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Molecular alteration patterns predict tumor behavior in papillary thyroid carcinoma independent of tumor size: insights from an international multicenter retrospective study

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Abstract

Background Molecular testing is a well-established tool that assists in the management of thyroid nodules and allows classification in distinct molecular alteration patterns: *BRAF*-like, *RAS*-like and non-*BRAF*-non-*RAS* (NBNR). Yet classical TNM classification and ATA guidelines currently rely on tumor size for risk stratification. In this study, we compared tumor behavior according to molecular alteration patterns versus tumor size.

Methods Retrospective multicenter multinational study of thyroid nodules that underwent preoperative molecular profiling with *ThyGenX/ThyGeNEXT* or *ThyroSeq V3* between 2015 and 2022.

Clinical characteristics, including demographics, cytology results, tumor size, surgical pathology, and molecular alterations, were analyzed.

Results The study included 718 patients who underwent surgery for papillary thyroid cancer, with a majority of 556 (77.4%) being female. The distribution of molecular alteration patterns was as follows: BRAF-like in 227 (31.6%), RAS-like in 171 (23.8%), NBNR in 59 (8.2%), BRAF/RAS overlap 8 (1.1%) and no detectable mutation in 224 (31.2%) cases. The median tumor size was 15 mm (IQR 10–24). Extrathyroidal extension (ETE) was observed in 6.2% of cases with gross ETE and 5.6% with minimal ETE. Notably, nodules with BRAF-like molecular alterations were more likely to exhibit ETE compared to those with RAS-like or NBNR alterations ($P < 0.001$). There was no significant correlation between ETE and median tumor size ($P > 0.05$).

Conclusion Molecular testing of thyroid nodules provides a more accurate prediction of tumor behavior compared to tumor size alone. These findings suggest that future staging systems could benefit from incorporating molecular alteration patterns into their algorithms.

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Highlights

- Retrospective multinational study on molecular profiling in thyroid cancer.
- Vast majority of patients had T1 and T2 tumors (less than 4cm).
- Nodules with *BRAF*-like alterations were more commonly associated with extrathyroideal extension and nodal metastasis.
- Tumor size alone was not a predictor of extrathyroideal extension and/or nodal metastasis.
- Molecular profiling may be a better predictor of tumor behaviour than tumor size, at least in tumors less than 4cm.

Keywords Thyroid Nodule, Thyroid Neoplasms, Molecular alteration, Radiation Exposure

Introduction

The importance of molecular profiling is increasingly recognized in the management of differentiated and advanced thyroid cancer [1–6]. Seminal molecular studies such as the TCGA have established three main phenotypes in follicular-derived cancer including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC): the *BRAF*-like tumors, *RAS*-like tumors, and non-*BRAF*-non-*RAS* tumors (NBNR) [7–9]. As shown earlier by our group [1, 9], *BRAF*-like molecular alterations are typically found in Bethesda V and VI nodules. Upon finally histology, they are typically associated with classical type PTC and the tall cell variant of PTC, frequent involvement of lymph nodes, higher recurrence rate, and the loss of the sodium-iodine symporter, and thus resistance to radioactive iodine [2, 9]. *RAS*-like molecular alterations are found more commonly in Bethesda III and IV nodules, are associated with more indolent upon final histology, including the follicular variant of PTC (FVPTC) and the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (formerly known as encapsulated non-invasive FVPTC) and are also found in follicular neoplasms such as follicular adenoma and carcinoma. They show infrequent nodal disease and recurrence [9–11]. NBNR tumors are a distinct novel group of thyroid tumors, often with oncocytic features, and harboring molecular alterations such as *DICER1*, *EZH1*, *EIF1AX*, *PTEN*, *THADA* fusion, and/or *PAX8/PPARg* [9, 12]. In a recent study by our group [1], NBNR molecular alterations were more commonly found in Bethesda III and IV nodules and were less likely to show extrathyroidal extension, nodal disease and/or aggressive subtypes of PTC. However, they were rarely but significantly associated with poorly differentiated thyroid carcinoma (PDTC).

