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Original research

Histopathology of telomerase reverse transcriptase promoter (*TERT*) mutated indeterminate thyroid nodules

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ABSTRACT

Objective: The objective of this study was to analyze the risk of malignancy and the histopathology of telomerase reverse transcriptase promoter *(TERT)* mutated cytologically indeterminate thyroid nodules (ITN).
Methods: A PUBMED search of molecularly tested ITN was conducted and data on *TERT* mutated ITN with histopathology correlation were extracted.
Results: Twenty-six manuscripts (published between 2014 and 2022) reported on 77 *TERT* mutated ITN. Sixty-five nodules were malignant (84 %), with 16 (25 %) described with high-risk histopathology, 5 (8 %) described as low-risk, and most without any description. Isolated *TERT* mutations were malignant in 26/30 ITNs (87 %) with 9 (35 %) described as high risk and none described as low risk. *TERT* + *RAS* mutated ITNs were malignant in 29/34 ITNs (85 %) with 3 (10 %) described as high risk and 4 (14 %) described as low risk. Finally, all 5 *TERT* + *BRAF*V600E mutated nodules were malignant and 3/5 (60 %) were described as high risk.
Conclusion: TERT mutated ITNs have a high risk of malignancy (84 %), and the current data does not show a difference in malignancy rate between isolated *TERT* mutations and *TERT* + *RAS* co-mutated ITNs. When described, *TERT* + *RAS* co-mutated ITNs did not have a higher rate of high-risk histopathology as compared to isolated *TERT* mutated lesions. Most *TERT* mutated ITNs did not have a description of histopathology risk and the oncologic outcomes, including rate of recurrence, metastases, and disease specific survival, are unknown. Further data is needed to determine if TERT mutated ITNs should be subjected to aggressive initial treatment.

Introduction

Telomeres are repetitive DNA-protein complexes at the end of chromosomes which prevent cell death by protecting chromosome ends from DNA fusions and damage [1]. Their length shortens each time with cell division, and critically shortened telomeres induce cell death. Telomerase is an enzyme that adds telomere segments to the ends of the telomere. This enzyme does not exist in normal human somatic cells, however, is enriched in cancer cells, which enables cellular immortality [2,3]. Cancer cells achieve overexpression of telomerase by activating the human *TERT* gene, which encodes part of the telomerase complex called telomerase reverse transcriptase (*TERT*). Mutations of *TERT* genes are reported in various cancers including thyroid cancer [4,5]. Landa et al. showed high prevalence of *TERT* mutations in aggressive thyroid cancers [6]: 40 % of poorly differentiated thyroid cancer (PDTC) and 73 % of anaplastic thyroid cancer (ATC) harbored *TERT* mutations whereas its prevalence was much lower at 9 % in well-differentiated papillary thyroid cancer (PTC) from The Cancer Genome Atlas [7]. Multiple studies have shown a correlation between *TERT* mutation with increased incidence of lymph node metastasis, extrathyroidal extension, distal

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metastasis, and cancer-specific mortality [8–12]. Often, *TERT* mutations are found either as an isolated mutation or with well-known driver mutations of thyroid cancer such as *RAS* and *BRAF*V600E among others [13]. It is now considered that *TERT* is mostly a late secondary-hit event in pre-existing early thyroid cancer, which accelerates the disease progression [6]. American Thyroid Association 2015 guideline has suggested incorporating the information on *TERT* mutation in assisting clinicians with proper risk stratification [14]. However, the impact of *TERT* mutations, whether as a single mutation or occurring with other driver mutations, in absence of high-risk clinical features is not well understood.

Recent advances in next-generation sequencing assays allowed the detection of *TERT* mutations in various case scenarios including molecular testing of thyroid nodules. Molecular testing from fine-needle aspiration (FNA) specimens of thyroid nodules have been widely used in real-world practice, particularly in aiding risk stratification for indeterminate thyroid nodule (ITN) [15]. There is a paucity of data on the prevalence, clinical behavior, and outcome of *TERT-mutated* thyroid nodules diagnosed based on FNA. This information may help decide if detection of *TERT* mutation at the time of biopsy can assist patients and clinicians in decision-making for initial management.

