COEXISTENCE OF TERT PROMOTER AND BRAF MUTATIONS IN METASTATIC MELANOMA

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Introduction

Despite of breakthrough in treatment with targeted therapy and immunotherapy with 5-year survival rate of 35-40 % that is encouraging, metastatic melanoma remains difficult to treat. The most common molecular alteration in metastatic melanoma is mutation in BRAF gene (approximately 60% of melanoma), but also several highly recurrent somatic sequence variations in the promoter region of the telomerase reverse transcriptase (TERT) gene where reported with clinicopathologic correlations reported in few studies, so far.

Materials and methods

Coexistence of TERT and BRAF mutation was tested in 123 patients with metastatic melanoma and correlation with clinicopathological features was analysed. All patients were tested for the BRAF V600E mutations using a IVD BRAF Mutation Analysis Kit for Real-Time PCR (Entrogen, USA) while mutation in TERT promoter gene where determined by Sanger sequencing. Clinicopatohologic characteristics (localization, Breslow thickness, presence of ulceration, number of mitoses, histologic subtypes, lymph nodes involvement) and disease course (progression, survival) were analysed between double wild type, BRAF only mutated, TERT-only mutated and double mutated tumors. For statistical analysis Chi-square or Fisher exact test was used *p* value under 0,05 was considered statistically significant. For survival analysis in treatment naive patients Kaplan-Meier was performed.

Results

A total of 123 IV stage melanoma patients, 76 (61,8%) where male and 47 (38,2%) female with median age 57,9 years. 69 (56,1%) patients harbor mutation in TERT promotor while 64 (52,0%) harbored mutation in BRAF which was exclusively 1799 T>A (V600E). 42 (34,1%) patient harbored mutation in BRAF and TERT (DM), 29 (23,6%) TERT only (TM), 23 (18,7%) BRAF only (BM) while 29 (23,6%) patients reported wild type for BRAF and TERT (DW). Oldest group of patients was TM (mean 62,72) followed by DW (mean 61,00), DM (mean 53,19) while patients carrying only BRAF mutation (BM) where youngest (mean 52,30). Majority of tumors where located on extremities (40,7%) and trunk (38,2%). While distribution across extremities was approximately equal beetwen groups, on the trunk most frequant were DM 21 (44,7%) and on extremities TM 15 (51.7%). According to Breslow, TM where thicker (mean 7,14) while DM were thinner (mean 5,53). Patients with TM and DW had more present ulceration then DW and BM.

Table 1. Clinicopathological correlation between coexistence TERT promoter and BRAF mutation status

	Total	DW (Double wild type)	BM (BRAF mutated)	TM (TERT mutated)	DM (Double mutated)	p
Gender						0.402
Female	47 (38,2%)	13 (44,8%)	11 (47,8%)	8 (27,6%)	15 (35,7%)	
Male	76 (61,8%)	16 (65,2%)	12 (52,2%)	21 (72,4%)	27 (64,3%)	
Age (mean)	57,95	61,00	52,30	62,72	53,19	**0.016** DW vs DM p=0,017 BM vs DW p= 0,045 TM vs DM p=0.011
Localization						0.290
Head and neck	25 (20,3%)	5 (17,2%)	7 (30,4%)	5 (17,2%)	8 (19,0%)	
Trunk	47 (38,2%)	12 (41,4%)	5 (21,7%)	9 (31,0%)	21 (50,0%)	
Extremities	50 (40,7%)	11(37,9%)	11 (47,8%)	15 (51,7%)	13 (31,0%)	
Unknown primary	1 (0,8%)	1 (3,4%)	0 %	0 %	0 %	
Histological type						0.335
SSM	43 (31,9%)	6 (25,0%)	8 (40,0%)	12(42,9%)	17 (44,7%)	
NM	58 (52,7%)	14 (58,3%)	12 (60,0%)	15 (53,6%)	17 (44,7%)	
other	9 (8,2%)	4 (16,7%)	0 (0%)	1(3,6%)	4 (10,5%)	
Breslow thickness (mean)	6,27	6,53	6,26	7,14	5,53	0.111
Ulceration						0.259
present	72 (75,0%)	16 (84,2%)	11 (64,7%)	22 (84,6%)	23 (67,6%)	
absent	24 (25,0%)	3 (15,8%)	6 (35,3%)	4 (15,4%)	11 (32,4%)	

