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Summer Undergraduate Research Program

Should BRAFV600E be incorporated into treatment recommendations for thyroid cancer?

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INTRODUCTION

- Around 90% of thyroid cancers are papillary thyroid carcinomas (PTC)[1]
- PTC has a recurrence rate of around 20%[1]
- Mortality rate for PTC is low at around 5%[2]
- Extrathyroidal extension, multifocality, positive margins, and lymph node metastases are predictors of more aggressive PTC[4]
- BRAFV600E occurs in 60% of PTCs[3]
- There is controversy whether BRAFV600E is an independent predictor of aggressiveness[5]

HYPOTHESIS

- BRAFV600E is not an independent predictor of recurrence and outcomes in PTC

METHODS

- Specimens and clinical data were obtained from the ICARE2 biospecimen and bioinformatics registry at UNMC
- Adult patients with PTC treated with surgery and greater than 6 months of post-operative follow-up were included
- Tissue microarrays (TMA) were made from well-differentiated tumors
- Immunohistochemistry for BRAFV600E was performed on all TMAs, positive cytoplasmic staining was inferred to represent the BRAF mutation
- BRAFV600E expression was calculated by an H-score: staining intensity (0-3) multiplied by quantity of staining (% positive)
- Statistical analysis was performed using Pearson Chi squared, Fisher's exact, and Wilcoxon rank-sum tests to determine factors associated with BRAFV600E
- Multivariable logistic regression used to determine independent factors associated with recurrence
- A Kaplan-Meier analysis was performed to assess for recurrence over time by BRAF status

Table 1: Clinical/Demographic Variables of Patients with PTC by BRAF Status

	All	BRAF WT	BRAFV600E	P-Value
Patients	160	65	95	
Age, years, mean (SD)	45.5 (14.2)	42.3 (14.3)	47.6 (13.7)	**0.0259**
Age over 55, n (%)	43 (26.9)	11 (16.9)	32 (33.7)	**0.019**
Gender, female, n (%)	125 (78.12)	56 (86.2)	69 (72.3)	**0.042**
Body mass index, kg/m^2, mean (SD)	31.41 (7.0)	30.4 (6.8)	32.1 (7.1)	0.108
Tumor size, cm, mean (SD)	2.0 (1.4)	2.2 (1.6)	1.9 (1.3)	0.1833
Histology				**0.0002**
FV Papillary thyroid carcinoma, n (%)	35 (22)	24 (36.9)	11 (11.7)	
Papillary thyroid carcinoma, n (%)	124 (78)	41 (63.1)	83 (88.3)	
Lymphocytic thyroiditis, n (%)	56 (35)	22 (33.9)	34 (35.8)	0.8
Extrathyroidal Extension, n (%)	34 (28.1)	9 (18.4)	25 (34.7)	**0.049**
Multifocality, n (%)	60 (37.5)	20 (30.8)	40 (42.1)	0.15
Positive margins, n (%)	22 (14)	4 (6.4)	18 (19.2)	**0.033**
Vascular Invasion	16 (11)	10 (16.4)	6 (7.1)	0.079
Lymphatic Invasion	17 (11.4)	9 (14.3)	8 (9.3)	0.32
Lymph node size, cm, mean (SD)	1.6 (1.3)	1.8 (1.4)	1.5 (1.3)	0.6531
Lymph node ratio, n, mean (SD)	0.19 (0.32)	0.13 (0.3)	0.23 (0.33)	**0.0106**
Extranodal extension, n (%)	21 (18.8)	9 (22.5)	12 (16.7)	0.45
Follow-up time, years, mean (SD)	6.0 (2.9)	6.1 (3.2)	6.0 (2.6)	0.91

Figure 1: H&E (1,3) and IHC (2,4) stained slides of tumors that are BRAF negative (1,2) and BRAF positive (3,4)