The objective of this study was to analyze the risk of malignancy and the resultant histopathology in indeterminate thyroid nodules (Bethesda III/IV - ITN) harboring *TERT* mutations in pre-operative thyroid nodule specimens.

Methods

A PUBMED literature search covering the years 2009–2022 was conducted using the search terms ((variant or variants or mutation or mutations or molecular diagnostics or molecular testing or mutational panel or mutation analysis) and (fine-needle or aspiration or thyroid nodule or thyroid nodules or thyroid neoplasm or thyroid cancer or thyroid carcinoma) and (indeterminate or Bethesda III or Bethesda IV or presurgical)). Fig. 1 shows a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram describing the search process and selection of studies [16]. Representative intended use cohorts for molecular testing of presurgical samples among thyroid nodules with Bethesda III or IV cytology nodules were included as previously described [17]. Studies were excluded if molecular testing was only performed on postsurgical tissue, and when data from Bethesda V nodules could not be separated from that of Bethesda III or IV nodules. Data was extracted from manuscripts reporting on molecularly tested ITNs with data on *TERT* mutations and histopathology correlation. The malignancy rate was calculated for *TERT* mutated ITNs overall and ITNs with isolated *TERT* mutations, *TERT* + *RAS*, and *TERT* + *BRAF*V600E co-mutated nodules (+/− additional mutations). Histopathology risk, when described, was assessed within each group. High risk cancers included anaplastic thyroid cancer, widely invasive follicular thyroid cancer, PDTC, and author descriptions of “aggressive behavior”. Non-invasive follicular thyroid neoplasm with papillary like features (NIFTP) was considered a low-risk malignancy as was minimally invasive follicular thyroid cancer, follicular tumor of uncertain malignant potential, and author descriptions of low-risk tumors. Comparisons of malignancy risk and type of histopathology across groups was assessed by the 3x2 chi-square test.

Results

Twenty-six manuscripts published between 2014 and 2022 reported a total of 77 *TERT* mutated ITN. The specific Bethesda category was reported in 21 cases (Bethesda III = 3, Bethesda IV = 18). Overall, 30 ITNs (39 %) had an isolated *TERT* mutation, 34 (44 %) had *TERT* + *RAS* (+/− a 3rd mutation), *5* (6 %) had TERT + BRAFV600E (+/− other mutations) and 8 (10 %) had *TERT* + other mutations (Table 1). Malignancy was confirmed in 65 nodules (84 %), with 16 (25 %) described