Although molecular testing-based classification into a distinct molecular profile pattern allows for the prediction of tumor behavior, traditional staging systems still use tumor size as a main prognosticator [13–17]. Our group and others, however, reported the relative importance of mutational profile over tumor size alone for prediction of tumor behavior, especially in tumors less than 4 cm [5, 18].

This has substantial clinical implications since the classical TNM classification and current American Thyroid Association (ATA) guidelines mainly on tumor size for risk stratification [19, 20]. Therefore, we performed an international multicenter retrospective study examining the relationship between molecular profile pattern (*BRAF*-like tumors, *RAS*-like tumors, and non-*BRAF*-non-*RAS* tumors (NBNR)), tumor size (maximal dimension) and surrogate markers of aggressiveness such as nodal yield and extrathyroidal extension.

Materials and methods

This study was conducted and reported according to the Equator Guidelines, specifically, according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [21].

Study population

We conducted a retrospective multi-institutional multinational cohort study of consecutive patients with thyroid nodules treated at the Sir Mortimer B. Davis-Jewish General Hospital (JGH) and Royal Victoria Hospital (RVH), McGill University, Montreal, QC, Canada, and the Sheba Medical Center (SMC), affiliated with Tel-Aviv University, Tel-Aviv, Israel, between January 1st, 2015 and June 1st, 2022. The study was approved by the local Research Ethics Committee (protocol number 2023–3312). Ethical guidelines were followed. Relevant clinicopathologic data was extracted and the data was handled in a coded fashion. Eligibility criteria included: previously untreated patients who were over 18 years of age when diagnosed with thyroid nodules that underwent a fine needle aspiration biopsy (FNAB). Indication for FNAB was done according to the TIRADS guidelines [22]. In patients with Bethesda III and IV nodules, discussion with the patient was carried out to do watchful waiting, molecular testing, or diagnostic lobectomy, according to the ATA guidelines [19]. For patients with Bethesda V

and VI, molecular testing was done as clinically indicated. Specifically, molecular testing was suggested for patients with small tumors for which a hemithyroidectomy may have been sufficient in case of indolent tumors, but for which a total thyroidectomy (respectively a completion thyroidectomy) might have been necessary in case of an aggressive phenotype. At the time of the study, molecular testing was not covered by health insurance, therefore was paid by the patients. Only patients who had Bethesda III, IV, V, VI nodules, underwent molecular testing, and had subsequent surgery were included in this study. The definitive surgical pathology was used as a gold standard for the conclusive histological diagnosis. We included only cases for which final pathology revealed a papillary thyroid cancer. Patients with benign histology (follicular adenoma e.g.), follicular cancer, medullary thyroid cancer, poorly differentiated thyroid cancer and/or anaplastic carcinoma were excluded. All surgical pathologies were reviewed by a dedicated thyroid pathologist.

Molecular testing

Different types of validated molecular tests were used pre-operatively: *ThyGenX*/*ThyGeNEXT or ThyroSeq V3* [23–26]. The choice to perform a molecular test and the type of test was determined by the patient following a discussion with the physician. Molecular testing was only performed once (on cytology specimen) and was not confirmed on surgical pathology.

Molecular patterns were grouped according to modern established molecular phenotypes described by Tang et al. [7] and as previously described by our group(1). Accordingly, four groups were formed: *BRAF*-like tumors included tumors with the presence of molecular alterations of *BRAFV600E*, *BRAF* fusions and *RET* fusions (*RET::PTC1, RET::PTC3*), *RAS*-like tumors included tumors with the presence of molecular alterations *BRAFK601E*, *KRAS*, *NRAS*, *HRAS,* and *TSHR* genes, *BRAF*-like/*RAS*-like overlap included *NTRK1-3* fusions, *ALK* fusions, and *FGFR2* fusions. Finally, Non–*BRAF*–Non–*RAS* (NBNR) tumors included tumors with the presence of the molecular alterations *DICER1*, *EZH1*, *EIF1AX*, *PTEN*, *THADA* fusion, and *PAX8/PPARg*.

