A Piece of the Puzzle: What Does BRAF Status Mean in the Management of Patients with Papillary Thyroid Carcinoma?

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Since the identification of the BRAFV600E (BRAF) mutation in thyroid cancer nearly 10 yr ago, it has become the focus of numerous studies (1, 2). BRAF has been detected in about 45% (range, 26–83%) of all papillary cancers and less frequently in poorly differentiated and anaplastic thyroid cancers (1, 2). Because papillary thyroid cancer (PTC) accounts for 85% of all thyroid cancers, it is the most common mutation found in thyroid cancer.

The detection of BRAF in cytological specimens is highly specific for thyroid cancer, even in lesions with indeterminate cytology (3). BRAF has been reported to be a marker of more aggressive and invasive cancer (1, 2). It has been associated with an increased risk for extrathyroidal extension, lymph node and distant metastases, higher TNM/AJCC stage, and an increased risk for recurrence (1, 2). These observations have led to suggestions that assessment of BRAF status should be added to other traditional risk factors to better predict outcome. It has also been suggested that ascertainment of BRAF status might be useful in directing the extent of initial surgery (including prophylactic neck dissection), the use or dose of I131, the intensity of follow-up and TSH suppression, and the choice of drugs for patients with progressive disease unresponsive to I131 (1, 2).

Not all studies, however, have supported the view that BRAF status is an independent predictor of the extent of disease or outcome (4). Some studies find it not to be predictive at all (5, 6); some find it only significant in univariate but not multivariate analysis (4), whereas others find it to be useful in addition to other specific clinical and histological features (7).

It is in this context, that Sancisi et al. (8) conducted their study of BRAF status in metastatic PTC reported in this issue of the JCEM. They identified 47 patients with well-differentiated PTC and distant metastases and assessed for the presence of BRAF in all the primary tumors and from the metastatic disease in five of the patients with BRAF+ primary tumors. As a control, they evaluated the primary tumor in 75 PTC patients who never had distant metastases and remained free of disease for at least 7 yr. In the control group, 44% of the tumors were BRAF positive, whereas in the group with metastatic disease only 29.8% were BRAF positive. Among the fatal cases, 30.1% were BRAF+. Among patients with distant metastases, the tall cell variant (TCPTC) accounted for 71.5% of the BRAF+ tumors, whereas among the disease-free patients, it accounted for only 30.3% of the BRAF+ tumor patients. Of those that could be assessed, all but four of the patients with metastatic disease also had extrathyroidal extension of the primary tumor, regardless of BRAF status, whereas among the disease-free patients it was absent in 50% of the BRAF− and 63.6% of the BRAF+ patients (8). In addition, two patients with BRAF+ primary lesions did not have the mutation detected in the metastatic focus. They conclude that BRAF positivity alone is not a predictor of distant metastases or fatal outcome and may not predict aggressive behavior.

When the BRAF mutation is expressed in the thyroid in animal models, they develop aggressive thyroid cancers (1). Most BRAF+ tumors do not carry mutations in RAS or the RET/PTC rearrangement (1). Activation of the MAPK pathway through BRAF has been shown to induce a number of cellular events that could promote refractoriness to iodine uptake and a stimulus for growth and invasion (1, 2). This does not prove, however, that in humans the presence of BRAF is a primary abnormality leading to the development of PTC or that BRAF+ tumors are inherently more aggressive. Several lines of evidence from...
the previous as well as more recent studies would support the concept that the presence of BRAF may not be the central event in tumorigenesis or an independent predictor of outcome.

Guerra et al. (9) evaluated 72 classic PTC (CPTC) tumors for the presence of the BRAF mutation as well as RAS and RET/PTC mutations. The BRAF mutation was detected in 41 tumors (56.9%). When analyzing the presence of the mutation quantitatively, in only four tumors was the mutant BRAF present in quantities consistent with a clonal event and heterozygosity in all cells (9). In 27 patient samples, the mutant BRAF accounted for 5.1–25% of BRAF, consistent with BRAF as a later, nonclonal event (9). Although primary PTC tumors and their distant metastases are usually concordant for BRAF status (10, 11), cases with BRAF+ primary tumors and BRAF− metastases (10) (as in the report by Sancisi et al., Ref. 8) as well as BRAF− primary tumors with BRAF+ metastases (11) have been reported. These findings support the concepts that the BRAF mutation may not be a clonal event and that the BRAF mutation can develop in a preexisting thyroid cancer.

Numerous studies have noted an association between BRAF status and increasing age (1, 5). Increasing age is strongly associated with the risk of death from thyroid cancer and is incorporated into almost all thyroid cancer staging systems. In evaluating a group of younger patients, Sassolas et al. (12) found that only two of 19 (10%) patients younger than 20 and none of the nine patients younger than 15 had BRAF+ tumors, compared with 17 of 85 (20%) patients between 20 and 35 yr of age (12). Almost all of the BRAF+ tumors were CPTC. The absence of BRAF in tumors in younger patients and the increasing rate with age would be consistent with other events as being primary and the BRAF mutation occurring as a later event.

