

Review Article

***BRAF V600E* mutation in prognostication of papillary thyroid cancer (PTC) recurrence**

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Abstract: Papillary thyroid cancer (PTC) offers excellent prognosis, however relapse risk or persistent disease is related to ~30%. Currently, attention is paid to the possibility of patient group selection of different risk of unfavorable outcome to match a particular therapeutic approach. Therefore, interest in new prognostic and predictive markers known preoperatively is observed. *BRAF V600E* mutation is such a marker. Many studies analyzing the prevalence of the mutation and its relationship with other clinico-pathological risk factors were reported but with controversial conclusions. The prognostic significance of *BRAF* mutation was confirmed by some single centre studies, a few meta-analyses and a large multicenter retrospective international study. They confirmed a correlation between the mutation and the risk of recurrence. The strongest argument against using *BRAF* mutation as an independent prognostic and predictive factor in PTC is its high prevalence (30–80%). At present it seems that *BRAF* mutation is one of the factors influencing the prognosis and it should be analyzed in correlation with other prognostic factors. The most recent ATA recommendations do not indicate a routine application of *BRAF* status for initial risk stratification in differentiated thyroid cancer due to a lack of evident confirmation of a direct influence of mutation on the increase in relapse risk. However, ATA demonstrates the continuous risk scale for the relapse risk assessment, considering *BRAF* and/or *TERT* status. At present, researchers are working on determining the role of *BRAF* mutation in patients from a low-risk group and its correlations with others molecular events. Currently, *BRAF* mutation cannot be used as a single, independent predictive factor. However, its usefulness in the context of other molecular and clinico-pathological risk factors cannot be excluded. They may be used to make modern prognostic scales of relapse risk and be applied to individualized diagnostic and therapeutic strategy for PTC patients.

Keywords: Papillary thyroid cancer (PTC); *BRAF V600E* mutation; cancer recurrence; risk-stratification

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Thyroid cancer as a population problem

The increase in the prevalence of thyroid cancer, which is the most common endocrine carcinoma has been observed within the last three decades. It is estimated

that by 2019 thyroid cancer will have been the third most prevalent malignant tumor in women in the USA (1). This phenomenon is observed worldwide. For instance, the standardized incidence rate in Poland was 4.9 per 100,000 inhabitants whereas in 1990 it was only 1.0 (2).

The fact whether it is a real increase in incidence or the increase in the detection due to the development of more precise diagnostic approaches (sensitive ultrasound, access to fine needle aspiration biopsy) is of lesser significance. As a consequence, the population of newly detected low-advanced thyroid cancers is constantly growing (3). This has one more time resulted in the discussion on optimization of therapeutic strategy. The strategy is related to avoid overtreatment (with unnecessary exposing patients to an increased risk of complications) and undertreatment (i.e., increase in the risk of recurrence and treatment failure) (4-7).

The risk of recurrence in papillary thyroid cancer (PTC)

PTC represents the majority of thyroid carcinomas (~80–90%). It is characterized by excellent prognosis, almost 100% probability of 5-year overall survival (particularly in low-advanced cases). Therefore, in PTC the risk of disease recurrence is most frequently analyzed in relation to the prognosis, i.e., the disease-free survival but not the overall survival unlike in other types of cancers with higher mortality rates (8).

The risk of relapse or persistent disease is related to about 30% of PTC patients and depends, among other things, on the adopted definition of recurrence (8).

The incidence of recurrence depends on whether clinical detection (structural disease) is considered alone or whether it is analyzed together with biochemical recurrence.

From the perspective of a surgeon, structural recurrence seems to be the most significant due to the fact that these patients are most frequently scheduled for surgery. In the context of the therapeutic strategy, the significance of biochemical recurrence cannot be omitted since such patients require a change in routine diagnostic and therapeutic management, e.g., additional treatment with radioactive iodine or increased follow-ups.

Prognostic scales of risk assessment

Currently, much attention is paid to the possibility of patient group selection of different risk of unfavorable outcome in order to match a particular therapeutic approach (8-11).

The issue is not new since for many years different prognostic scales have been employed on the basis of which the risk of relapse and the management are prepared. The TNM staging classification, introduced in 1987 by UICC

and later accepted by AJCC, is the most common system of cancer classification, including thyroid carcinomas. It allowed to select four stages of clinical advancement, depending on the prognosis. In the case of differentiated thyroid carcinomas, the above classification additionally considers the age factor (12) (*Table 1*).

Additionally, some centers individualized their approach to the assessment of prognosis for differentiated thyroid carcinoma by establishing their own prognostic scales, the aim of which is to group patients into adequate risk groups, which allows optimization of treatment modality. The following are the most commonly employed scales: AGES, AMES and MACIS (13-15). All of them consider two major prognostic factors, i.e., age at diagnosis and the presence of distant metastases. Furthermore, the following are analyzed, depending on the scale: tumor size, local advancement, extent of surgery and histological grading (*Table 2*).

