IN PAPILLARY THYROID CANCER *TERT* PROMOTER MUTATIONS HAVE A WORST IMPACT ON OUTCOME THAN *BRAF* MUTATIONS

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TELOMERASE

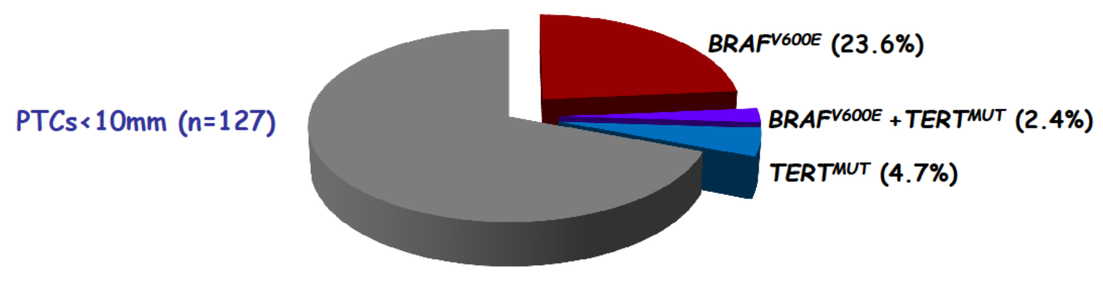
Telomerase is a ribonucleoprotein polymerase that maintains telomere ends and plays a role in cellular senescence, being repressed in postnatal somatic cells. Mutations in the promoter of telomerase reverse transcriptase (TERT), the catalytic subunit of telomerase, were recently reported in thyroid tumors, with a prevalence ranging 8-25% in papillary thyroid cancer (PTC). A strong association between *TERT* mutations and a poor outcome has been reported in PTC, while discordant data are available about the clinical impact of the coexistence of *TERT* and $BRAF^{V600E}$ mutations.

AIMS OF THE STUDY:

1. To investigate the prognostic role of both *TERT* promoter ($TERT^{MUT}$) and $BRAF^{V600E}$ mutations in a large series of PTCs with a long follow-up;
2. To evaluate the possible additive effect on the outcome of the coexistence of the two genetic alterations

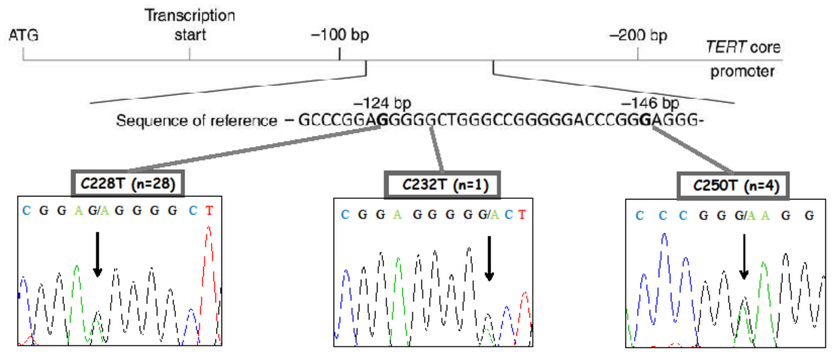
RESULTS

PREVALENCE OF *TERT* PROMOTER AND $BRAF^{V600E}$ MUTATIONS IN PTCs



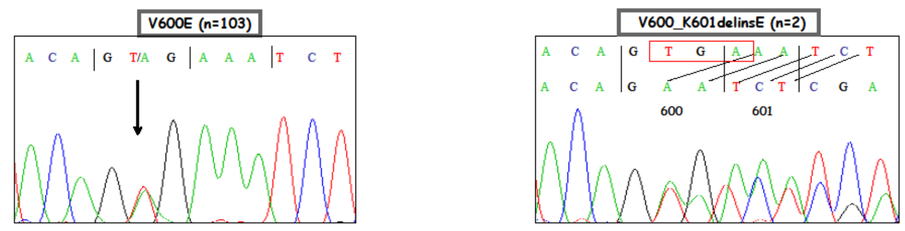
The prevalence of $BRAF^{V600E}$ mutation was 30% in micro PTCs and 36% in macro PTCs, while *TERT* promoter mutations were found in 7% micro PTCs and in 12% macro PTCs.

TERT PROMOTER MUTATIONS



Among *TERT* mutated patients, C228T mutation was the most frequent (85%).

BRAF MUTATIONS



In two cases V600_K601delinsE *BRAF* mutation was found.

CLINICAL FEATURES OF PTC PATIENTS (MEDIAN FOLLOW-UP: 74 MONTHS)

PTCs (n=327)		$BRAF^{V600E}$ only n=92 (28%)	$TERT^{MUT}$ only n=20 (6%)	$BRAF^{V600E}$+ $TERT^{MUT}$ n=13 (4%)	BRAF/TERT wt n=202 (62%)	P BRAF vs wt	P TERT vs wt	P BRAF+TERT vs wt
Age at diagnosis (years)	Mean ±SD	44.9 ±15	53.3 ±15	56 ± 17.5	46.7 ± 15.5	ns	ns	ns
	range	17-74	24-79	29-82	14-83			
Male gender		22 (24%)	9 (45%)	6 (46%)	42 (21%)	ns	0.02	ns
Mean tumor size (mm)	Mean ±SD	18.1 ± 12.2	21.3 ± 15.4	23.2 ± 14.7	14.4 ± 12.8	0.02	ns	0.05
Multifocality		41 (46%)	12 (60%)	4 (30.7%)	87 (43.5%)	ns	ns	ns
Extrathyroid invasion		44 (50.5%)	11 (57.8%)	7 (53.8%)	75 (37%)	0.04	ns	ns
Lymph-nodes	N1/N0/NX	54/18/20 (58.7%)	7/3/10 (35%)	4/4/5 (30.7%)	11/42/48 (55%)	ns	ns	ns
Histological variants	conventional	77 (84.6%)	11 (55%)	8 (61.6%)	148 (73.5%)	0.05	ns	ns
	follicular/ oncocytic/ sclerosing	14	9	5	52			
RAI treatment		67 (87%)	12 (70.5%)	8 (72%)	91 (63%)	<0.0001	ns	ns
Outcome	persistence or recurrence	13 (15%)	7 (37%)	4 (31%)	30 (15%)	ns	0.02	ns

$BRAF^{V600E}$ mutation was significantly associated with larger tumors, extrathyroid invasion, and RAI treatment, but **NOT** with a worst outcome; *TERT* promoter mutations significantly correlated with male gender and poorer outcome. Moreover, *TERT* mutated tumors showed a trend towards a higher prevalence of multifocality and extrathyroidal extension, though not statistically significant likely due to the limited number of mutated cases. Similarly, the number of cases harboring both $BRAF^{V600E}$ and *TERT* promoter mutations was low and did not allow to evaluate possible difference in the outcome between PTCs with $TERT^{MUT}$ alone and those harboring both *TERT* and $BRAF^{V600E}$ mutations.

CONCLUSIONS

In the present large series of PTCs, *TERT* promoter mutations were confirmed to be a major indicator of poor prognosis.

$BRAF^{V600E}$ mutation correlated with worst clinicopathological features at diagnosis but not with the outcome.

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