Histopathology of Telomerase Reverse Transcriptase Promoter (*TERT*) Mutated Indeterminate Thyroid Nodules

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INTRODUCTION

Thyroid cancers with telomerase reverse transcriptase promoter (*TERT*) mutations have worse disease-free and disease-specific survival than thyroid cancers with wild type *TERT*. Additionally, *TERT* mutations are enriched in high risk, poorly differentiated, and anaplastic thyroid cancer. Conversely, most thyroid cancers arising from thyroid nodules with indeterminate cytology (Bethesda III/IV - ITNs) are not aggressive. The objective of this study is to analyze the risk of malignancy and the resultant histopathology of *TERT* mutated ITNs.

METHODS

A PubMed search (2009-2022) of molecularly tested ITNs was conducted and data on *TERT* mutated ITNs with histopathology correlation were extracted. Thyroid nodules with Bethesda V cytology were excluded. The malignancy rate was calculated for all *TERT* mutated ITNs, 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 included anaplastic thyroid cancer, widely invasive follicular thyroid cancer, poorly differentiated thyroid cancer, and descriptions of “aggressive behavior”. NIFTP was considered a low-risk malignancy as was minimally invasive follicular thyroid cancer, follicular tumor of uncertain malignant potential, and descriptions of low-risk tumors.

RESULTS

- Twenty-six manuscripts (published between 2014-2022) reported on 77 *TERT* mutated ITNs. **(Figure 1)**
- Thirty ITNs (39%) had an isolated *TERT* mutation, 34 (44%) had *TERT* + *RAS* (+/- a 3rd mutation), 5 (6%) had *TERT* + *BRAF*V600E (+/- other mutations) and 8 (10%) had *TERT* + other mutations. **(Table 1)**
- 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 (86.7%) with 9 malignancies (35%) described as high risk and none described as low risk. *TERT* + *RAS* mutated ITNs were malignant in 29/34 ITNs (85.3%) with 3 malignancies (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. **(Figure 2).** There was no significant difference in risk of malignancy between *TERT* alone, *TERT* + *RAS*, and *TERT* + *BRAF*V600E (p=0.97, 3x2 chi-square test). With regards to aggressive histology, there was no difference between the three groups (p=0.18, 3x2 chi-square test) or between *TERT* alone and *TERT* + *RAS* (p = 0.08, 2x2 chi-square test).