All of the scales and the assessment of other histological risk factors (e.g., histological subtype, multifocality, angioinvasion, thyroid capsule infiltration) are possible after obtaining the results of postoperative histological examination. Consequently, they do not offer the possibility for planning the extent of surgery and only allow to establish the adjuvant treatment, e.g., 131-iodine therapy.

Therefore, interest in new prognostic and predictive markers known preoperatively has been observed recently. *BRAF V600E* mutation is an example of such a marker (16).

BRAF mutation—one of the most frequent events in the pathogenesis of PTC

The beginning of 2000 marked the interest in *BRAF* gene mutation in thyroid cancer. At that time studies on the role of the mutation in other cancers (e.g., melanoma, colon cancer) had been already known (15). *BRAF* gene is localized on chromosome 7.

It codes cytoplasmic serine/threonine kinase which influences the activation of mitogen-activated pathway kinases (MAPK). *BRAF* gene mutations activate the MAPK pathway resulting in the intensity of cellular proliferation, inhibition of differentiation and apoptosis. In other words, they lead to a loss of control over the cellular cycle, initiating the development of malignancy as a result. *BRAF* mutation is one of the most prevalent molecular events in the pathogenesis of PTC in adults (16). Point mutation T1799A is the most common and the most examined mutation of all *BRAF* gene mutations. It results in the exchanging valine to glutamate at residue 600 near the

Table 1 Staging system (TNM classification for differentiated cancers) (12)

Stage	T feature (tumor)	N feature (lymph node metastases)	M feature (distant metastases)
Age <45 years of age			
Stage I	Each T	Each N	M0
Stage II	Each T	Each N	M1
Age >45 years of age			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3; T1–T3	N0; N1a	M0; M0
Stage IV			
IVa	T4a; T1–T3	N0 or N1a; N1b	M0; M0
IVb	T4b	Each N	M0
IVc	Each T	Each N	M1

T1, tumor of up to 2 cm in diameter (largest dimension), limited to the thyroid; T2, tumor of 2–4 cm diameter (largest dimension), limited to the thyroid; T3, tumor >4 cm (largest dimension), limited to the thyroid or the tumor minimally invasive, e.g., infiltration of the strap muscle or infiltration of the perithyroid tissue; T4a, tumor of any size infiltrating the subcutaneous tissue, larynx, trachea, esophagus or recurrent laryngeal nerve; T4b, tumor of any size infiltrating prevertebral fascia, carotid artery, mediastinal vessels; N1a, metastases to cervical lymph nodes of the central system; N1b, metastases to lateral cervical lymph nodes; M1, distant metastases; N0 or M0, no corresponding metastases.

Table 2 The most commonly applied prognostic scales in papillary differentiated carcinomas

AGES scale	MACIS scale	AMES scale
Algorithm: $PS = 0.05 \times \text{age in years}$ (patients <40 years of age =0), +1 for G2 or +2 for G3 or G4, +1 if extracapsular invasion, +3 if distant metastases, +0.2× tumor size (diameter of cancer in cm)	Algorithm: $PS = 3.1 \times (\text{age} < 39 \text{ years})$ or $0.08 \times (\text{age} > 40 \text{ years})$, +0.3× tumor size in cm, +1 if partial thyroidectomy was done, +1 if cancer is locally advanced, +3 if distant metastases	Assessment of age and sex, the presence of distant metastases, local advancement, extrathyroidal extension, size tumor in cm
Risk groups depending on the calculated risk rate of PS: I, 0–3.99; II, 4–4.99; III, 5–5.99; IV >6	Risk groups depending on the calculated risk rate of PS: I, 0–5.99; II, 6–6.99; III, 7–7.99; IV >8	Risk group I—low risk: men <41 years of age, women <51, no distant metastases, cancer limited to the thyroid, tumor diameter <5 cm; risk group II—high risk: men >40 years of age, women >50, distant metastases, extracapsular extension, tumor diameter >5 cm

PS, prognostic score.

catalytic center of the protein (*BRAF V600E* mutation). Finding this mutation is possible not only in postoperative material but also, which is more significant, in fine needle aspiration biopsy material and may be known at diagnosis of PTC (17,18).

