KRAS Mutations and Prognostic Implications in Appendiceal Cancers

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INTRODUCTION

- Despite shared embryonic origin, appendiceal cancers (AC) have distinct clinical and molecular features compared to colorectal cancers (CRC).
- Detection of mutant KRAS has been associated with worse survival in CRC, whereas in AC the prognostic significance of mutant KRAS (55-65% prevalence) has yet to be characterized.

METHODS AND STATISTICS

- AC tissues from 891 individual patients underwent DNA (592, NextSeq, or WES, NovaSeq) and WTS (NovaSeq) sequencing at Caris Life Sciences (Phoenix, AZ). Low-grade appendiceal mucinous neoplasms were excluded.
- Chi-square, Fishers-exact, and Mann Whitney U tests were used to determine statistical significance and were adjusted for multiple hypothesis testing (p<0.05).
- Overall survival was calculated using insurance claims of AC patients from time of sample collection to last contact.
- Hazard ratios (HRs) were calculated using the Cox proportional hazards model (log-rank test).
- Multivariate regression analysis was performed on age, sex, histology and $KRAS^{mut}$. vs $KRAS^{wt}$.

RESULTS

- AC histological subtypes comprised mucinous adenocarcinoma (44.9%), signet ring cell carcinoma (13.4%), goblet cell carcinoma (23.8%) and adenocarcinoma- not otherwise specified (NOS, 18%).
- Among all AC specimens, KRAS was the most common mutation (49 %).
- $KRAS^{mut}$ vs $KRAS^{wt}$ tumors were more frequently associated with *TP53*^{mut} (48.6% vs. 36.8%, respectively; p<0.01) and $GNAS^{mut}$ (42.8% vs. 5.7%, respectively; p<0.00001).
- Most frequent co-mutant gene with *KRAS* was TP53 (61.2%) in adenocarcinoma-NOS, and GNAS (46.9%) in mucinous adenocarcinomas.
- KRAS G12D is the most common mutation.
- Median OS among $KRAS^{mut}$ vs $KRAS^{wt}$ was 35.0 vs. 24.1 months, respectively (HR=0.65, 95% CI: 0.54-0.80, p<0.0001).
- $KRAS^{mut}$ was associated with a trend towards improved survival in mucinous adenocarcinomas (HR 0.61; 95% CI:0.43-0.86, p0.005) but not with signet ring cell (HR 1.20; 95% CI:0.66-2.20, p 0.53) or goblet cell carcinoma (HR 1.17; 95% CI: 0.58-2.34, p 0.648).
- On multivariate analysis $KRAS^{mut}$ was an independent prognostic factor for improved survival among all AC (HR 0.63, 95% CI:0.51-0.80, p 0.0001).
- Notably, $GNAS^{mut}$ was associated with improved survival (HR 0.57, 95% CI:0.47-0.70, p<0.00001), while $TP53^{mut}$ was associated with poorer survival (HR 1.58, 95% CI:1.35-1.86, p<0.00001) among all AC.

CONCLUSIONS

- KRAS was one of most frequently mutated genes in ACs. In contrast to CRC, $KRAS^{mut}$ was associated with significantly improved survival.
- This observed survival advantage remained consistent in the histologic subgroup of mucinous adenocarcinoma, but not in goblet and signet ring cell cancers.
- Prospective trials evaluating survival advantage of KRAS mutations and its implications in choosing future targeted therapies should be performed as well as analysis on response to current therapy.

Table 1: **Baseline characteristics**

	All cancers	Mucinous Adenocarcinoma	Signet Ring Cell Carcinoma	Goblet | Neuroendocrine	Adenocarcinoma-NOS	
Total cases	891	400	119	212	160	
Median age [range]	62 [22 – 90]	61 [29 – 90]	63 [40 – 88]	62 [22 – 90]	60 [28 – 85]	
	N (%)	N (%)	N (%)	N (%)	N (%)	Chi-square (p-value)
Male Gender	458 (51.4)	180 (45.0)	62 (52.1)	86 (40.6)	96 (60)	16.12 (0.001)
Race						
White	493/639 (73.8)	209/291 (71.8)	73/90 (81.1)	132/172 (76.7)	79/115 (68.7)	
African American	97/639 (14.5)	41/291 (14.1)	13/90 (14.4)	16/172 (9.3)	27/115 (23.5)	20.29 (0.016)
Asian Pacific Islander	32/639 (4.8)	15/291 (5.1)	2/90 (2.2)	12/172 (7.0)	3/115 (2.6)	
Others	46/639 (6.9)	26/291 (8.9)	2/90 (2.2)	12/172 (7.0)	6/115 (5.2)	
Ethnicity						
Hispanic	89/641 (13.2)	53/300 (17.7)	10/90 (11.1)	11/161 (6.8)	15/117 (13.0)	11.18 (0.011)
Non-Hispanic	579/641 (86.7)	247/300 (82.3)	80/90 (88.9)	150/161 (93.2)	102/117 (87.0)	

