**BRAF Mutation in Papillary Thyroid Carcinoma in a Japanese Population: Its Lack of Correlation with High-Risk Clinicopathological Features and Disease-Free Survival of Patients**

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**Abstract.** Recent studies have demonstrated that BRAF\(^{V600E}\) mutation is a common event in papillary thyroid carcinoma and a majority of these lesions have shown a direct relationship between BRAF\(^{V600E}\) mutation and aggressive characteristics, including a worse patient prognosis. However, there are no studies from Japan regarding this issue in a large series with adequate postoperative follow-up periods. We investigated BRAF\(^{V600E}\) mutation in 631 patients with papillary carcinoma having median follow-up periods of 83 months. The prevalence of BRAF\(^{V600E}\) mutation was 38.4%, and the rate was higher in carcinoma larger than 1.0 cm but did not successively increase with tumor size. Furthermore, the prevalence did not significantly increase in cases demonstrating high-risk biological features such as clinically apparent lymph node metastasis, massive extrathyroid extension, advanced age, distant metastasis at surgery, and advanced Stage. The disease-free survival of patients with BRAF\(^{V600E}\) mutation did not differ from that of those without BRAF\(^{V600E}\) mutation. These findings indicate that, although BRAF\(^{V600E}\) mutation may play some roles in local carcinoma development, there is no evidence that BRAF\(^{V600E}\) mutation significantly reflects the aggressive characteristics and poor prognosis of patients with papillary carcinoma in Japan.

**Key words:** BRAF mutation, Papillary carcinoma, Thyroid, Prognosis

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**PAPILLARY** carcinoma of the thyroid is the most common malignancy arising from thyroid follicular cells. Although papillary carcinoma frequently metastasizes to the regional lymph node, it generally shows an indolent character and grows slowly. However, cases displaying certain characteristics are progressive, show a dire prognosis and are considered high-risk. There are several classification systems evaluating the progression of thyroid carcinoma and among these, the UICC/AJCC TNM staging system is the most widely adopted [1]. It consists of three components; T factor, tumor size and extrathyroid extension; N factor, lymph node metastasis; M factor, distant metastasis. Then, each case is staged based on the TNM classification and patient age. This system is evaluated on preoperative imaging studies (TNM and Stage) and also on postoperative pathological examination (pTNM and pStage). We previously demon-
strated that, of the components of TNM classification system, T4 (massive extrathyroid extension regardless of tumor size), pT4 and N1b (clinically apparent lateral node metastasis) affected disease-free survival (DFS) and cause-specific survival (CSS) of papillary carcinoma patients [2–4]. Furthermore, male gender, age 55 years or older and tumor larger than 4 cm also predicted worse DFS and CSS of these patients [2–4]. It is therefore suggested that these are high-risk features for a worse prognosis in papillary carcinoma. Regarding Stage, patients with Stage IV showed significantly worse DFS and CSS of patients. Similar findings could be observed in patients with pStage IV, although pStage less keenly reflects the patient prognosis than Stage [4].

Besides, there are many histological variants in papillary carcinoma as defined in the WHO classification [5] and some of them showed a different prognosis from conventional papillary carcinoma. For example, tall cell variant is known to have a dire prognosis compared with conventional papillary carcinoma [6–8] and in contrast, in a Japanese population, patients with Warthin-like tumor that is an oncocytic variant showing abundant chronic inflammatory cells displayed an excellent prognosis [9]. Furthermore, carcinoma having a poorly differentiated lesion proposed by Sakamoto et al. [10] is more likely to show recurrence, although, in our experience, it does not independently affect the cause-specific survival (CSS) of patients on multivariate analysis [8].

BRAF is one of the three Raf kinases [11, 12] and, among these three kinases, it is the most potent activator of the MAPK pathway, which contributes to various cellular events such as cell proliferation, apoptosis, survival, differentiation, and tumorigenesis [13–16]. To date, BRAF gene mutations have been found in various human carcinomas [17–20]. Although there have been more than 40 mutations identified in the BRAF gene, the most significant hot-spot mutation of the BRAF gene site is a thymine-to-adenine transversion at nucleotide 1799 (T1799A) in exon 15, resulting in a valine-to-glutamate substitution at residue 600 (V600E) [21]. Studies regarding BRAF V600E mutation in thyroid carcinoma have been intensively investigated in various countries, demonstrating that the prevalence of BRAF V600E mutation ranged from 28% to 83% in papillary carcinoma [22–41]. Previous studies showed controversial findings regarding the clinical significance of BRAF V600E mutation, but a majority of studies demonstrated that BRAF V600E mutation was directly linked to one or more high-risk clinicopathological features and/or a poor prognosis for the patient [22, 24, 26–38]. In Japan, studies on the BRAF V600E mutation in papillary carcinoma have been performed [26, 27], but there are no studies in a large series with an adequate postoperative follow-up period. In this study, therefore, we investigated BRAF V600E mutation in 631 patients and analyzed its prognostic value to elucidate its clinical significance in papillary carcinoma in Japan.