The relationship of *BRAF* mutation with other clinico-pathological risk factors

The first reports on the significance of *BRAF* mutation

in the pathogenesis of PTC (19–23) were noted in 2003. Further studies focused on searching the relationship between the mutation and other features of an unfavorable course of the disease (22–31). As early as in 2003 Nikiforova *et al.* (23) paid attention to the relationship between *BRAF* mutation and advanced age of patients and also histological subtypes of cancer (classic and tall cell PTC, extracapsular extension and a frequent incidence in patients in III and IV stages. The authors also indicated a more prevalent presence of the mutation in low-differentiated and

Table 3 Correlation of *BRAF* mutation with selected clinico-pathological prognostic factors in selected publications (24-33)

Author	Type of analysis	Number of <i>BRAF</i> (+) [%]	Age	Sex	Extrathyroidal, extension	Lymph node metastases	Distant metastases
Rosenbaum <i>et al.</i> (24)	Univariate	54 [65]	0.0001	–	–	–	–
Kim <i>et al.</i> (25)	Univariate; multivariate	149 [73]	NS	0.0060; 0.0400	0.0600; 0.0050	NS; 0.0200	–
Kebebew <i>et al.</i> (26)	Univariate	133 [49]	0.0300	NS	NS	NS	NS
Lupi <i>et al.</i> (27)	Univariate; multivariate	217 [44]	NS	NS	0.0001; NS	0.0009; NS	–
Elisei <i>et al.</i> (28)	Univariate	38 [37]	0.0200	NS	NS	NS	NS
Costa <i>et al.</i> (29)	Univariate	27 [55]	NS	–	NS	–	NS
Wang <i>et al.</i> (30)	Univariate; multivariate	54 [50]	0.0200	NS	0.0200; 0.0050	–	–
Frasca <i>et al.</i> (31)	Univariate; multivariate	125 [39]	–	–	0.0001; 0.0003	0.0001; 0.0070	–
Ito <i>et al.</i> (32)	Univariate; multivariate	242 [38]	0.0500	NS	NS	0.0050; 0.0001	NS
Guan <i>et al.</i> (33)	Univariate	639 [62]	NS	NS	0.0030	0.0050	NS

NS, non-statistical significance; –, non-analyzed.

anaplastic cancers, which suggested the possibility for the mutation to be related to undifferentiation of PTC, which may result in a less favorable prognosis. Other observations were noted in the following years. A number of studies from single centers were reported, which analyzed the prevalence of the mutation and its relationship with other clinico-pathological risk factors (24-33). However, the studies resulted in different, often conflicting results, which were related to differences in methodology, i.e., group selection, group size, time of the follow-up and the type of statistical analyses (uni- and/or multi-variable), the differences in *BRAF* mutation occurrence in different populations, the methodology of *BRAF* identification and also lack of the results of validations. Interestingly, initially none of the studies demonstrated the relationship of the mutation with the presence of distant metastases, i.e., the relationship with the strongest factor of an unfavorable prognosis in PTC, most probably due to rare occurrence of metastases (24-33) (Table 3).

Only in a few studies a relationship between the presence of the mutation and the decrease in disease-free survival was observed (26,28,34). Elisei *et al.* in 2008 demonstrated the relationship between the presence of *BRAF* mutation and a decrease in overall and disease-free survival in a group of 102 patients with the mean follow-up of 10 years or longer (28). That study strongly indicated *BRAF* mutation as an independent, unfavorable prognostic factor in PTC.

Due to a silent biology of PTC and the generally favorable clinical course of this cancer, it is necessary to analyze groups large in size with a long follow-up to observe

any significant differences between them. Consequently, no objective prospective, randomized clinical trials were conducted in the past, which could have been the basis for an evidence-based medicine.

Meta-analyses assessing the prognostic significance of *BRAF* mutation

Four meta-analyses were conducted due to the lack of possibility to run prospective studies for the objective assessment of prognostic significance of *BRAF* mutation.

In 2007 Lee *et al.* (35) analyzed 12 papers confirming the relationship between *BRAF* mutation and the extent of clinical advancement, extrathyroid extension and a histological sub-type. Five years later Li *et al.* analyzed 32 studies and additionally demonstrated the coexistence of the mutation with the presence of lymph node (LN) metastases, more advanced age and the male sex (36). However, in these papers the relationship between the mutation and the prognosis was not analyzed. Such a study was done by Kim *et al.* (37). Based on 27 papers these authors also confirmed the relationship between the mutation and extrathyroid extension, LN metastases and the diagnosis of more advanced cancer (according to the TNM). However, in eight papers the relationship between the mutation and a higher risk of persistent disease or recurrence was also confirmed [patients with the mutation had 2.14-fold increased risk of recurrent and persistent disease (95% CI, 1.67–2.74)].

