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Introduction

- Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and therapy-resistant cancer with an overall 5-year survival rate of almost 12%, making it among the most lethal of all major cancers.[1]
- PDAC has a distinct genomic profile, with somatic KRAS proto-oncogene mutations in ~90% of cases.[2,3]
- Current literature has not reached a consensus on disease prognosis based on KRAS mutation subtype.[2-5]

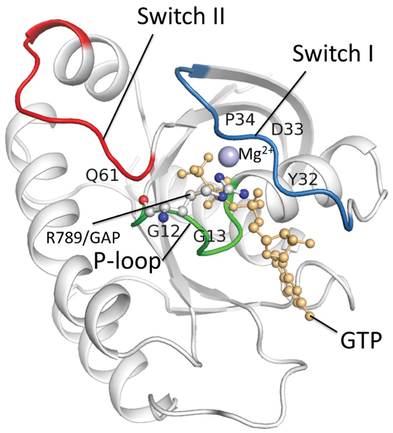

Figure 1. Model of Human KRAS.

- ✧ Mutant KRAS (mKRAS) drives PDAC replication, invasion, metabolic reprogramming, and therapy resistance.
- ✧ KRAS codons 12, 13, and 61 are prone to mutations and display differing effects on patient survival.[2-5]
- ✧ Mutations in G12 and G13 decrease GTPase activating protein (GAP) binding.
- ✧ Q61 mutations impair the intrinsic GTPase function of KRAS.
- ✧ Both mechanisms ultimately result in a stable GTP-bound KRAS and over-activation of the RAS pathway.[4]

Objective

- The goal is to measure the overall survival (OS) of resected PDAC patients based on common KRAS mutations compared to wild-type KRAS (wtKRAS) from Thomas Jefferson University Hospital.

Methods

- IRB-approved retrospective cohort study: medical chart review using Epic electronic health records system.
- Initial study cohort of 454 PDAC patients who underwent curative-intent pancreatic resection at Jefferson Pancreas, Biliary and Related Cancer Center between 2016-2021.
- Metastatic and non-PDAC cases with perioperative mortality, defined as death within 30 days of surgery, were excluded to yield a final study cohort of 280 patients.
- Demographic, perioperative, histologic, genetic, and oncologic outcome data were recorded.
- Genetic data from surgical specimens were obtained from next-generation sequencing assays in mutation-prone regions of the KRAS gene on chromosome 12p, including the hotspot codons 12, 13, and 61.
- Compared OS of patients with common mKRAS versus wtKRAS.
- Kaplan-Meier (KM) survival analyses were used to study effects of different mKRAS on length of survival after resection.
- Investigated additional variables known to impact survival: age at surgery, tumor size, lymph node involvement, perineural invasion, and lymphovascular invasion.[2-5]
- Cox hazard regression models were used for multivariate analysis of KRAS genetics and the negative prognostic factors listed above on OS.

Results

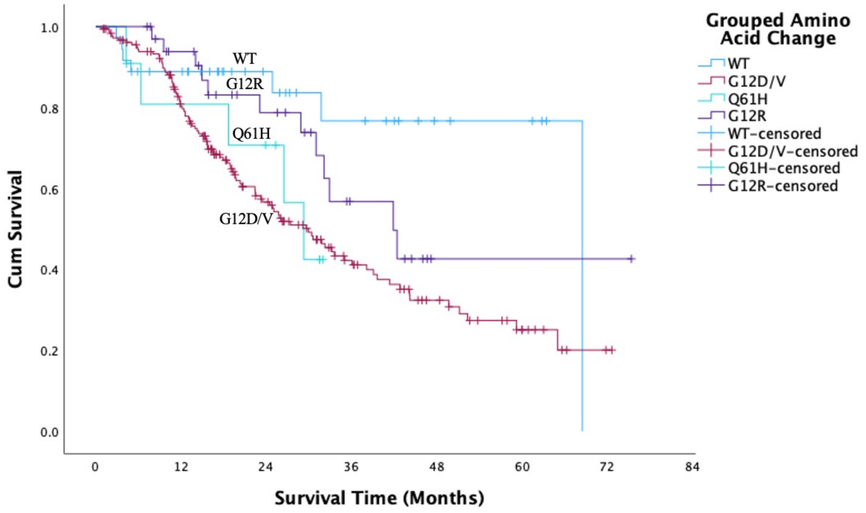

Figure 2. Kaplan-Meier model. Overall survival outcomes of 280 PDAC patients based on KRAS subtype. WT = wild-type. P = 0.007.