**Patients and Methods**

**Patients**

We performed BRAF V600E mutation analysis using a section from paraffin-embedded specimens of 897 patients who underwent initial surgical treatment for primary papillary carcinoma at Kuma Hospital between 1996 and 2000. Of these patients, we obtained informative results for 631 patients (69.2%) and these patients were enrolled in this study. These 631 patients consisted of 67 males and 564 females, and the mean patient age at surgery was 50.5 years. Total or near total thyroidectomy (thyroidectomy with an estimated remnant thyroid under 1 gram) was performed for 369 patients (58.5%), whereas the remaining patients underwent more limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy. We performed lymph node dissection in 609 patients (96.5%), and all of these patients underwent central node dissection. Furthermore, dissection of the lateral compartment (modified radical neck dissection [MND]) was performed in 518 patients (82.1%), and 72 of these patients underwent bilateral MND. Dissection of the mediastinal compartment was also performed in 2 patients. Three patients underwent only palliative surgery because of severe local invasion of the primary tumor or metastatic lymph nodes.

**Diagnosis of histological variants of papillary carcinoma according to the WHO classification**

The histology of 631 patients with papillary carcinoma was blindly re-reviewed by one of the coauthors who specialized in thyroid pathology (H.M.), according to the WHO classification [5]. Five hundred and
eighty-three were diagnosed as conventional papillary carcinoma and 38 of them were classified as having poorly differentiated lesion as proposed by Sakamoto et al. [10]. Furthermore, 20 patients were diagnosed as follicular variant, 12 as tall cell variant, 9 as Warthin-like tumor, 3 as macrofollicular variant, 3 as diffuse sclerosing variant, and 1 as cribriform morular variant.

**Evaluation of biological characteristics of carcinoma according to the UICC/AJCC TNM staging system**

We graded all cases into T, N and M categories and staged them based on the 6th edition of UICC/AJCC TNM classifications [1]. Using the UICC/AJCC TNM staging system, the biological characteristics of carcinomas were preoperatively evaluated on imaging studies. Patients routinely underwent preoperative examination by ultrasonography to evaluate the size and location of the tumor and the presence of nodal metastasis. Chest computer tomography (CT) scan was also performed for patients having tumors suspected of extension to the adjacent organs. Patients having recurrent laryngeal nerve paralysis due to the invasion of carcinoma located on the dorsal surface of the thyroid or those having tumors with definite invasion to the trachea on imaging studies or fiberscope were classified as T4, regardless of tumor size. Patients who were diagnosed as having clinically apparent node metastasis in the lateral compartment or only in the central compartment on ultrasonography based on the criteria described previously [42] were classified as N1b and N1a, respectively. Furthermore, chest CT scan was routinely performed to evaluate distant metastasis and metastasis to the mediastinal compartment preoperatively. Lung metastasis was preoperatively detected in 3 patients, who were classified as M1.

pN was evaluated based on postoperative pathological findings. Regarding pT, tumors demonstrating massive extrathyroid extension such as the recurrent laryngeal nerve, trachea, esophagus, sternohyoid muscle and jugular vein on intra-operative findings and/or pathological examination were diagnosed as pT4, regardless of tumor size. Tumors with only minimal extrathyroid extension to perithyroidal tissue or sternothyroid muscle on intra-operative and pathological examination were classified as pT3. pStage was evaluated based on these pT and pN findings.

**Postoperative evaluation of recurrence and metastasis**

The median follow-up period was 83.0 ± 35.0 months. Those patients who underwent surgical treatment were followed once to a few times per year by ultrasonography, chest roentgenography, and/or CT scan. Seventy patients underwent whole body scan using 3–13 mCi of radiiodine after total or near total thyroidectomy, because they had tumors showing aggressive characteristics such as clinically apparent nodal metastasis, extrathyroid extension and high post-operative serum thyroglobulin levels. One patient who showed abnormal uptake in the lung was also classified as M1 together with the 3 patients indicated above. Ablation therapy using 100 mCi of radiiodine was performed in 11 patients, including 4 patients classified as having M1 disease.