Another meta-analysis by Tufano *et al.* assessed the

correlation between *BRAF* mutation and recurrence or persistent disease (38). It analyzed 14 papers (the number of patients assessed from 9 countries was 2,470 in total). The authors considered only the reports which discussed the relationship between the recurrence rate and *BRAF* mutation and other classic clinico-pathological factors (e.g., LN metastases, extrathyroid extension, and more advanced disease; III and IV stages; AJCC). That study confirmed a significantly higher risk of relapse in a group of patients with confirmed *BRAF* mutation [*BRAF* (+)] as compared to a group of patients with *BRAF* wild type [*BRAF* (-)] (24.9% vs. 12.6%; $P < 0.00001$). However, in the papers included in this analysis, the risk of relapse ranged significantly, i.e., for *BRAF* (+) patients from 11–40% (mean 26.5%) and for *BRAF* (-) patients from 2–36% (mean 9.5%).

The results of a multicenter retrospective study of the relationship of *BRAF* mutation with the prognosis

Xing designed and coordinated a large retrospective international multicentre study to eliminate limitations of meta-analyses for the assessment of the relationship of *BRAF* mutations with the prognosis in PTC.

The analysis of the relationship of the mutation and the risk of death

The first stage included the assessment of the relationship of *BRAF* mutation with the risk of death in PTC patients. Xing *et al.* analyzed 1,849 patients treated in 13 centers in seven countries with the mean follow-up of 33 months (39).

The mortality in these patients was 3% (56/1,849). The mortality rate was significantly lower in patients with *BRAF* mutation ($P < 0.001$), 45 deaths (5.3%) were reported in a group of *BRAF* (+) patients and only 11 (1.1%) in a group of *BRAF* (-) patients. The overall survival was lower in patients in whom the mutation was present. The additional analysis of the overall survival depending on the presence of the mutation and LN metastases demonstrated that *BRAF* (+) patients with LN metastases constituted the group with the most unfavorable prognosis. The assessment of interactions between *BRAF* mutation and other risk factors such as LN metastases, distant metastases, age of patients, extrathyroid extension and IV stage of clinical involvement demonstrated a strong relationship between the mutation and each of the above factors except for extrathyroid extension. However, in the multivariate analysis after adding the features of

unfavorable disease course such as age, sex, extrathyroid extension, LN metastases or distant metastases, the relationship between *BRAF* and mortality lost a statistical significance, probably due to a low incidence of deaths.

The analysis of the relationship of the mutation with the risk of recurrence

The next stage was based on the assessment of the relationship between *BRAF* mutation and the risk of recurrence. Two thousand ninety nine patients from 16 centers and eight countries with the mean follow-up of 36 months were enrolled in the analysis (40). Recurrence was defined altogether as local recurrence, distance recurrence and persistent disease. *BRAF* mutation was done on postoperative material therefore its status did not have an influence on the treatment applied. Disease recurrence was noted in 16.1% of patients. Recurrence was more frequent in patients with the mutation (20.9%) as compared to *BRAF* (-) patients (11.6%) ($P = 0.000$). A higher risk of relapse was typical of *BRAF* (+) patients. The relationship was observed also in the multivariable analysis which considered age, sex, the center from which patients came from, tumor size, extrathyroid extension, LN metastases, multifocality and a histological subtype of the cancer. Disease-free survival was significantly lower in patients with PTC in whom the mutation was diagnosed (log-rank, 28.1; $P < 0.01$). This relationship was also observed in the classic subtype and in follicular subtype of PTC. Additionally, the worst disease-free survival was noted in *BRAF* (+) patients in whom LN metastases were diagnosed (log-rank, 143.6; $P < 0.001$). A similar observation was related to the coexistence of the mutation with extracapsular infiltration and with the age of patients (>60 years of age) (log-rank, 68.9; $P < 0.001$).

The relationship of *BRAF* mutation with a higher risk of relapse was also confirmed in low-risk patients (I and II AJCC stages and in microcarcinoma). The study demonstrated that *BRAF* mutation was an independent unfavorable prognostic factor related to a higher risk of recurrence.

Critical remarks concerning a multicentre retrospective analysis of the relationship between the mutation and disease recurrence

These observations, however, did not dispel the controversy concerning prognostic and predictive significance of *BRAF*

mutation in PTC. After publishing the results of the analysis, the discussion in *Journal of Clinical Oncology* on the real relationship between the mutation and the cancer relapse was initiated. Bal *et al.* (41) argued that inaccurate definition of recurrence was used and the definition was applied also for persistent disease. The accusations were also related to a short median follow-up (36 months) and a relatively high incidence of recurrence. These accusations are not fully legitimate (42). In PTC persistent disease is commonly linked with the real recurrence due to the fact that routine follow-ups occur every 6 or 12 months and it is not possible to fully differentiate recurrence from persistent disease as defined in the classic oncological definition. Recurrence is the symptom occurrence after complete remission lasting up to 6 months after the end of treatment.

The majority of relapses occur in the first years of the follow-up, therefore a 3-year follow-up may be considered sufficient, and the reported percentage of recurrence (16%) is within the range given by other authors (9,42).