FIGURE 1—Identification of studies via databases and registers

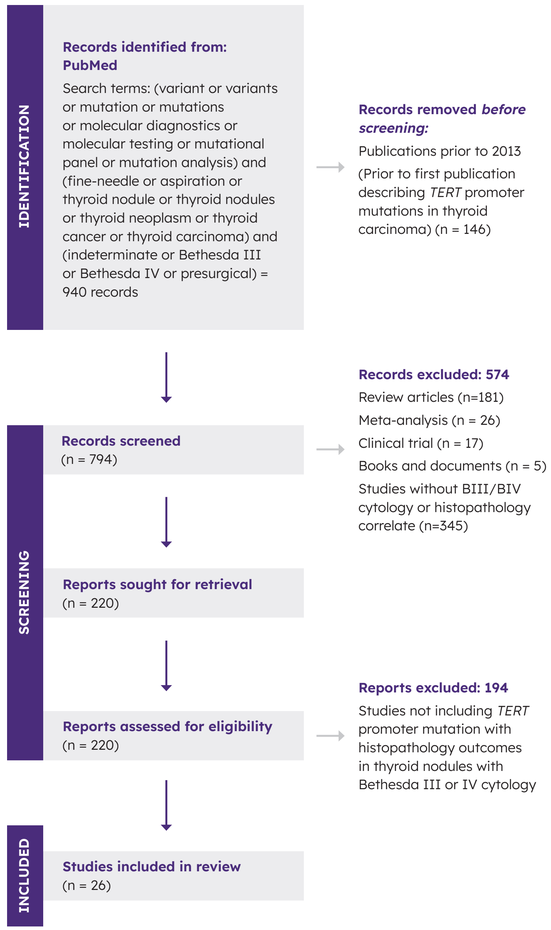


TABLE 1—*TERT* mutations in isolation and with co-mutations from ITN

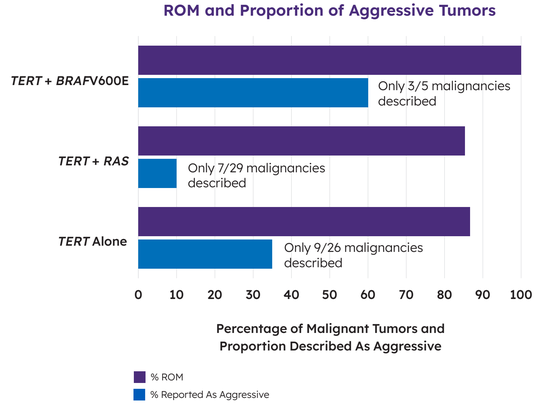
The table includes the publication, percent malignancy and histopathologic description when provided

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

TERT Mutation/Co-mutation	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
*TERT*C228T	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
*TERT*C250T	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
*NRAS*61+*TERT*C228T	29085338		3	3	100.0%	FVPTC (2) and FTC-WI (only 1 is aggressive)
	35625691	3	1	1	100.0%	FTC
*NRAS*G12 + *TERT*C228T	35625691	4	1	1	100.0%	Follicular tumor of uncertain malignant potential
*NRAS*Q61R + *TERT*C228T	33640868	4	1	0	0.0%	FA
*NRAS*Q61R + *EIF1AX* + *TERT*C228T	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
*KRAS*12+*TERT*C228T	29085338		1	1	100.0%	FVPTC
*KRAS*61 + *EIF1AX* + *TERT*C228T	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
*HRAS*Q61R + *EIF1AX* + *TERT*C228T	34075760	4	2	2	100.0%	FTC and infiltrative FVPTC
*BRAF*V600E + *TERT*	34734965		1	1	100.0%	malignant (no other details)
	35247035		1	1	100.0%	ATC
*BRAF*V600E + *TERT* + *PIK3CA*	32671653	4	1	1	100.0%	PTC with ETE, VI, > 5 LN
*BRAF*V600E + *TERT* + *PTEN*	34734965		1	1	100.0%	malignant (no other details)
*BRAF*V600E + *TERT* + *PIK3CA* + *AKT1*	27283257		1	1	100.0%	malignant — sub cm and “aggressive biological behavior”
*BRAF*K601E + *TERT*C228T	29094776	4	1	1	100.0%	FVPTC — pT2N0, no ETE, no vascular invasion and no recurrence
*BRAF*K601E + *TERT*C250T	29085338		1	1	100.0%	FTC-WI
EIF1AX + *TERT*	34627720		1	0	0.0%	FA
EIF1AX + *TERT*C228T	34075760	3	1	1	100.0%	FTC
TP53 + *CNA* + *TERT*C228T	34264855	4	1	1	100.0%	HCC
TP53 + *CNA* + *EIF1AX* + *TERT*C228T	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%**	

FIGURE 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



DISCUSSION

Only 77 *TERT* mutated ITNs with histopathology correlation have been reported over the last 8 years. *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*, *TERT* + *RAS*, or *TERT* + *BRAF*V600E co-mutated ITNs. Interpretations of differences with *TERT* + *BRAF*V600E co-mutated lesions are likely limited by the small sample size (n = 5). Though only a small number of malignancies were described, perhaps unexpectedly, *TERT* + *RAS* co-mutated ITNs did not have a higher rate of high-risk histopathology as compared to isolated *TERT* mutated lesions. 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 risk in the majority of *TERT* mutated ITNs. Furthermore, 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.