Operative approach and histopathological analysis

Patients either underwent a total thyroidectomy or a hemithyroidectomy and central neck dissection as required according to the ATA guidelines [19]. In some cases, sentinel lymph node biopsy was done following institutions' practice [5, 13]. For cases with clinically positive nodal disease to the lateral neck, therapeutic neck dissection Level II-IV and VI was done according to ATA guidelines [19]. Histological diagnosis, tumor size, and extrathyroidal extension (none, minimal, or gross) were examined by experienced thyroid pathologists at our institutions [27]. The tumors were classified according to the 2017 WHO classification of thyroid tumors [13]. The nodal yield was defined as the number of positive lymph nodes divided by the total number of dissected nodes [1].

Statistics

For continuous variables, distribution was evaluated for normality according to Gauss' theorem. For normally distributed variables, mean and standard deviations are given. Binary variables were associated with a contingency table and the Mantel–Haenszel common odds ratio estimate was calculated. Normally distributed variables were compared using ANOVA, meanwhile non-normally distributed variables were compared using the Kruskal Wallis test. Correlation between two continuous variables were done with Spearman correlation (for non-normally distributed data).

A *p*-value lower than 0.05 was considered to indicate statistical significance [28]. Scientific exponential notation was used, that is exponential values were written using the "E" for exponent (e.g. $1.\times10^{-27}$ is written as 1.6E-27. Statistical analyses were performed using SPSS® 30.0.0.0 software (IBM®, Armonk, NY, USA).

Results

Baseline characteristics (Table 1)

The study included a total of 718 patients. There were 556 female patients (77.4%) and 162 male patients (22.6%) in the study cohort. The mean age was 50.6 years (SD 14.5). *ThyGenX/ThyGeNext* was the most used molecular test (478 patients, 66.6), followed by *ThyroSeqV3* (240 patients, 33.4%).

As per inclusion criteria, the final pathology was PTC with 718 cases (100.0%) cases. The variant of PTC was classical in 432 (60.2%) cases, follicular variant of PTC (incl. NIFTP) in.

128 (17.8%), tall cell variant in 135 (18.8%), hobnail in 16 (2.2%), and columnar/diffuse sclerosing in 7 (1.0%). Median tumor size was 15 mm (IQR 10–24).

A total of 174 patients (24.2%) underwent central neck dissection, while 13 patients (1.8%) underwent lateral neck dissection. For patients with central neck dissection, the median number of dissected nodes was 4.5 (IQR 2–8), and for patients with lateral neck dissection, it was 22 (IQR 14.5–29).

The median number of positive nodes dissected was 2 (IQR 1–4) for patients with central neck, and 7 (IQR 4–10.5) for patients with lateral neck dissection. The median nodal yield was 33% (IQR 0–72%) for the whole cohort.

Table 1 Baseline characteristics of the study cohort *N* = 718

Gender	
Female	556 (77.4%)
Male	162 (22.6%)
Age	
Mean (standard deviation)	50.6 (14.5)
Bethesda category	
III	146 (20.3%)
IV	146 (20.3%)
V	187 (26.0%)
VI	239 (33.3%)
Histology	
Papillary thyroid cancer	718 (100%)
Variant	
• Classical	432 (60.2%)
• Follicular variant (incl. NIFTP)	128 (17.8%)
• Tall cell	135 (18.8%)
• Hobnail	16 (2.2%)
• Columnar/diffuse sclerosing	7 (1.0%)
Molecular test	
ThyGenX/ThyGeNext	478 (66.6%)
ThyroSeqV3	240 (33.4%)
Any mutation	
Yes	494 (68.8%)
No	224 (31.2%)
***BRAF*-like mutation**	
Yes	227 (31.6%)
No	491 (68.4%)
***RAS*-like mutation**	
Yes	171 (23.8%)
No	547 (76.2%)
***BRAF/RAS* overlap**	
Yes	8 (1.1%)
No	710 (98.9%)
NBNR mutations	
Yes	59 (8.2%)
No	659 (91.8%)
Nodal disease	
Yes	167 (23.3%)
No	551 (76.7%)
Extrathyroideal extension	
Yes	85 (11.8%)
• Minimal	• 40
• Gross	• 45
No	633 (88.2%)