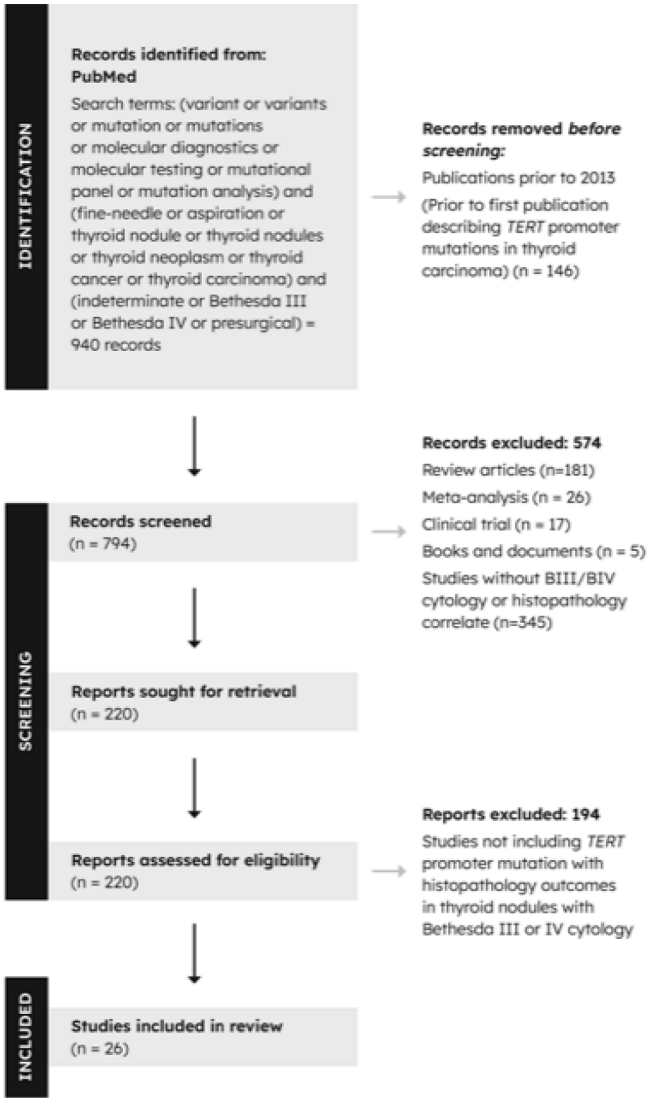

Fig. 1. Identification of studies via PUBMED.

with high-risk histopathology, 5 (8 %) described as low-risk, and the majority without any description. Isolated *TERT* mutations were malignant in 26/30 ITNs (87 %) with 9/26 (35 %) described as high risk and none described as low risk (Fig. 2). *TERT* + *RAS* mutated ITNs were malignant in 29/34 ITNs (85 %) with 3/29 (10 %) described as high risk and 4/29 (14 %) described as low risk. Finally, all 5 *TERT* + *BRAF*V600E mutated nodules were malignant and 3/5 (60 %) were described as high risk. There was no statistical difference between the risk of malignancy ($p = 0.97$)) and the proportion of aggressive histology when described ($p = 0.08$).

Discussion/Conclusion

Most of the data on the prevalence and prognostic implications of thyroid tumors harboring *TERT* mutations are from studies of known thyroid cancers. Our analysis is novel in its investigation of pre-operative detection of *TERT* promoter mutations in cytologically ITN. We found that only 77 *TERT* mutated ITNs (specific to Bethesda III or IV cytology) with histopathology correlation have been reported over the last 8 years. While most histology was malignant and some demonstrated aggressive behavior, 16 % *TERT* mutated ITN were histologically benign, and some malignancies were reported as histologically low risk.

Liu et al reported the first investigation of the diagnostic and

Table 1
TERT mutations in isolation and with co-mutations from ITN. The table includes the publication, percent malignancy and histopathologic description when provided. The American Thyroid Association risk categories for malignancies were rarely described in the studied manuscripts.