Most patients with PTC will have good outcomes with conventional therapy. Only about 10% will have distant metastases, 20–30% will have local recurrences, and less than 5% will die of the disease (1). It is difficult to reconcile the high frequency of BRAF in PTC and the usual good outcomes with the concept that it is a predictor of high-risk disease. Handkiewicz-Junak et al. (4) estimated that 31% of all PTC patients and 39% of those with stage I-II disease would be overtreated if treatment decisions were based on the BRAF positivity of their tumors.

Paulson et al. (13) examined the relationship between BRAF status and the presence of lymph node metastases (LNM) in the central neck in a series of 209 patients who all underwent an adequate central neck dissection. Positive risk factors for LNM included extracapsular extension and higher T stages (T3 and T4) (13). The follicular variant (FVPTC) was present in only 4.4% of patients with LNM but in 47.1% without (13). The BRAF mutation was more common in CPTC and less common in FVPTC (13). Among the patients with CPTC, the BRAF mutation was present in 81.5% of those without LNM and 73.6% with LNM (13). Similar to the findings of this report for distant metastases (8), BRAF status did not independently predict metastases to the lymph nodes (13).

Two recent reports note marked increases in the number of PTC that are BRAF+ over a 15-yr period divided into three 5-yr periods (14, 15). In the U.S. report, the rate of BRAF+ tumors increased from 51% in 1991–1995 to 88% in 2001–2005 (14). In the Italian report, the rate of BRAF+ tumors increased in Pisa from 28% in 1996–2000 to 58% in 2006–2010 and in Sicily from 39 to 65% over the same time periods (15). Despite the marked increase in BRAF+ tumors, neither study noted a change in the presence of LNM, distant metastases, or invasion at the time of diagnosis (14, 15). The marked change in frequency without a change in the rate of invasive or metastatic tumors supports the concept that BRAF status alone does not determine risk.

Across multiple studies, several histological features that are themselves predictors of more or less aggressive behavior have been found to be related to the presence or absence of the BRAF mutation (5, 6, 10, 16–19). As in this study (8), the TCPTC has been noted to have an increased propensity for invasion and metastases. In studies that subtyped PTC, TCPTC tumors always have a much higher rate of BRAF positivity than CPTC or FVPTC (6, 7, 17). Conversely, as in this study (8), FVPTC has a much lower rate of invasion and LNM (5, 6, 16–20). In studies that subtyped PTC, FVPTC primary tumors have a much lower rate of BRAF positivity than CPTC (5, 6, 16–19). These findings suggest that it may be the association between BRAF positivity and specific subtypes of PTC that results in the association between BRAF and poorer outcomes. Ito et al. (6) reported that among 610 Japanese patients with PTC, the BRAF mutation was present in 50% of TCPTC, 39.5% of CPTC, and only 20% of FVPTC patients; in multivariate analysis, disease-free status correlated with age and the presence of lateral neck LNM, but BRAF status alone did not correlate with stage at presentation or disease-free survival (6). In a series of 410 PTC patients, the presence of LNM, extrathyroidal extension, and vascular invasion was best predicted by the PTC subtype, with an increased risk with CPTC and a much lower risk with FVPTC (16). When patients were separated by PTC subtype, among the CPTC patients the risk for LNM, extrathyroidal extension, and vascular invasion was actually higher among those tumors without the BRAF mutation (16). Other histological features, especially incomplete tumor encapsulation and extrathyroidal extension have also been shown to be predictors of more aggressive behavior and may also be the source of the association between BRAF status and outcome. Ricarte-Filho et al. (7) reported that in a series of 246 patients with PTC who presented with LNM, the risk for recurrence was best predicted by the number of metastatic lymph nodes.
No patient under age 45 with less than three nodes positive recurred. No patients with FVPTC recurred, and the recurrence rate was higher for TCPTC than CPTC (7). BRAF status alone was not predictive of the risk of recurrence, but the combination of extranodal extension and BRAF+ predicted a higher recurrence rate (7).

In summary, a number of studies, including the current study by Sancisi et al. (8), suggest that the BRAF mutation may not be the initiating event in BRAF+ tumors and may not, independent of histology, predict the risk of aggressive disease. So, based on our current knowledge, how should clinicians use BRAF status to manage their patients? For patients with typical papillary cancer on cytology, genotyping is not needed for diagnosis. For patients with an indeterminate lesion, a positive test for BRAF (obtained as part of a more comprehensive panel because BRAF alone would be insufficiently sensitive) is almost diagnostic of papillary cancer, and those patients should have a total thyroidectomy. At this time, the evidence is insufficient to warrant routine preoperative BRAF testing to determine the extent of surgery or testing of the primary tumor to direct subsequent treatment. The determination of BRAF status and the choice of tyrosine kinase inhibitors or other agents for patients with progressive, iodine-refractory disease remains investigational. More pieces of the puzzle will be needed before we have a clear picture of the place of BRAF status in the management of patients with thyroid cancer.

Acknowledgments

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Disclosure Summary: The author has nothing to declare.

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