BRAF-like mutations: *BRAFV600E, BRAF fusions and RET fusions (RET-PTC1, RET-PTC3)*

RAS-like mutations: *BRAFK601E*, *KRAS*, *NRAS*, *HRAS* and *TSHR*

BRAF-like/*RAS*-like overlap: *NTRK1-3* fusions, *ALK* fusions and *FGFR2* fusions

NBNR: Non-*BRAF*-Non-*RAS* mutations: *DICER1*, *EZH1*, *EIF1AX, PTEN, THADA* fusion, and/or *PAX8-PPARg*

Aggressive subtypes of PTC: tall cell, columnar, hobnail, solid, diffuse sclerosing

Preoperative molecular testing of fine needle aspirates (Table 1)

The relative frequency of the preoperative Bethesda category was 146 (20.3%) for Bethesda III, 146 (20.3%) for Bethesda IV, 187 (26.0%) for Bethesda V, and 239 (33.3%) for Bethesda VI.

Accordingly, 292 (40.7%) patients had an indeterminate cytology (Bethesda III and IV), meanwhile 426 (59.3%) had Bethesda V and VI.

BRAF-like molecular alterations (*BRAFV600E, BRAF fusions and RET fusions (RET::PTC1, RET::PTC3)*) were detected in 227 (31.6%) of cases, meanwhile *RAS*-like molecular alterations (*BRAFK601E*, *KRAS*, *NRAS*, *HRAS* and *TSHR*) were detected in 171 (23.8%), *BRAF/RAS* overlap (*NTRK1-3* fusions, *ALK* fusions and *FGFR2* fusions) were detected 8 cases (1.1%). Non-*BRAF*-Non-*RAS* (NBNR) molecular alterations (*DICER1, EZH1, EIF1AX, PTEN, THADA* fusion, and/or *PAX/PPARg*) were detected in 59 (8.2%) cases.

As reported earlier [1], *BRAF*-like molecular alterations were most likely to be found in Bethesda 5 and 6 nodules and show extrathyroidal extension, nodal disease and/or aggressive subtypes of PTC($P < 0.001$ for all). *RAS*-like molecular alterations were more commonly found in Bethesda III and IV nodules, were less likely to show extrathyroidal extension, nodal disease and/or aggressive histology ($P < 0.001$ for all). NBNR molecular alterations were more commonly found in Bethesda III and IV nodules, were less likely to show extrathyroidal extension, nodal disease and/or aggressive subtypes of PTC ($P < 0.001$ for all, except $P = 0.15$ for extrathyroideal extension).

Relationship between molecular alteration pattern and age at diagnosis

We first explored the relationship between the molecular alteration pattern (*BRAF*-like, *RAS*-like, Non-*BRAF*-Non-*RAS* (NBNR)). For simplicity purposes we excluded

Table 2 Contingency table showing the relative frequency of ETE (none, minimal, gross) according to molecular alteration pattern

	BRAF-like	***RAS*-like**	**NBNR**	
No ETE	156 (70.9%)	200 (97.6%)	49 (100%)	
Minimal ETE	29 (13.2%)	3 (1.5%)	0	
Gross ETE	35 (15.9%)	2 (1.0%)	0	$P = 2.2E-14$
All patients	220 (100%)	205 (100%)	49 (100%)	$N = 474$

ETE: extrathyroidal extension

BRAF-like: *BRAFV600E, BRAF fusions and RET fusions (RET::PTC1, RET::PTC3)*)

RAS-like: *BRAFK601E*, *KRAS*, *NRAS*, *HRAS* and *TSHR*

Non-*BRAF*-Non-*RAS* (NBNR): *DICER1, EZH1, EIF1AX, PTEN, THADA* fusion, and/or *PAX::PPARg*