Furthermore, Yarchoan *et al.* appreciated the value of the studies of Xing *et al.* as the largest multicenter retrospective study on prognostic significance of *BRAF* mutation (43).

These authors argue that current knowledge does not offer enough evidence on the application of *BRAF* status to the clinical practice. The authors stressed that it may unnecessarily result in anxiety among patients since the significance of *BRAF* for an unfavorable prognosis is still not strong enough. However, Yarchoan *et al.* argues that patients from low-risk groups may gain some benefit due to the knowledge on *BRAF* status (43). It is probable that patients classified into a low-risk group based on the classic prognostic factors and *BRAF* (-) could be treated conservatively, which is consistent with a current international trend.

Disease recurrence and LN metastases

LN metastases are the most common cause of disease recurrence in PTC. The possibility of a preoperative assessment of the risk of LN metastases would be significant for a surgeon. As a result, patients might be properly qualified for central lymphadenectomy to avoid this prophylactic procedure and an unnecessary increase in incidence risk of postoperative complications (44,45).

The attempt was made to use *BRAF* mutation in predicting the risk of metastases to cervical LNs (46). Based on uni- and multivariable analyses Joo *et al.* confirmed the relationship between the mutation and a higher risk of

metastases to the central LNs, suggesting that prophylactic central neck dissection should be based on the assessment of *BRAF* mutation diagnosed in the fine needle aspiration (5). Howell *et al.* presented similar conclusions and their study confirmed the relationship between *BRAF* mutation and a risk of metastases to the central LNs (47). These authors expressed the opinion according to which preoperative assessment of *BRAF* mutation may be used to plan the extent of surgical treatment.

Xing *et al.* in the multicenter study also confirmed a correlation between the mutation and the risk of LN metastases and a higher risk of recurrence (40). However, some studies did not confirm the presence of such a relationship (7,48,49).

The observed divergence is obviously related to a retrospective nature of the analyses, different group selection (different group size) and different time of follow-up.

It is obvious that well designed prospective study could solve the existing controversies.

Sadly, performing such a study does not seem to be real. Carling *et al.* assessed that it would be necessary to enroll almost 6,000 patients in the prospective analysis in order to demonstrate the benefit of prophylactic central lymphadenectomy (50).

A critical approach to the practical application of the analysis of BRAF mutation as an independent molecular prognostic and predictive factor

The strongest argument against using *BRAF* mutation analysis as an independent prognostic and predictive risk factor in patients with PTC is its high prevalence (30–80%) whereas the risk of persistent disease or recurrence is related to about 30% of population (depending on the adopted definition of recurrence).

At present, it seems that *BRAF* mutation is one of the factors influencing the prognosis and it should be analyzed in correlation with other prognostic factors (51).

The most recent revision of ATA recommendations [2015] is also related to it.

Despite the fact that previously Prescott *et al.* demonstrated that adding *BRAF* status to different commonly applied risk scales (AGES, AMES, MACIS, TNM and 2009 ATA initial risk stratification system) improves the possibility of the proper patient classification (52). It allows for a better prediction related to the risk of relapse. The 5-year cumulative recurrence incidence observed by these authors was 20% in *BRAF* (+) *vs.*

2015 ATA Modified Initial Risk Stratification System	
The tree-tiered risk system	The continuum risk system
<p>High risk: Gross extrathyroidal extension Incomplete tumor resection, distant metastases, or lymph node >3 cm</p> <p>Intermediate risk: Aggressive histology, minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2–3 cm)</p> <p>Low risk: Intrathyroidal DTC 5 ≤ lymph node micrometastases (<0.2 cm)</p>	<p>The highest risk ↓</p> <p>FTC, extensive vascular invasion (~30–50%) pT4a gross ETE (~30–40%) pN1 with extranodal ext. >3 LN involved (~40%) PTC >1 cm, TERT mut. ± BRAF mut. (>40%) pN1, any LN >3 cm (~30%) PTC, extrathyroidal, BRAF mut. (~10–40%) PTC, vascular invasion (~15–30%) Clinical N1 (~20%) pN1, >5 LN involved (~20%) Intrathyroidal PTC, <4 cm, BRAF mut. (~10%) pT3 minor ETE (~3–8%) pN1, ≤5 LN involved (~5%) pN1, all LN <0.2 cm (~5%) Intrathyroidal PTC 2–4 cm (~5%) Multifocal PTMC (~4–6%) pN1 without extranodal extension, ≤3 LN involved (2%) Minimally invasive FTC (~2–3%) Intrathyroidal, <4 cm, BRAF wt. (~1–2%) Intrathyroidal unifocal PTMC, BRAF mut. (~1–2%) Intrathyroidal, encapsulated, FV-PTC (~1–2%) Unifocal PTMC (~1–2%)</p> <p>The lowest risk ↑</p>

