[Comments on the Ito et al. article (Endocr J. 2008 Oct 8. Epub ahead of print)]
The Lack of Clinicopathological Correlation of BRAF Mutation in Papillary Thyroid Cancer Needs to Be Interpreted with Caution

To the Editor;

In their recent article in the Journal on a large series of papillary thyroid cancers (PTC) in Japan [1], Ito et al. investigated the relationship between BRAF mutation and clinicopathological outcomes. The authors failed to show a significant correlation and concluded that BRAF mutation might not be a risk factor for aggressive pathological features and recurrence of PTC in Japanese patients. These results are inconsistent with the reports of significant correlations in most of the studies in other countries [2]. The results are also inconsistent with two previous Japanese studies that had demonstrated a significant association of BRAF mutation with distant metastasis, advanced stages, extrathyroidal invasion, and lymph node metastasis of PTC [3, 4]. One [3] of the two previous Japanese studies was cited in the Ito et al. report.

Due to several limitations, the conclusions in the Ito et al. study may need to be cautioned. A significant portion (41.5%) of the patients in this study only received partial thyroidectomy as opposed to total or near-total thyroidectomy routinely performed in other studies that showed an association of BRAF mutation with aggressive pathological features [2]. Partial thyroidectomy is inherently associated with relatively limited surgical exploration, including possibly limited lymph node dissection, even though the latter procedure is commonly pursued in Japan [1]. Consequently, incomplete or varying characterization of pathological characteristics of the tumor, including the status of lymph node metastasis, may occur. If such factors are not evenly weighted between the BRAF mutation-positive and -negative groups, the conclusion on the relationship of BRAF mutation with pathological characteristics of PTC could be biased. Out of the 631 patients, apparently only 11 patients received radioiodine ablation treatment, in contrast to many other studies in which radioiodine ablation was routinely administered [2]. This is an important confounding factor in PTC recurrence correlation studies on BRAF mutation. A key mechanism for the association of BRAF mutation with PTC recurrence is that BRAF mutation-positive PTC has often decreased or even completely silenced expression of iodide-handling genes and, hence, decreased or lost response of the tumor to radioiodine treatment and subsequent disease recurrence [2]. Thus, the effect of BRAF mutation on PTC recurrence could have been masked by the lack of radioiodine treatment in patients. Another important limitation of the Ito study was the use of mainly imaging methods (apparently not radioiodine body scanning) for identification of PTC recurrence, which may be insensitive and can also be false positive for thyroid cancer, compared with serum thyroglobulin testing and radioiodine body scanning that were commonly used as standard studies to identify thyroid cancer recurrence in other studies [2]. This may partially account for, in addition to other factors, the relatively low recurrence rate of PTC in the Ito et al. study [1] in comparison with other studies [2]. Given these limitations, as partly discussed by the authors, the lack of clinicopathological correlation of BRAF mutation in PTC in the Ito et al. study may need to be interpreted with caution.

References

2. Xing M (2007) BRAF mutation in papillary thyroid