2.2E-14: scientific exponential notation for 2.2×10^{-14}

BRAF/RAS overlap since it was overall rare [1] and did not show any significant association with any of the study outcomes. Mean age of patients with *BRAF*-like molecular alterations was 47.3 (SD 14.6), with *RAS*-like molecular alterations was 50.5 (SD 14.2), and NBNR was 55.4 (SD 13.8). Statistical analysis revealed significant imbalance (ANOVA P = 0.00005) between the three groups. Pairwise analysis showed that patients with *BRAF*-like were significantly younger than with *RAS*-like molecular alterations (P = 0.022) and NBNR molecular alterations ($P = 0.00002$). Patients with RAS-like molecular alterations were significantly younger than with NBNR molecular alterations ($P = 0.023$).

Impact of molecular alteration pattern on tumor size

We then explored the relationship between the molecular alteration pattern (*BRAF*-like, *RAS*-like, Non-*BRAF*-Non-*RAS* (NBNR) and tumor size (maximal dimension upon final pathology).

Median tumor size was 13 mm (IQR 10–20) in patients with *BRAF*-like, 17 mm (IQR 12–26) in *RAS*-like, and 18 mm (IQR 12–27) in NBNR molecular alterations.

Statistical analysis revealed that tumor size (maximal dimension) was significantly smaller in patients with *BRAF*-like than *RAS*-like and/or NBNR molecular alterations (Kruskal Wallis, $P = 0.00004$ resp. 0.04). The median tumor size was not significantly different between *RAS*-like and/or NBNR mutations ($P = 0.94$).

Impact of molecular alteration pattern on nodal yield and extrathyroidal extension

Next, we explored the relationship between molecular alteration pattern *BRAF*-like, *RAS*-like, Non-*BRAF*-Non-*RAS* (NBNR) and surrogate pathological markers for aggressiveness, specifically extrathyroidal extension, number of positive nodes.

There were statistically significant imbalances between the groups with ETE being more likely in nodules with *BRAF*-like molecular alterations and less likely in nodules with *RAS*-like and NBNR molecular alterations (Table 2). For number of positive nodes, statistical analysis revealed signifance imbalance between the groups (ANOVA, $P = 0.0004$). The mean number of nodes was 2.68 (SD 2.8) in patients with *BRAF*-like molecular alterations, 0.89 (SD 0.94) in *RAS*-like and 0.25 (SD 0.5) in NBNR molecular alterations.

Lack of association between tumor size, nodal yield, and/or extrathyroidal extension

We finally explored the relation between tumor size (maximal dimension), nodal yield, and extrathyroidal extension.

Using Spearman correlation, tumor size and number of positive nodes did not show any statistically significant association ($P = 0.057$).

Median tumor size (maximal dimension) was 15 (IQR 9–24)mm in the no ETE group, meanwhile it was 15 (IQR 12–21) and 15 (IQR 10–25) in the minimal and gross ETE groups, respectively.

Statistical analysis did not reveal any significant imbalance between tumor size and ETE ($P = 0.456$, Fig. 1).

Discussion

This large retrospective multi-institutional international study showed that molecular alterations patterns, *BRAF*-like, *RAS*-like, and non-*BRAF*-non-*RAS* (NBNR), may be associated with tumor behavior, predicting aggressive