We regarded patients as showing carcinoma recurrence when recurrence became clinically apparent on imaging studies. To date, 51 (8.2%) of 624 patients who underwent locally curative surgery and did not have distant metastasis at surgery showed carcinoma recurrence. Forty-eight patients showed local recurrence only. Thirteen patients showed recurrence to distant organs and 11 of these patients also had local recurrence. The organs to which carcinoma showed recurrence were the lymph node in 49 patients, remnant thyroid in 6 patients, other local lesions in 2 patients, lung in 10 patients, and bone in 3 patients. Twelve patients showed recurrence in two or more organs. To date, 2 patients (0.3%) have died of carcinoma.

**BRAF**\(^{V600E}\) mutation analysis

The experimental protocol was approved by the local ethical committee. A 10-µm section from paraffin-embedded tissue was placed on a film-coated glass slide (90FOIL-SL25, Matsunami, Osaka, Japan), then the tumor area (approximately 0.5 cm\(^2\)) was cut for DNA extraction. Genomic DNA was isolated using a DEXPAT (Takara, Shiga, Japan). DNA extracted from each tumor sample was examined by direct sequencing after amplification by polymerase chain reaction (PCR). To avoid carry-over contamination, Platinum Quantitative PCR SuperMix-UDG (Invitrogen Japan, Tokyo, Japan) was used for PCR amplification. Fifty µl of PCR mixture contained 0.5 µM of each primer, 1 µl of 50 mM magnesium
chloride, 3 µl of extracted DNA and 25 µl of Platinum Quantitative PCR SuperMix-UDG. The primers used were

BRA: 5’-CACAAAATGGATCCAGACAACGTTC-3’ and BRB: 5’-CTTGCCTCTGATAGGAAGATGCTACCTGC-3’

The PCR conditions were 50°C for 2 min, 95°C for 2 min and 40 cycles of 95°C for 15 sec, 55°C for 30 sec and 72°C for 30 sec. The PCR products were separated on agarose gel and extracted with a MagExtractor PCR & Gel Clean Up (Toyobo, Osaka, Japan). Purified fragments were sequenced using a BigDye Terminator Cycle Sequencing FS Ready Reaction Kit with an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Tokyo, Japan) and a sequencing primer, BS: TTTCCTTTACTTACTACCTCAGA.

All primers were purchased from Operon (Tokyo, Japan).

**Statistical analyses**

Fisher’s exact test was used to analyze the relationships between BRAF<sup>V600E</sup> mutation and clinicopathological parameters. The Kaplan-Meier method and log rank test were adopted to analyze time-dependent variables. Furthermore, Cox regression model was adopted for multivariate analysis. A p value less than 0.05 was regarded as significant and that between 0.05 to 0.1 was considered marginally significant.

**Results**

We investigated the BRAF<sup>V600E</sup> mutation in 631 papillary carcinoma patients. Of these patients, 242 (38.4%) showed the BRAF<sup>V600E</sup> mutation. Table 1 shows the relationship between BRAF<sup>V600E</sup> mutation and tumor size. BRAF<sup>V600E</sup> mutation was observed in 28.2% of patients with papillary microcarcinoma, papillary carcinoma measuring 1.0 cm or less. Of patients having carcinoma larger than 1.0 cm, 40.5% showed the BRAF<sup>V600E</sup> mutation and the incidence was significantly higher than that in patients with microcarcinoma (p = 0.0175). However, the incidence did not successively increase with size in patients having tumors larger than 1.0 cm.

Table 2 summarizes the relationship between BRAF<sup>V600E</sup> mutation and other clinicopathological features that were recognized as having prognostic significance [2–4]. The incidence of BRAF<sup>V600E</sup> mutation was not linked to patient age, gender, massive extrathyroid extension (pT4), pathologically confirmed lymph node metastasis (pN1), or distant metastasis at diagnosis (M1). Patients with N1b were even less likely to show BRAF<sup>V600E</sup> mutation than those with N0 or N1a. Furthermore, as shown in Table 3, BRAF<sup>V600E</sup> mutation was not related to Stage or pStage on UICC/AJCC staging system.