TERT mutation/co-mutation	Paper Pubmed ID	Bethesda Cytology (if stated)	# histology truth	# malignant (including NIFTP)	PPV%	Final histology (if described)
TERT	29094776	4	2	2	100.0 %	malignant (no other details)
	34734965		4	4	100.0 %	malignant (no other details)
	35247035		1	1	100.0 %	HTC
	32671653	4	1	1	100.0 %	PDTC (with vascular invasion)
	33914382		2	0	0.0 %	FA hyperplastic nodule
	29590358		2	1	50.0 %	FA and PDTC
	33193891		1	1	100.0 %	malignant (no other details)
	34510770		5	4	80.0 %	"aggressive thyroid cancer" – 1 with LN mets
	35307577	4	1	1	100.0 %	FTC-WI oncocytic type
	35189676	4	2	2	100.0 %	FTC
TERTC228T	29085338		1	1	100.0 %	FTC-WI
	33640868	4	3	3	100.0 %	FTC pT2NX, FTC pT1bNX, FTC pT3mNX
	25209362	4	2	2	100.0 %	malignant (no other details)
	29704233		1	1	100.0 %	FTC
TERTC250T	29085338		1	1	100.0 %	FTC-WI
	35625691	4	1	1	100.0 %	malignant (no other details)
RAS + TERT	34734965		7	6	85.7 %	5 malignant (no other details) and 1 NIFTP
NRAS + TERT	32671653	4	1	1	100.0 %	PDTC
	34605038		1	1	100.0 %	FVPTC, focal LV invasion and 0/0 LN
	34627720		1	1	100.0 %	FTC
	25209362	4	2	2	100.0 %	malignant (no other details)
	31245935		1	0	0.0 %	nodular hyperplasia
	32339438		2	2	100.0 %	FVPTC (1 with vascular invasion)
	33914382		1	1	100.0 %	FVPTC
NRAS61 + TERTC228T	29085338		3	3	100.0 %	FVPTC (2) and FTC-WI (only 1 is aggressive)
	35625691	3	1	1	100.0 %	FTC
NRASG12 + TERTC228T	35625691	4	1	1	100.0 %	Follicular tumor of uncertain malignant potential
NRASQ61R + TERTC228T	33640868	4	1	0	0.0 %	FA
NRASQ61R + EIF1AX + TERTC228T	34075760	3	1	1	100.0 %	FTC
NRAS + TSHR + TERT	33067175		1	1	100.0 %	PTC
KRAS + TERT	33067175		1	1	100.0 %	PTC
	34627720		1	1	100.0 %	FVPTC
KRAS12 + TERTC228T	29085338		1	1	100.0 %	FVPTC
KRAS61 + EIF1AX + TERTC228T	34075760	4	1	1	100.0 %	FTC
HRAS + TERT	32671653	4	1	1	100.0 %	FTC (ATA low risk)
	33300952		1	1	100.0 %	FTC-MI
	34605038		1	0	0.0 %	FA
HRAS + EIF1AX + TERT	33067175		1	0	0.0 %	FA
HRASQ61R + EIF1AX + TERTC228T	34075760	4	2	2	100.0 %	FTC and infiltrative FVPTC
BRAFV600E + TERT	34734965		1	1	100.0 %	malignant (no other details)
	35247035		1	1	100.0 %	ATC
BRAFV600E + TERT + PIK3CA	32671653	4	1	1	100.0 %	PTC with ETE, VI, > 5 LN
BRAFV600E + TERT + PTEN	34734965		1	1	100.0 %	malignant (no other details)
BRAFV600E + TERT + PIK3CA + AKT1	27283257		1	1	100.0 %	malignant - sub cm and "aggressive biological behavior"
BRAFK601E + TERTC228T	29094776	4	1	1	100.0 %	FVPTC - pT2N0, no ETE, no vascular invasion and no recurrence
BRAFK601E + TERTC250T	29085338		1	1	100.0 %	FTC-WI
EIF1AX + TERT	34627720		1	0	0.0 %	FA
EIF1AX + TERTC228T	34075760	3	1	1	100.0 %	FTC
TP53 + CNA + TERTC228T	34264855	4	1	1	100.0 %	HCC
TP53 + CNA + EIF1AX + TERTC228T	34264855	4	1	0	0.0 %	FA
CNA + TERT	33030808		1	1	100.0 %	HCC
ZNF148 + TERT	32976686		1	0	0.0 %	FA
SUM			77	65	84.4 %	

HTC/HCC: Hürthle/Oncocytic Carcinoma, **PDTC**: Poorly Differentiated Thyroid Carcinoma, **FA**: Follicular Adenoma, **FTC-WI**: Follicular Thyroid Carcinoma – Widely Invasive, **FVPTC**: Follicular Variant of Papillary Thyroid Carcinoma, **NIFTP**: Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features, **PTC**: Papillary Thyroid Carcinoma, **FTC-MI** Follicular Thyroid Carcinoma: – Minimally Invasive,
ATC: Anaplastic Thyroid Carcinoma.

prognostic value of preoperative thyroid FNA *TERT* testing. They found 0 % TERT mutations in benign thyroid nodules and 7 % *TERT* mutations in differentiated thyroid cancer (DTC), representing a 100 % diagnostic specificity. Three *TERT* positive samples from ITN represented FTC. Seven of their 9 total patients with *TERT* promoter mutations showed aggressive tumor behavior with poor clinical outcomes. Our methodology excluded their 3 ITN cases from our investigation as we could not exclude Bethesda V cytology [5]. The prevalence of *TERT* in classic PTCs