Figure 1 The risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy (according to ATA 2015). The risk of structural disease recurrence associated with selected clinico-pathological features are shown as a continuum of risk with percentage (ranges, approximate values). In the left column, the three-tiered risk system proposed as the modified initial risk stratification system is shown. While analysis of *BRAF* and/or *TERT* status is not routinely recommended for initial risk stratification 2015 ATA recommendations included these findings to assist clinicians in proper risk stratification in cases where this information is available (53). FTC, follicular thyroid carcinoma; PTC, papillary thyroid cancer; FV, follicular variant; PTMC, papillary thyroid microcarcinoma; LN, lymph node; ETE, extrathyroidal extension; mut., mutated; wt., wild type.

8% in *BRAF* (-) patients. *BRAF* was associated with the time to recurrence when it was added to the following risk-scales: AMES—HR 2.43, MACIS—HR 2.46, TNM—HR 2.51, ATA recurrence risk category—HR 2.44.

Due to a lack of evident confirmation of a direct influence of mutation on the increase in relapse risk, ATA most recent recommendations do not indicate a routine application of *BRAF* status for initial risk stratification in differentiated thyroid cancer. However, due to the fact that a clinician may possess such knowledge, ATA demonstrates the continuous risk scale for the assessment of the risk of relapse, considering *BRAF* and/or *TERT* status (Figure 1) (53).

Future perspectives and research directions

Currently, researchers are working on determining the role

of *BRAF* mutation in the relapse risk assessment in patients from a low-risk group as indicated by the ATA scale.

Elisei *et al.* (54) initiated such studies and observed only 3% of structural relapse in patients with thyroid limited carcinoma (T1–T2N0M0). However, in the case of *BRAF* (+) carcinoma, the recurrence rate was 8% as compared to the population of *BRAF* (-) 1% (P=0.0003). In the multivariable analysis only *BRAF* mutation was a predictive factor of persistent disease in a 5-year follow-up. If these observations were confirmed by other studies, the analysis of *BRAF* mutation for patients with carcinoma limited to the thyroid could result in better selection of low and intermediate risk groups, as suggested by Yarchoan *et al.* (43).

Recent reports suggest that tumors in which *BRAF* mutation coexists with other mutations such as *TERT*, *PIK3CA* and/or *TP53* may be characterized by more

aggressive clinical course. It is believed that more accurate tumor prognostication is possible due to a genetic analysis (55-58).

Studies on the formation of sensitive and specific molecular classifiers are being conducted. Such classifiers might help in better assessment of the risk of relapse. Additionally, they might be valuable in the assessment of an unfavorable course of the disease and might be useful in personalized therapeutic strategy. Currently, it seems that the analysis of molecular factors will be one of the major research trends in the following years (59-62).

Summary

The opinion of Puxeddu according to which we cannot use the analysis of *BRAF* mutation as a single, independent predictive factor in clinical practice seems to be the correct approach (63). However, its usefulness in the context of other molecular and clinico-pathological risk factors cannot be excluded. In the future they may be used to make modern prognostic scales of relapse risk and, as a result, may be applied to plan individual optimal diagnostic and therapeutic strategy for patients with PTC, which is consistent with the most recent ATA recommendations.

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Footnote

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References

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* 2014;140:317-22.
2. Wojciechowska U, Didkowska J, Zatoński W. Cancer in Poland in 2012. Available online: <http://onkologia.org.pl/wp-content/uploads/Rok2012.pdf>
3. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. *Cancer Epidemiol Biomarkers Prev* 2013;22:1252-9.
4. Pelizzo MR, Dobrinja C, Casal Ide E, et al. The role of BRAF(V600E) mutation as poor prognostic factor for the outcome of patients with intrathyroid papillary thyroid carcinoma. *Biomed Pharmacother* 2014;68:413-7.
5. Joo JY, Park JY, Yoon YH, et al. Prediction of occult central lymph node metastasis in papillary thyroid carcinoma by preoperative BRAF analysis using fine-needle aspiration biopsy: a prospective study. *J Clin Endocrinol Metab* 2012;97:3996-4003.
6. Xing M. BRAF mutation in papillary thyroid microcarcinoma: the promise of better risk management. *Ann Surg Oncol* 2009;16:801-3.
7. Danilovic DL, Lima EU, Domingues RB, et al. Pre-operative role of BRAF in the guidance of the surgical approach and prognosis of differentiated thyroid carcinoma. *Eur J Endocrinol* 2014;170:619-25.
8. Omry-Orbach G. Risk Stratification in Differentiated Thyroid Cancer: An Ongoing Process. *Rambam Maimonides Med J* 2016;7.
9. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid* 2010;20:1341-9.
10. Malandrino P, Latina A, Marescalco S, et al. Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin. *J Clin Endocrinol Metab* 2011;96:1703-9.
11. Krajewska J, Jarzab M, Czarniecka A, et al. Ongoing risk stratification for differentiated thyroid cancer (DTC) - stimulated serum thyroglobulin (Tg) before radioiodine (RAI) ablation, the most potent risk factor of cancer recurrence in M0 patients. *Endokrynol Pol* 2016;67:2-11.
12. Edge SB, Byrd DR, Compton CC, et al. editors. *AJCC cancer staging manual*. 7th ed. New York: Springer, 2010.
13. Cady B. Hayes Martin Lecture. Our AMES is true: how an old concept still hits the mark: or, risk group assignment points the arrow to rational therapy