We then investigated the prevalence of BRAF<sup>V600E</sup> mutation in various histological variants of papillary carcinoma (Table 4). Of 583 conventional papillary carcinomas, 230 (39.5%) showed BRAF<sup>V600E</sup> mutation. Thirty-eight of these were diagnosed as having poorly differentiated lesion. BRAF<sup>V600E</sup> mutation was observed in 14 (36.8%) of these patients, and its prevalence was similar to that of those without poorly dif-

| Table 1. Relationship between BRAF<sup>V600E</sup> mutation and tumor size |
|---------------------------------|---------------|--------|--------|
| Tumor size (cm)    | BRAF<sup>V600E</sup> mutation (%) |        |        |
|                    | Present | Absent | Total |
| 1.0 or less        | 31 (28.2) | 79 (71.8) | 110   |
| Larger than 1.0    | 211 (40.5) | 310 (59.5) | 521   |
| 1.1–2.0            | 86 (37.2) | 145 (62.8) | 231   |
| 2.1–3.0            | 69 (48.3) | 74 (51.7) | 143   |
| 3.1–4.0            | 32 (42.1) | 44 (57.9) | 76    |
| 4.0 or more        | 24 (33.8) | 47 (66.2) | 71    |

P = 0.0175 (1.0 cm or less vs >1.0 cm)

| Table 2. Relationship between BRAF<sup>V600E</sup> mutation and clinicopathological features |
|---------------------------------|---------------|--------|--------|
| Age (yrs)   | BRAF<sup>V600E</sup> mutation (%) |        | p values |
| Present | Absent | Total |
| 50.6 ± 14.1 | 50.2 ± 14.3 | N.S.   |
| Male       | 25 (37.3) | 42 (62.7) | 67     |
| Female     | 217 (34.5) | 347 (65.5) | 564    |
| *pT4       | 34 (39.1) | 53 (60.9) | 87     |
| *pT1-3     | 208 (38.2) | 336 (61.8) | 544    |
| *N1b       | 36 (27.5) | 95 (72.5) | 131    |
| N0 or N1a  | 206 (41.2) | 294 (58.8) | 500    |
| *pN1       | 173 (39.4) | 266 (60.6) | 439    |
| pN0        | 69 (36.0) | 123 (64.0) | 192    |
| *M1        | 1 (25.0) | 3 (75.0) | 4     |
| M0         | 241 (38.4) | 386 (61.6) | 627    |

* according to UICC/AJCC TNM staging system
The prevalences of BRAF\textsuperscript{V600E} mutation in follicular variant and Warthin-like tumor were low at 20.0% and 11.1%, respectively, and that in tall cell variant was high at 50.0% compared with that in conventional papillary carcinoma. However, there was no significant difference in the incidence of BRAF\textsuperscript{V600E} mutation among histological variants. Regarding the other rare histological variants, 33.3% of macrofollicular carcinoma showed BRAF\textsuperscript{V600E} mutation, but none of the cases with diffuse sclerosing variant and cribriform morular variant were positive for BRAF\textsuperscript{V600E} mutation.

We also investigated whether BRAF\textsuperscript{V600E} mutation affected disease-free survival (DFS). In our series, 4 patients were classified as M1 and 3 underwent only locally palliative surgery. Therefore, 624 patients (631 patients excluding 7) were enrolled in the analysis. To date, 51 patients showed recurrence and 18 of these were BRAF\textsuperscript{V600E} mutation positive. Fig. 1 shows Kaplan-Meier curves of DFS of patients with and without BRAF\textsuperscript{V600E} mutation. The DFS of patients with BRAF\textsuperscript{V600E} mutation did not differ from that of those without BRAF\textsuperscript{V600E} mutation. Carcinoma recurrence to the distant organs was observed in 13 patients.

### Table 3. Relationship between BRAF\textsuperscript{V600E} mutation and Stage

<table>
<thead>
<tr>
<th>Stage (UICC/AJCC)</th>
<th>BRAF\textsuperscript{V600E} mutation (%)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>I</td>
<td>152 (37.4)</td>
<td>254 (62.6)</td>
</tr>
<tr>
<td>II</td>
<td>42 (56.7)</td>
<td>48 (53.3)</td>
</tr>
<tr>
<td>III</td>
<td>16 (40.0)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>IV</td>
<td>32 (33.6)</td>
<td>63 (66.4)</td>
</tr>
</tbody>
</table>