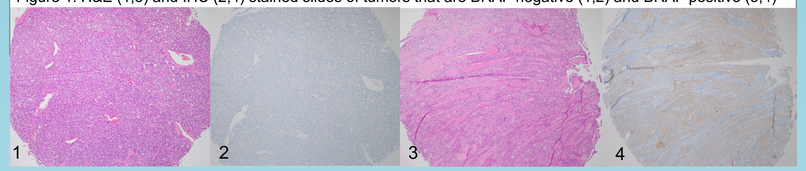
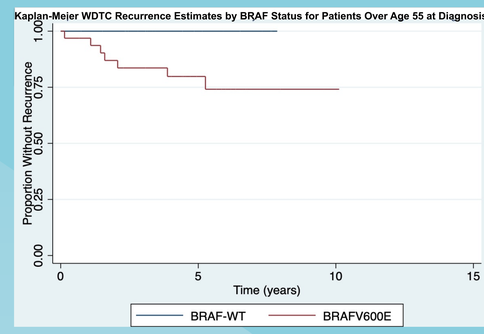


Table 2. Cancer Staging for Patients with WDTC by BRAF Status

	All	BRAF WT	BRAFV600E	P-Value
Patients	160	65	95	
T stage				0.58
T1a, n (%)	34 (21.4)	14 (21.5)	20 (21.3)	
T1b, n (%)	44 (27.7)	18 (27.7)	26 (27.7)	
T2, n (%)	35 (22)	18 (27.7	17 (18.1)	
T3, n (%)	44 (27.7)	14 (21.5)	30 (31.9)	
T4a	2 (1.3)	1 (1.5)	1 (1.1)	
N stage				**0.015**
N0, n (%)	101 (63.5)	49 (75.4)	52 (55.3)	
N1a, n (%)	35 (22)	9 (13.85)	26 (27.7)	
N1b, n (%)	23 (14.5)	7 (10.8)	16 (17)	
M stage				0.81
M0, n (%)	156 (99..4)	62 (98.1)	92 (97.9)	
M1, n (%)	3 (1.91)	1 (1.59)	2 (2.13)	
AJCC 8 stage				**0.0042**
I, n (%)	111 (69.8)	63 (96.9)	77 (81.9)	
II, n (%)	15 (9.4)	2 (3.1)	16 (17)	
III, n (%)	1 (0.63)	0 (0)	1 (1.1)	

	All	BRAF WT	BRAFV600E	P-Value
ATA risk category				**0.018**
Low, n (%)	77 (48.7)	40 (61.5)	37 (39.8)	
Intermediate, n (%)	66 (41.8)	19 (29.2)	47 (50.5)	
High, n (%)	15 (9.5)	6 (9.2)	9 (9.7)	
Radioactive iodine treatment, n (%)	82 (51.3)	29 (44.6)	53 (55.8)	0.17
Recurrence, n (%)	22 (13.8)	6 (9.2)	16 (16.9)	0.17
Recurrence time, years, mean, (SD)	1.9 (2.0)	0.84 (0.94)	2.3 (2.1)	**0.0487**
Mortality, n (%)	6 (3.8)	2 (3.1)	4 (4.3)	0.7

Response to therapy				0.93
Excellent, n (%)	112 (70.4)	45 (70.3)	67 (70.5)	
Indeterminate, n (%)	31 (19.5)	12 (18.8)	19 (20)	
Biochemically incomplete, n (%)	14 (8.8)	6 (9.4)	8 (8.4)	
Structurally incomplete, n (%)	2 (1.3)	1 (1.6)	1 (1.1)	



Features associated with recurrence

Variable	Odds Ratio	p value
BRAFV600E mutation	1.5	0.704
Age	0.96	0.159
Lymph node ratio	9.9	0.071
Extrathyroidal extension	43.5	0.001
Positive margin	2.8	0.33
Histology	0.99	0.982
Gender	4.5	0.173

Conclusion

- BRAFV600E is not an independent predictor of recurrence in this cohort
- BRAFV600E is associated with extrathyroidal extension, male gender, age, positive surgical margins, lymph node ratio, histology, ATA risk category, N stage, and AJCC 8 stage in univariate analysis
- Response to therapy is no different in BRAFV600E and WT groups
- Multivariable analysis showed only extrathyroidal extension as an independent predictor of recurrence
- Current treatment recommendations based on risk of recurrence appear to be appropriate and should not incorporate BRAFV600E as an independent variable

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