTMC's might be associated with lymph node metastases or subsequent recurrence. Thus, Lee et al. [4] proposed a tumor size of 7 mm as the cut off point for PTMC having noted that tumors <7 mm were less likely to have aggressive features, such as lymph node metastases (30.6 %), compared to larger tumors of 7–10 mm of which 47.8 % had central compartment lymph node metastases. Experience has taught us that the TNM pathologic classification of risk status is suboptimal or poorly applicable to many patients with thyroid cancer. Other recommendations for risk stratification that establish the risk of recurrence or establish subsequent risk based on responses to initial therapy are becoming more useful [5, 6], and could be considered in the postoperative decision for or against radioiodine ablation. Even when the preoperative diagnosis is uncomplicated PTMC, a decision might be made to recommend radioiodine ablation postoperatively on the basis of either the operative findings (e.g., incomplete tumor resection, aggressive histologic type, etc.) or a higher than expected serum thyroglobulin. Such patients would be re-stratified from "low risk" to "intermediate risk" for whom RAI ablation serves to facilitate disease surveillance and offers some benefit in improving the overall survival or reducing the risk of local relapse of disease.

What criteria or characteristics of PTMC might be useful as risk factors for recurrence? Male gender and lateral cervical node metastases were found by Kim et al. [7] to be associated with recurrence, and Zhang et al. [8] identified multifocality, male gender, tumor size >6 mm, and extrathyroidal extension as risk factors for lymph node metastasis. Their presence in patients with PTMC might warrant central neck lymph node dissection as well as

subsequent radioiodine ablation. Opinions on this issue are polarized, and on the basis of the generally excellent clinical outcomes with the overwhelming majority of PTMC's, Pacini impugned the importance of risk factors including lymph node metastases as having no major impact on outcome even when identified [9]. I would caution against overly generalized recommendations in clinical medicine, even though the latter opinion is likely to be correct in the majority of cases. Rather, I believe that we must develop better approaches to a clinically based differentiation of those PTMC's that will exhibit biologically benign behavior from those that will not.

In the very near future, it is likely that we will be looking to some aspect of molecular mutational analysis of these tumors to determine which mutations in a microcarcinoma are associated with extrathyroidal extension, multifocality, or lateral neck lymph node metastases [9, 10]. The group of Nikiforov et al. [11] proposed risk stratification of patients with PTMC based upon their BRAF status , and several studies [12, 13], but not all [14, 15] associate the presence of BRAF with more aggressive biological behavior. Clearly, all PTMC's will not exhibit the same behavior, and we are likely to have only "scratched the surface" in the discovery and understanding of other genomic mutations that impact biological behavior and clinical outcomes. While the analysis of Gallicchio et al. implies some benefit of radioiodine ablation for PTMC, we should remain mindful that there are pitfalls inherent in the potential adverse effects of overly aggressive radioisotope therapy [10]. As in most things, a balanced approach is required and we await further clarification by mutational analysis of a rational basis for decision making in the management of PTMC.

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