### Table 4. Relationship between BRAF\textsuperscript{V600E} mutation and histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>BRAF\textsuperscript{V600E} mutation (%)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Conventional</td>
<td>230 (39.5)</td>
<td>353 (60.5)</td>
</tr>
<tr>
<td>Follicular variant</td>
<td>4 (20.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Tall cell variant</td>
<td>6 (50.0)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Warthin-like tumor</td>
<td>1 (11.1)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Macrofollicular variant</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Diffuse sclerosing variant</td>
<td>0</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Cribriform morular variant</td>
<td>0</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

### Table 5. Univariate and multivariate analyses of DFS for clinicopathological features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Hazard ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥55 yrs)</td>
<td>0.0490</td>
<td>0.0333</td>
<td>1.84 (1.05–3.21)</td>
</tr>
<tr>
<td>Males</td>
<td>0.0613</td>
<td>0.7027</td>
<td>1.15 (0.55–2.40)</td>
</tr>
<tr>
<td>N1b</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>5.00 (1.78–3.42)</td>
</tr>
<tr>
<td>pN1</td>
<td>0.0005</td>
<td>0.1395</td>
<td>1.66 (2.66–9.43)</td>
</tr>
<tr>
<td>pT4a</td>
<td>0.0001</td>
<td>0.3216</td>
<td>1.37 (0.73–2.57)</td>
</tr>
<tr>
<td>Tumor size (&gt;4 cm)</td>
<td>0.0003</td>
<td>0.0718</td>
<td>2.09 (0.95–3.55)</td>
</tr>
</tbody>
</table>
and 5 of these were positive for BRAF\textsuperscript{V600E} mutation. As shown in Fig. 2, distant metastasis-free survival of patients was not linked to BRAF\textsuperscript{V600E} mutation. We investigated the prognostic significance of conventional prognostic factors that were adopted for comparison with BRAF\textsuperscript{V600E} mutation in Table 2 in our series. The results of univariate and multivariate analyses are summarized in Table 5. Advanced age, male gender, N1b, pN1b, pT4a and large tumor size had significant or marginally significant prognostic value for DFS of patients on univariate analysis. On multivariate analysis, age and N1b were recognized as independent prognostic factors for DFS of patients and tumor size showed marginal significance.

To date, 2 of 13 patients who showed recurrence to distant organs died of carcinoma. These two patients were BRAF\textsuperscript{V600E} mutation positive.

### Discussion

To date, in Japan, two departments have studied BRAF\textsuperscript{V600E} mutation in papillary carcinoma. Fukushima et al. demonstrated that 40 of 76 papillary carcinoma patients (52%) showed BRAF\textsuperscript{V600E} mutation [26]. Namba et al. showed that BRAF\textsuperscript{V600E} mutation was observed in 29% of 170 patients and was directly linked to distant metastasis at diagnosis and advanced Stage, but analysis regarding the prognostic significance of BRAF\textsuperscript{V600E} mutation was lacking [27]. This is the first study investigating BRAF\textsuperscript{V600E} mutation in papillary carcinoma in Japan in a large series of 631 patients who underwent surgical treatment under a uniform concept and its prognostic significance was determined with a median follow-up period of 83 months, that is, 6.9 years. We demonstrated that the prevalence of BRAF\textsuperscript{V600E} mutation was 38.4% of papillary carcinoma, which is intermediate between the findings of two previous studies. The prevalence of BRAF\textsuperscript{V600E} mutation in carcinoma larger than 1 cm was significantly higher than that in microcarcinoma. Therefore, BRAF\textsuperscript{V600E} mutation may play some role in the local development of papillary carcinoma. However, we previously demonstrated that tumor larger than 4 cm is an independent prognostic factor of DFS and CSS [2–4]. The prevalence of BRAF\textsuperscript{V600E} mutation did not successively increase with tumor size and the prevalence in tumor larger than 4 cm was not greater than that in tumor measuring 1.1–4 cm (Table 1). Therefore, our findings regarding the relationship between BRAF\textsuperscript{V600E} mutation and tumor size do not indicate that BRAF\textsuperscript{V600E} mutation significantly reflects biologically aggressive behavior of papillary carcinoma.