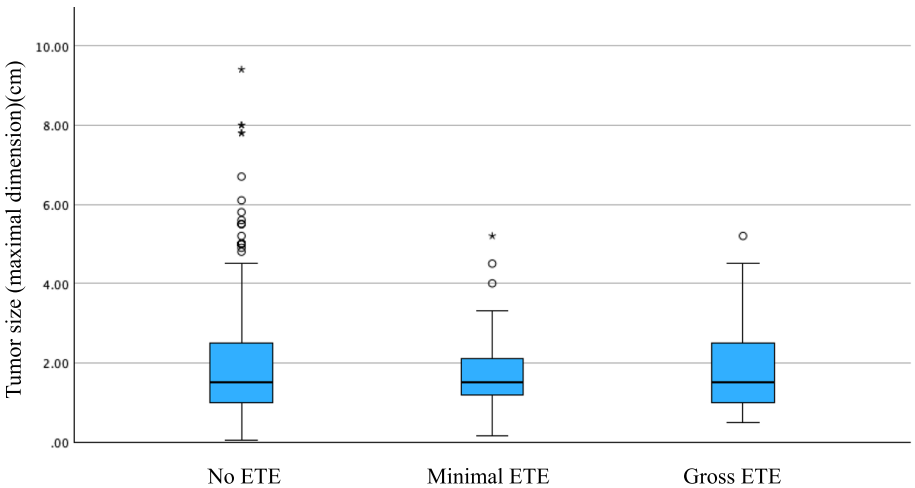

Fig. 1 Box plot demonstrating no siginficant difference in tumor size across patients with no extrathyroideal extension (ETE), minimal ETE and gross ETE ($P > 0.456$)). Gross ETE was however highly correlated with molecular alteration pattern (Table 2)

features such as nodal metastasis and extrathyroidal extension better than tumor size [29, 30]. This should be interpreted in the context of our cohort, which had a majority of relatively small PTC (< T3).

Studies preceding the advent of molecular profiling have reported an association between tumor size and prognosis [31].Tumor size has been used as a staging factor not only for the TNM [13], but also for other traditional staging systems for thyroid cancer such as AMES (Age, distant Metastases, Extent,Size) [14], the AGES (Age, tumor, Grade, Extent, Size), MACIS scores (Metastases, Age, Completeness of resection, Invasion, Size [15, 16]) and The National Thyroid Cancer Treatment Cooperative Study Prognostic system(NTCTCS) [17].

However, some traditional staging systems such as EORTC [32] did not include tumor size as a prognostic factor. This might reflect the fact that size alone is not a strong factor. Studies comparing different staging systems in PTC showed EORTC and TNM provide the most accurate prognosis prediction [33].

Moreover, according to a recent study with over 9000 patients with PTC or FTC, it appears that the impact of T stage is limited to big tumors in young patients (in other words: for T3 and T4 in patients younger than 55 years, T stage has an impact, else (small tumor and/or older patients: no impact of T stage) [18]. This also implies that the distinction between T1a, T1b and T2 does not carry relevant prognostic implications.

Those findings are consistent with our study, which showed no statistical correlation between tumor size and the presence of ETE and/or number of nodes, and consistent with previous report by our group based on a smaller study cohort [5]. Interestingly, our study also has mostly young patients with small tumors, as the median tumor size was 15 mm (interquartile range 10–24 mm). In other words, only a few patients were staged T3 because of tumor size alone. Also, the mean age of the study cohort was 50.6 years, that is below the cutoff of 55 years. This is below the cutoff for staging of the most recent version of the TNM system and also consistent with the previously cited study showing lack of association between small tumors and prognosis [13, 18].

Those findings may be explained by the fact that most of the thyroid tumors in populations with access to health care are nowadays detected at an early stage, before they become symptomatic [34]. These small tumors may not have time yet to show their true malignant potential. They did not have enough time to become clinically aggressive. In that context, it seems important to consider their molecular alterations pattern, which in our cohort, showed a strong correlation with adverse prognostic features, unlike tumor size. In resume, it seems that early detection of thyroid nodules leads to significant time bias, that makes tumor size irrelevant (since time was not given to the tumor to grow). Relying on molecular alteration patterns may overcome that issue, allowing a better reading of these small tumors.

Interestingly, a recent study showed that RAS-like mutations alone did not predict risk of malignancy of indeterminate thyroid cytologies [35], but the differentiation between RAS-like and BRAF-like very well did (as showed in this paper).