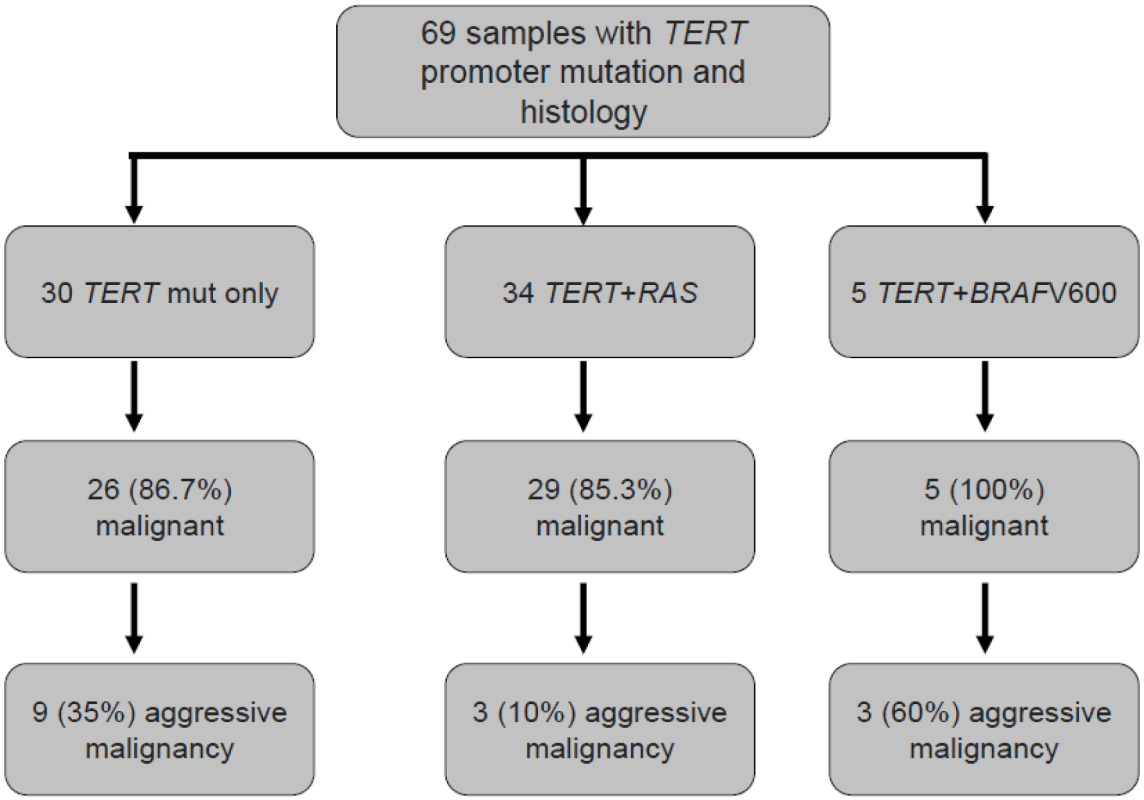

Fig. 2. Risk of malignancy (ROM) in ITN with *TERT* mutation in isolation, *TERT* + *RAS* family variant, and *TERT* + *BRAF*V600E. There was no statistically significant difference in malignancy rate or proportion of aggressive malignancies when reported. Most studies did not provide details regarding thyroid cancer histology risk.

has been reported to be as low as 2 % and as high as 25 %. There is consensus that the prevalence is higher in more aggressive and dedifferentiated epithelial thyroid cancer, with *TERT* being reported as high as 75 % in ATC [3]. In a study of molecularly tested thyroid nodules, the overall prevalence of *TERT* was 3.3 %. Notably, > 50 % of these samples were from nodules with Bethesda V and VI cytology [18]. In that cohort, 50 % of *TERT* positive nodules were co-mutated with BRAFV600E, 29 % had isolated *TERT* mutations and 17 % were co-mutated with a *RAS* variant. In a recent study of more than fifty thousand molecularly tested thyroid nodules with Thyroseq® v3, 873 nodules across Bethesda III-VI cytology were *TERT* positive (1.7 %). The relative rate of *TERT* positivity was highest in nodules with Bethesda V and VI cytology, though the absolute number was higher in Bethesda III and IV nodules (by virtue of a higher number of this cytology group being tested) [19].