In our series, age, male gender, N1b, pN1, pT4a, and tumor size showed prognostic value for DFS of patients on univariate analysis and can be considered high-risk features, which is not discrepant with our previous reports [2–4]. Furthermore, among these factors, age, N1b and tumor size independently affected patient prognosis on multivariate analysis. It is therefore suggested that our series is a reliable basis for analyzing prognostic factors. However, BRAF\textsuperscript{V600E} mutation did not show any relationship with these prognostic factors. Furthermore, we previously demonstrated that patients with Stage IV as well as pStage IV showed worse prognosis than other patients [4], but in this series, the prevalence of BRAF\textsuperscript{V600E} mutation did not increase with advanced stage. We also analyzed the prognostic value of BRAF\textsuperscript{V600E} mutation by the Kaplan-Meier method. In our series, however, the DFS of patients with BRAF\textsuperscript{V600E} mutation did not differ from that of those without BRAF\textsuperscript{V600E} mutation. Furthermore, same results were obtained on analysis for distant metastasis-free survival. Although two patients who died of distant metastasis of carcinoma were BRAF\textsuperscript{V600E} mutation positive, it is suggested that BRAF\textsuperscript{V600E} mutation does not more keenly reflect patient prognosis of papillary carcinoma patients compared with conventional prognostic factors.

Previous studies in other countries have shown positive relationships between BRAF\textsuperscript{V600E} mutation and one or more high-risk characteristics such as extrathyroid extension, lymph node metastasis, and advanced stages [12, 24, 26–38], although some studies demonstrated negative findings [23, 25, 39–41]. The reason for a large discrepancy regarding BRAF\textsuperscript{V600E} mutation between Japan and other countries remains unknown, but one possible reason is the difference in treatment strategies for papillary carcinoma between Japan and Western countries. In most Western countries, total thyroidectomy with radioidine ablation therapy is almost routinely performed but lymph node dissection is not considered important. In Japan, radioidine therapy is less prevalent partly because of Japanese legal restrictions, and more limited thyroidectomy than total or near total thyroidectomy is adopted with high prevalence. However, traditionally, extensive lymph
node dissection has been performed. In many institutes in Japan, including our department, central node dissection has been routinely performed and not only therapeutic but also prophylactic MND has been performed in high prevalence, especially for carcinoma demonstrating aggressive clinicopathological features. Since the organ to which papillary carcinoma is most likely to show recurrence is the lymph node and the lymph node recurrence rate is significantly higher in patients with large tumor size and massive extrathyroid extension [43, 44], the surgical procedures in Japan could largely contribute to reducing carcinoma recurrence and improving patient prognosis. We can therefore hypothesize that treatment strategy in Japan is one of the reasons for the discrepancy of the clinical significance of BRAF\textsuperscript{V600E} mutation between Japan and many Western countries, although further studies are necessary to elucidate this issue.

In our series, the incidence of BRAF\textsuperscript{V600E} mutation varied according to histological type of papillary carcinoma, although there was no significant difference. Follicular variant was less likely and tall cell variant was more likely to show BRAF\textsuperscript{V600E} mutation, which are not discrepant with previous studies [34, 35, 45]. We showed that the prognosis of follicular variant was the same as that of conventional papillary carcinoma [9], but previous studies on molecular and protein levels demonstrated a difference in biological character between follicular variant and conventional papillary carcinoma [46–48]. This may be a reason for less prevalence of BRAF\textsuperscript{V600E} mutation in follicular variant. Tall cell variant is known to show an aggressive behavior in Western countries and Japan [6–8]. Furthermore, Warthin-like tumor in Japan was reported to be more indolent than conventional papillary carcinoma and, in our series, BRAF\textsuperscript{V600E} mutation in this variant was less likely observed than that in conventional papillary carcinoma [9]. It is therefore possible that BRAF\textsuperscript{V600E} mutation prescribes the biological behavior in these histological variants to some extent.

In summary, we analyzed BRAF\textsuperscript{V600E} mutation for 631 cases of papillary carcinoma with 83 months follow-up on average and found that BRAF\textsuperscript{V600E} mutation was a rather common event in papillary carcinoma in a Japanese population, but was not related to high-risk clinicopathological features or patient prognosis, indicating that BRAF\textsuperscript{V600E} mutation analysis in the primary lesion is not useful to evaluate its biological characteristics or prognosis. Vasko et al. demonstrated that de novo BRAF mutation was observed in lymph node metastasis of papillary carcinoma without BRAF\textsuperscript{V600E} mutation in primary lesions [49]. Studies of this issue may be useful to determine clinical applications of BRAF mutation analysis for papillary carcinoma in a Japanese population.

References