* Race and ethnicity data is only available for 70% of patients

Figure 1: **Frequency of KRAS mutation subtypes**

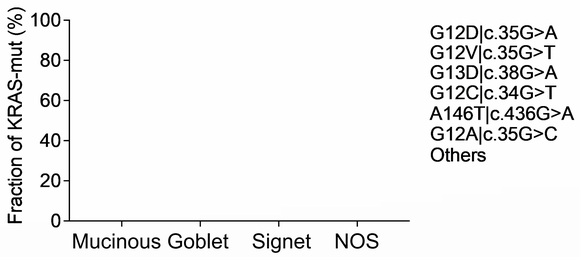


Figure 2: MPAS score

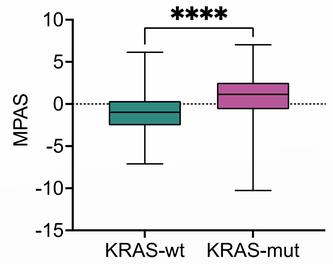


Figure3: **Molecular profiling: KRAS mutant vs. wild type**

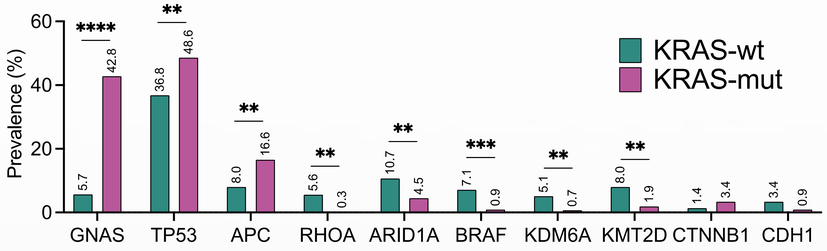
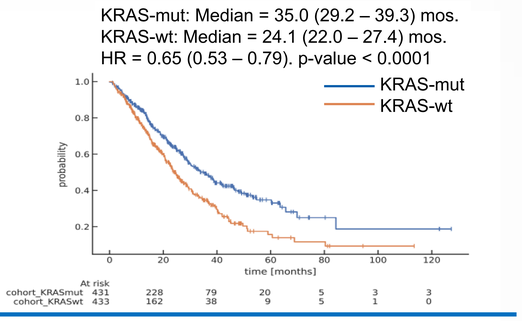


Table 2: **Multivariate regression analysis**

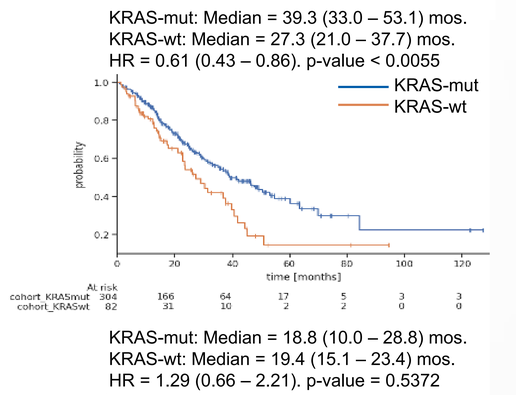
	All cancers		Mucinous Adenocarcinoma	
	HR (95% CI)	P*	HR (95% CI)	P*
Age Group				
<50 years	Reference		Reference	
≥ 50 years	1.30 (1.01 – 1.67)	0.042	1.40 (0.94 – 2.09)	0.092
Sex				
Male	Reference		Reference	
Female	0.96 (0.79 – 1.16)	0.700	0.78 (0.57 – 1.07)	0.121
Race				
White	Reference		Reference	
African American	0.62 (0.39 – 1.12)	0.11	1.07 (0.47 – 2.43)	0.878
Asian or Pacific islander	0.75 (0.53 – 1.06)	0.104	0.80 (0.45 – 1.44)	0.460
Others	0.70 (0.44 – 1.11)	0.131	1.05 (0.54 – 2.06)	0.878
Mutation Profile	Reference - wild type			
KRAS -mutant	0.63 (0.51 – 0.80)	0.0001	0.64 (0.43 – 0.96)	0.031
TP53 -mutant	1.6 (1.3 – 1.96)	0.0	1.84 (1.33 – 2.56)	0.0002
BRAF -mutant	0.8 (0.49 – 1.32)	0.389	0.58 (0.23 – 1.50)	0.263
APC -mutant	1.02 (0.75 – 1.39)	0.877	1.13 (0.65 – 1.98)	0.659
GNAS -mutant	0.84 (0.63 – 1.11)	0.220	0.83 (0.58 – 1.18)	0.291

Figure 4: **Survival analysis - KRAS mutant vs wild type**

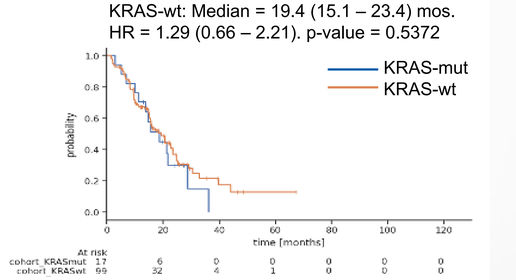
All appendiceal cancers



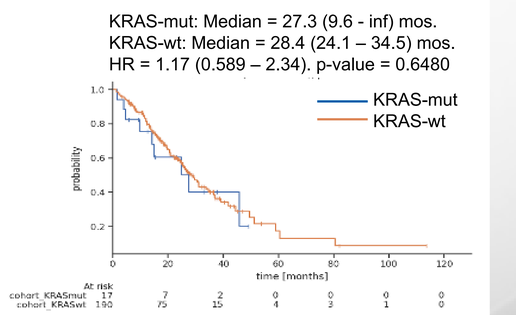
Mucinous adenocarcinoma



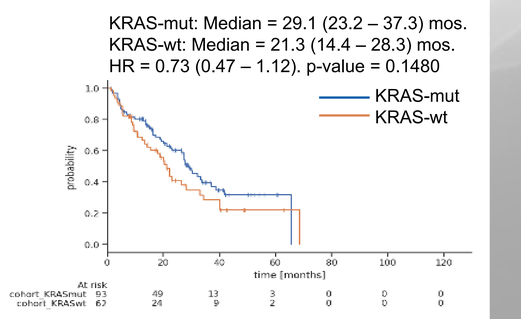
Signet Ring Carcinoma



Goblet|Neuroendocrine



Adenocarcinoma - NOS



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