- selection in differentiated thyroid cancer. *Am J Surg* 1997;174:462-8.
14. Fraker DL, Skarulis MC, LiVolsi VA. Cancer of endocrine system. Thyroid tumors. In: DeVita VT Jr, Hellman S, Rosenberg SA. Editors. *Cancer. Principles and practice of oncology*. Philadelphia: J.B. Lippincott, 2001.
 15. Handkiewicz-Junak D, Czarniecka A, Jarzab B. Molecular prognostic markers in papillary and follicular thyroid cancer: Current status and future directions. *Mol Cell Endocrinol* 2010;322:8-28.
 16. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr Rev* 2007;28:742-62.
 17. Nam JK, Jung CK, Song BJ, et al. Is the BRAF(V600E) mutation useful as a predictor of preoperative risk in papillary thyroid cancer? *Am J Surg* 2012;203:436-41.
 18. Xing M, Clark D, Guan H, et al. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J Clin Oncol* 2009;27:2977-82.
 19. Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinoma. *J Natl Cancer Inst* 2003;95:625-7.
 20. Soares P, Trovisco V, Rocha AS, et al. BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. *Oncogene* 2003;22:4578-80.
 21. Xu X, Quiros RM, Gattuso P, et al. High prevalence of BRAF gene mutation in papillary thyroid carcinomas and thyroid tumor cell lines. *Cancer Res* 2003;63:4561-7.
 22. Fukushima T, Suzuki S, Mashiko M, et al. BRAF mutations in papillary carcinomas of the thyroid. *Oncogene* 2003;22:6455-7.
 23. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. *J Clin Endocrinol Metab* 2003;88:5399-404.
 24. Rosenbaum E, Hosler G, Zahurak M, et al. Mutational activation of BRAF is not a major event in sporadic childhood papillary thyroid carcinoma. *Mod Pathol* 2005;18:898-902.
 25. Kim TY, Kim WB, Rhee YS, et al. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. *Clin Endocrinol (Oxf)* 2006;65:364-8.
 26. Kebebew E, Weng J, Bauer J, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. *Ann Surg* 2007;246:466-70; discussion 470-1.
 27. Lupi C, Giannini R, Ugolini C, et al. Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2007;92:4085-90.
 28. Elisei R, Ugolini C, Viola D, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. *J Clin Endocrinol Metab* 2008;93:3943-9.
 29. Costa AM, Herrero A, Fresno MF, et al. BRAF mutation associated with other genetic events identifies a subset of aggressive papillary thyroid carcinoma. *Clin Endocrinol (Oxf)* 2008;68:618-34.
 30. Wang Y, Ji M, Wang W, et al. Association of the T1799A BRAF mutation with tumor extrathyroidal invasion, higher peripheral platelet counts, and over-expression of platelet-derived growth factor-B in papillary thyroid cancer. *Endocr Relat Cancer* 2008;15:183-90.
 31. Frasca F, Nucera C, Pellegriti G, et al. BRAF(V600E) mutation and the biology of papillary thyroid cancer. *Endocr Relat Cancer* 2008;15:191-205.
 32. Ito Y, Yoshida H, Maruo R, et al. 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. *Endocr J* 2009;56:89-97.
 33. Guan H, Ji M, Bao R, et al. Association of high iodine intake with the T1799A BRAF mutation in papillary thyroid cancer. *J Clin Endocrinol Metab* 2009;94:1612-7.
 34. Fugazzola L, Mannavola D, Cirello V, et al. BRAF mutations in an Italian cohort of thyroid cancers. *Clin Endocrinol (Oxf)* 2004;61:239-43.
 35. Lee JH, Lee ES, Kim YS. Clinicopathologic significance of BRAF V600E mutation in papillary carcinomas of the thyroid: a meta-analysis. *Cancer* 2007;110:38-46.
 36. Li C, Lee KC, Schneider EB, et al. BRAF V600E mutation and its association with clinicopathological features of papillary thyroid cancer: a meta-analysis. *J Clin Endocrinol Metab* 2012;97:4559-70.
 37. Kim TH, Park YJ, Lim JA, et al. The association of the BRAF(V600E) mutation with prognostic factors and poor clinical outcome in papillary thyroid cancer: a meta-analysis. *Cancer* 2012;118:1764-73.
 38. Tufano RP, Teixeira GV, Bishop J, et al. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. *Medicine (Baltimore)* 2012;91:274-86.
 39. Xing M, Alzahrani AS, Carson KA, et al. Association