The current data suggests that overtreatment in patients with ITN harboring *TERT* mutations is possible, even when co-mutated with *RAS*. However, there is literature-based evidence that *TERT* mutations worsen thyroid cancer prognosis. *TERT* mutated cancers have significantly greater rates of lymph nodes metastasis, higher risk disease (stage III and IV), tumor recurrence and thyroid cancer related death relative to cancers with wildtype *TERT* [12]. Song et al. reported a 20-fold adjusted hazard ratio for disease-specific death from *TERT* mutated DTC relative to wild type [13]. Still, the greatest adverse impact of *TERT* mutations is among high risk and advanced stage cancers. Conversely, the impact among low-risk and low-stage tumors is less clear. Song et al. showed no significant influence on prognosis with *TERT* mutated stage 1 and 2 cancers, whereas Park et al. found worse prognosis across all cancer stages [13,20]. Kuchareczko et al. showed no significant differences in risk stratification, response to primary treatment, clinical course, or final disease status in papillary microcarcinomas with concomitant *TERT* + *BRAF*V600E mutations versus no mutations with an overall five-year survival rate of 99.5 % [21]. This raises questions about risks and benefits to increased therapeutic aggression based solely on the presence of a TERT mutation for a neoplasm that, if malignant, pre-operatively does not otherwise appear to be a high-risk cancer.

Our analysis shows that isolated *TERT* mutated ITNs have a high rate of malignancy (84 %), and the current data does not show a difference in malignancy rate between isolated *TERT*, *TERT* + *RAS*, or *TERT* + *BRAF*V600E co-mutated ITNs. Interpretations of malignancy rate differences with *TERT* + *BRAF*V600E co-mutated lesions from our study are likely limited by the small sample size (n = 5).

Among ITN in general, most malignancies are low to intermediate risk. Though only a small number of the malignancies were histologically described in our study, *TERT* + *RAS* co-mutated ITNs did not have a higher rate of high-risk histopathology as compared to isolated *TERT* mutated lesions. This somewhat contrasts with data showing that *TERT* + *RAS* co-mutated thyroid cancers had worse disease-free survival and a trend towards worse disease specific survival than cancers with *TERT* or *RAS* variants in isolation [13]. The very limited *TERT* + *BRAF*V600E co-mutated data in our study is more consistent with the significantly worse outcomes with *TERT* + *BRAF*V600E mutated thyroid cancers that have been described [8,13]. Whether there is a difference in *TERT* mutated thyroid cancer outcomes (with or without co-mutations) associated with indeterminate cytology versus with Bethesda V or VI cytology is unknown.

One should be cautious in attempting to draw conclusions on the differences or similarities in thyroid cancer behavior with *TERT* promoter mutations, whether in isolation or with *RAS* or *BRAF*V600E co-mutations, arising from ITNs. The current data does not describe the histopathology in the majority of *TERT* mutated ITNs. Furthermore, the oncologic outcomes, including rate of recurrence, metastases, and disease-specific survival, are unknown. This highlights the limitations of published data regarding ITNs with *TERT* promoter mutations. Several studies show that when controlled for American Joint Committee on Cancer (AJCC) stage of thyroid cancer, *TERT* mutated DTCs have significantly poorer prognosis than those with *TERT* wildtype

[13,14,20]. Still, it is unknown if their outcomes are improved by intensified treatment. Prospective, randomized trials assessing the clinical outcomes and harms of aggressive initial treatment in *TERT* mutated ITNs will inform optimal therapeutic approaches to these lesions.

Clinical relevance

The first comprehensive literature review of *TERT* mutated ITNs showed a cancer risk of 84 %. There was no statistical difference between the risk of malignancy and the proportion of aggressive histology between various combinations of *TERT* and other driver mutations, however further data is needed to confirm this finding.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Atanas Kaykov, Joshua P. Klopper, Richard T. Kloos, Mohammed Alshalalfa, Yangyang Hao, and Jing Huang are employees and equity owners of Veracyte, Inc.

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