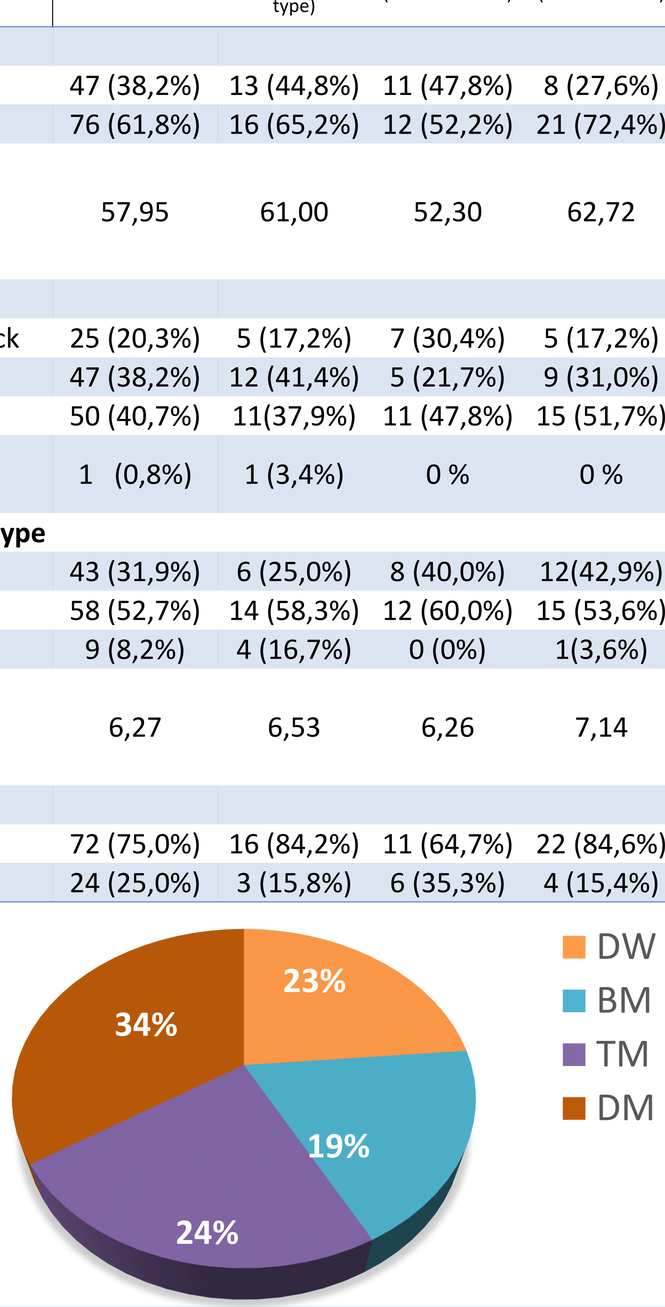
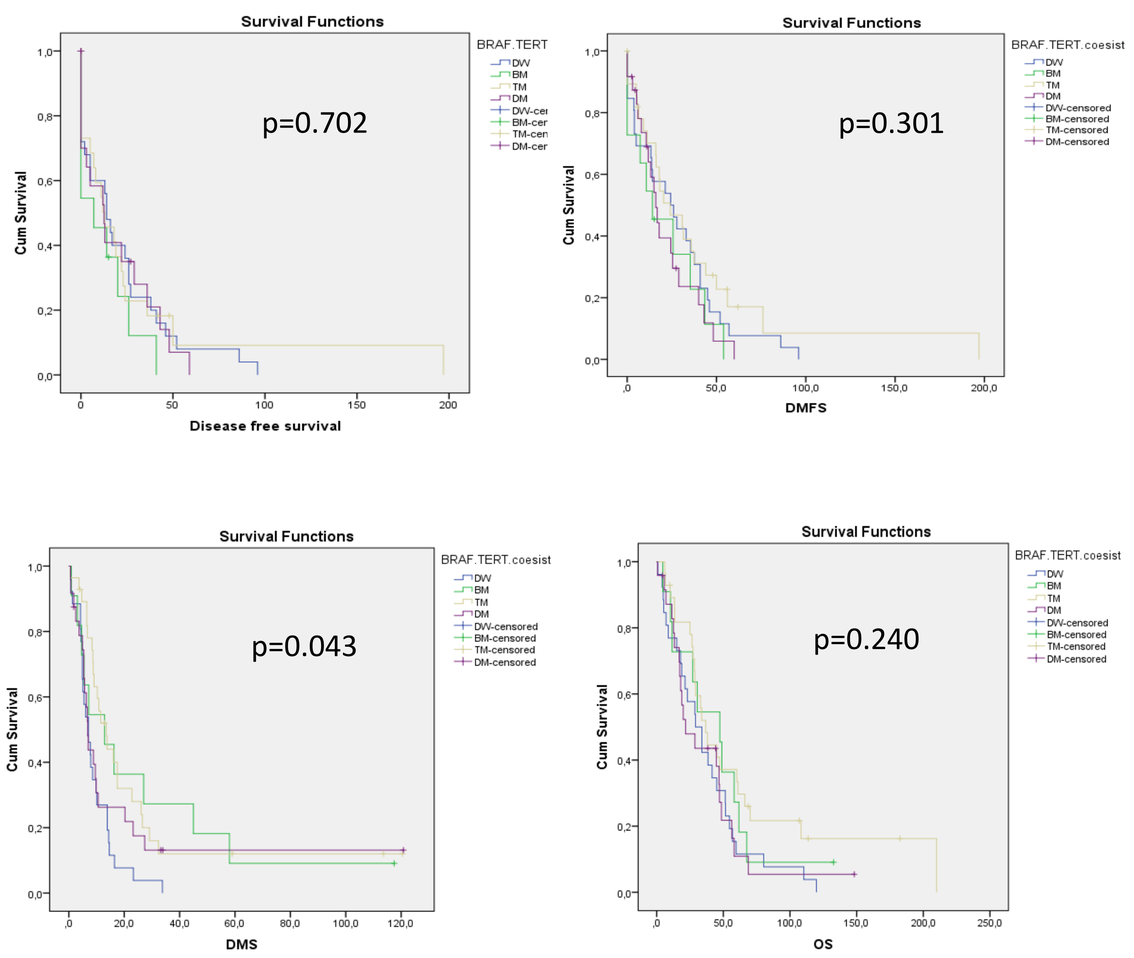


Figure 1. Survival analysis



	DMS p=0,043
DW	7,1 (95% CI 4,2-9,9)
BM	12,9 (95% CI 1,2-24,5)
TM	13,5 (95% CI 8,6-18,3)
DM	6,8 (9 5% CI 5,7-7,8)

Conclusions

There is strong correlation between BRAF and TERT promotor mutational status (p=0.001). Coexistence of TERT promotor and BRAF mutation are more frequent event to younger people (p=0.016). Tumors that carry both BRAF and TERT promoter mutation have lower Breslow thickness. Double mutated tumors had shorter distant metastasis interval compared with BRAF only or TERT mutated tumors.