- between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. *JAMA* 2013;309:1493-501.
40. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. *J Clin Oncol* 2015;33:42-50.
 41. Bal C, Ballal S. Is There Any True Association Between BRAF V600E Mutation and Recurrence, Particularly in Low-Risk, Papillary Thyroid Cancer? *J Clin Oncol* 2015;33:2481.
 42. Xing M. Reply to C. Bal et al. *J Clin Oncol* 2015;33:2483-4.
 43. Yarchoan M, LiVolsi VA, Brose MS. BRAF mutation and thyroid cancer recurrence. *J Clin Oncol* 2015;33:7-8.
 44. Czarniecka A, Jarzab M, Krajewska J, et al. Prognostic value of lymph node metastases of differentiated thyroid cancer (DTC) according to the local advancement and range of surgical excision. *Thyroid Res* 2010;3:8.
 45. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid* 2012;22:1144-52.
 46. Alzahrani AS, Xing M. Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND. *Endocr Relat Cancer* 2013;20:13-22.
 47. Howell GM, Nikiforova MN, Carty SE, et al. BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer. *Ann Surg Oncol* 2013;20:47-52.
 48. Niederer-Wüst SM, Jochum W, Förbs D, et al. Impact of clinical risk scores and BRAF V600E mutation status on outcome in papillary thyroid cancer. *Surgery* 2015;157:119-25.
 49. Chakraborty A, Narkar A, Mukhopadhyaya R, et al. BRAF V600E mutation in papillary thyroid carcinoma: significant association with node metastases and extra thyroidal invasion. *Endocr Pathol* 2012;23:83-93.
 50. Carling T, Carty SE, Ciarleglio MM, et al. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. *Thyroid* 2012;22:237-44.
 51. Czarniecka A, Kowal M, Rusinek D, et al. The Risk of Relapse in Papillary Thyroid Cancer (PTC) in the Context of BRAFV600E Mutation Status and Other Prognostic Factors. *PLoS One* 2015;10:e0132821.
 52. Prescott JD, Sadow PM, Hodin RA, et al. BRAF V600E status adds incremental value to current risk classification systems in predicting papillary thyroid carcinoma recurrence. *Surgery* 2012;152:984-90.
 53. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1-133.
 54. Elisei R, Viola D, Torregrossa L, et al. The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. *J Clin Endocrinol Metab* 2012;97:4390-8.
 55. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol* 2014;32:2718-26.
 56. Huang Y, Liao D, Pan L, et al. Expressions of miRNAs in papillary thyroid carcinoma and their associations with the BRAFV600E mutation. *Eur J Endocrinol* 2013;168:675-81.
 57. Song YS, Lim JA, Choi H, et al. Prognostic effects of TERT promoter mutations are enhanced by coexistence with BRAF or RAS mutations and strengthen the risk prediction by the ATA or TNM staging system in differentiated thyroid cancer patients. *Cancer* 2016;122:1370-9.
 58. Lee SE, Hwang TS, Choi YL, et al. Prognostic Significance of TERT Promoter Mutations in Papillary Thyroid Carcinomas in a BRAF(V600E) Mutation-Prevalent Population. *Thyroid* 2016;26:901-10.
 59. Wu JX, Young S, Hung ML, et al. Clinical Factors Influencing the Performance of Gene Expression Classifier Testing in Indeterminate Thyroid Nodules. *Thyroid* 2016;26:916-22.
 60. Kloos RT, Barth NM. Gene Expression Classifier Testing and the Surgical Decision-Making Process for Patients With Thyroid Nodules. *JAMA Otolaryngol Head Neck Surg* 2016;142:806-7.
 61. Scott E, Learoyd D, Clifton-Bligh RJ. Therapeutic options in papillary thyroid carcinoma: current guidelines and future perspectives. *Future Oncol* 2016. [Epub ahead of print].

62. Wylie D, Beaudenon-Huibregtse S, Haynes BC, et al. Molecular classification of thyroid lesions by combined testing for miRNA gene expression and somatic gene alterations. *J Pathol Clin Res* 2016;2:93-103.
63. Puxeddu E, Filetti S. BRAF mutation assessment in papillary thyroid cancer: are we ready to use it in clinical practice? *Endocrine* 2014;45:341-3.

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