According to Berker et al., reduced uncertainty leads to less stress [36]. This highlights the main rationale behind this study, which is to improve upon patient care physically and psychologically. The findings of this study, which suggest that molecular alterations provide invaluable additional knowledge, will therefore lead to reduced anxiety among patients. This increased understanding of the tumour 's potential would be less taxing on the mind and lead to more satisfied outcomes [36]. Overall, certainty will produce less anxiety and lead to a better quality of life.

Our study has significant limitations. First, we only include patients who had available preoperative molecular testing and for whom final pathology showed PTC. Further, our study included patients before the latest WHO revision of thyroid histology (that is before the description of oncocytic carcinoma as a separate entity [37]. However, the main aim of the study was to analyze the impact of positive molecular testing (that is proof of a specific molecular alteration (pattern)) on the phenotype of the tumor, not to discuss the general prevalence of molecular alterations among several Bethesda category of thyroid nodules.

Further, during most of the period studied, the cost of molecular testing was not reimbursed by health insurance in the province of Quebec, Canada, thus making molecular testing more likely to be performed in patients with higher socioeconomic status.

The majority of molecular testing was performed with ThyGenX/ThyGeNext (with a total of 42 genes) [25], while a minority of patients had ThyroSeq V3, a more comprehensive test with 112 genes [23]. Since most of the molecular alterations defining each phenotype (*BRAF*-like, *RAS*-like and NBNR) are included in both panels, the introduced bias should be relatively small and not likely to impact significantly on our results.

We only performed molecular testing on cytology samples and did not "confirm" molecular alterations on final pathology, as described in the methods. However, studies have shown high concordance in molecular testing results between the cytology and final pathology [38]. The rate of false negatives is also dependent on the quality of the cytology specimen. In our study, the senior authors (RJP and GA) performed the vast majority

of ultrasound guided fine-needle aspiration biopsies (USFNAB), therefore limiting the false-negative rate [39]. The main expected clinical benefit of molecular testing for Bethesda V and VI nodules is, although not fully validated yet and not part of current guidelines, not to better predict the risk of malignancy but to identify those with a higher risk of being aggressive and treating them optimally, in a single surgical procedure [40].

Finally, our results mainly apply for small tumors, since the maximal tumor size was less than 4 cm in 93.8% of the patients. This means that our results show, for small early-detected tumors less than 4 cm that molecular alterations pattern may be more important that tumor size alone. How tumor size and molecular alteration pattern interplay for bigger (>4 cm) tumors shall be investigated in future studies.

In conclusion, in the current era, relying solely on tumor size as a prognostic marker in papillary thyroid carcinoma may be inadequate, as early-detected small tumors might not fully exhibit their aggressive potential. Our findings suggest that molecular alteration patterns—such as BRAF-like, RAS-like, and NBNR—provide a more accurate prediction of aggressive behavior. Integrating molecular profiling into clinical practice could enhance the precision of treatment strategies, particularly for early-stage, small tumors. The additional certainty regarding the prognosis is expected to translate to decreased stress and reduced anxiety in patients.

Authors' contributions

Basic study idea by GBM, RJP and GA. Data extraction by IT and JK. Study protocol, ethics review board and data transfer agreement by GBM. Manuscript drafting by GBM. Tables, figures and statistics by GBM. Manuscript editing and review by IT, SET, KEP, MN, JK, TY, MPP, RJP, and GA. All authors have participated substantially to the study and approved the final version of the manuscript.

Meeting presentation

This study was presented as the 2024 ATA annual meeting in Chicago, Illinois, USA.

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Data availability

The datasets generated for this study can be obtained upon reasonable request by email to the corresponding author.

Declarations

Ethics approval and consent to participate

The retrospective study was approved by the local ethics review board committee, Comité d'éthique de la recherche du CIUSSS du Centre-Ouest-de-l'Île-de-Montréal, protocol number 2023–3312 and Sheba Medical Center review board.
All patients gave their written informed consent.

Consent for publication

All authors approved the final version of the manuscript and consented to its publication in its actual form.

Competing interests

The authors declare no competing interests.

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