- 36 wtKRAS patients with a mean OS of 56.47 ± 4.82 months.
- 36 G12R patients with a mean OS of 48.13 ± 5.51 months.
- 184 G12D or G12V patients with a mean OS of 35.76 ± 2.15 months.
- 11 Q61H patients with a mean OS of 24.37 ± 3.16 months.
- Mean OS of entire cohort was 39.93 ± 2.00 months.

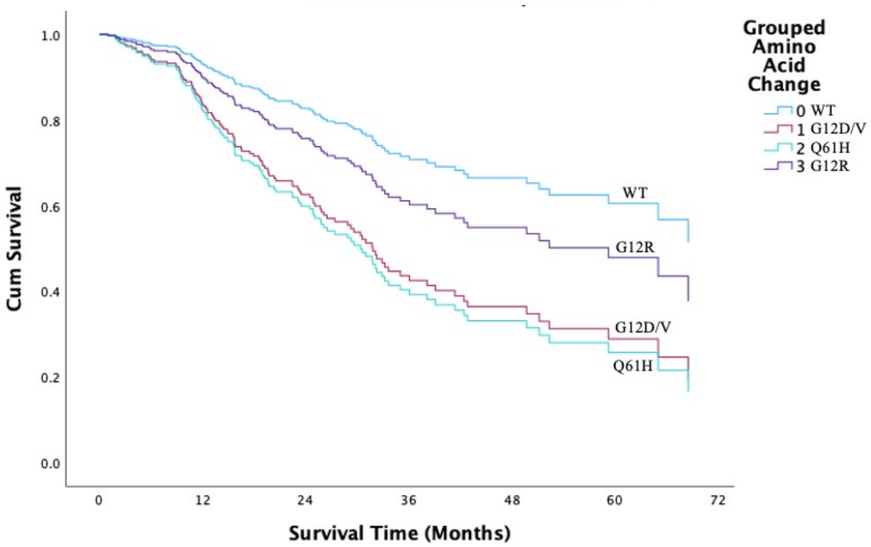

Figure 3. Cox Regression Model. Overall survival outcomes of 280 PDAC patients based on KRAS subtype, age at surgery, tumor size, perineural invasion, and lymphovascular invasion. WT = wild-type. P < 0.001.

Results (Continued)

Table 1. Cox Regression Analysis. Impact of covariates on overall survival (P < 0.001).

	HR	95% CI		P-Value
		Lower	Upper	
Age At Surgery (years)	1.030	1.008	1.052	0.007
Tumor Size (cm)	1.129	0.963	1.323	0.136
Perineural Invasion	2.070	1.093	3.921	0.026
Lymphovascular Invasion	1.916	1.257	2.922	0.003
KRAS Wild-Type	Reference Category			--
KRAS G12D/G12V	2.474	1.036	5.909	0.041
KRAS Q61H	2.707	0.787	9.314	0.114
KRAS G12R	1.467	0.512	4.210	0.476

- Since KM and Cox analyses (not shown) initially revealed G12D and G12V mutations to be similar in terms of OS, these patients were grouped together.
- Patients with either G12D or G12V were correlated with worse overall survival (HR 2.5, P = 0.04) compared to those with wtKRAS.
- Q61H, while not significant, also trended toward conferring worse survival compared to wtKRAS (HR 2.7, P = 0.11).
- G12R did not significantly differ in survival compared to wtKRAS (HR 1.5, P = 0.48).

Conclusions

- Kaplan-Meier analysis revealed KRAS mutational status to be associated with significant variability in OS **(Figure 2)**.
- Cox regression analysis revealed worse survival with increased age and the presence of perineural and lymphovascular invasion (P < 0.05) (**Table 1**).
- In resected PDAC patients, G12D and G12V mutations were associated with worse overall survival compared to wtKRAS, whereas G12R was not significantly different than wtKRAS.
- This study is limited to early-stage (resectable) PDAC and underpowered from single-institutional data. Due to the retrospective design, it can potentially source patient records of poor quality. Improvements in statistical significance can be found with a multi-institutional study.
- The small sample size of this study warrants further research to elucidate survival differences between KRAS mutations and investigate other mKRAS to predict patient prognosis and guide targeted therapies (e.g., Sotorasib: G12C inhibitor) to improve survival.

Acknowledgements

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