The Prognostic Significance of *TP53* Mutations in Patients with Right-Sided and Left-Sided Colorectal Cancer

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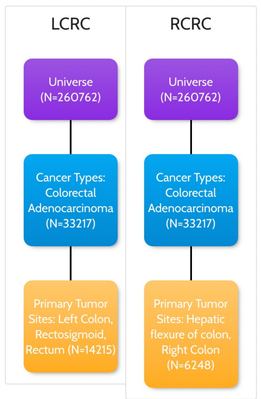
Background

- In patients with colorectal cancers (CRCs), prior studies have reported that various *TP53* mutations (*mTP53)* have prognostic significance.
- The anatomic location of CRC and the *mTP53 or abnormal nuclear accumulation of p53* influence patient survival (Manne et. al).
- Pan et. al reported that poorer survival of patients with metastatic right-sided CRC (RCRC) versus left-sided CRC (LCRC) appeared to be restricted to the subset with non-gain of function (GOF) mutp53, whereas GOF versus non-GOF mutp53 was associated with poorer survival only among patients with LCC.
- Pan et. al also suggested that the approach of collectively classifying mutp53 into GOF and non-GOF provides new insight for prognostic stratification and for understanding the mechanism of sidedness-dependent prognosis. If confirmed, future CRC clinical trials may benefit from incorporating this approach.
- In this study, we explored the prognostic significance of *mTP53* classified as GOF or non-GOF in patients with RCRC and LCRC in a larger cohort.

Materials and Methods

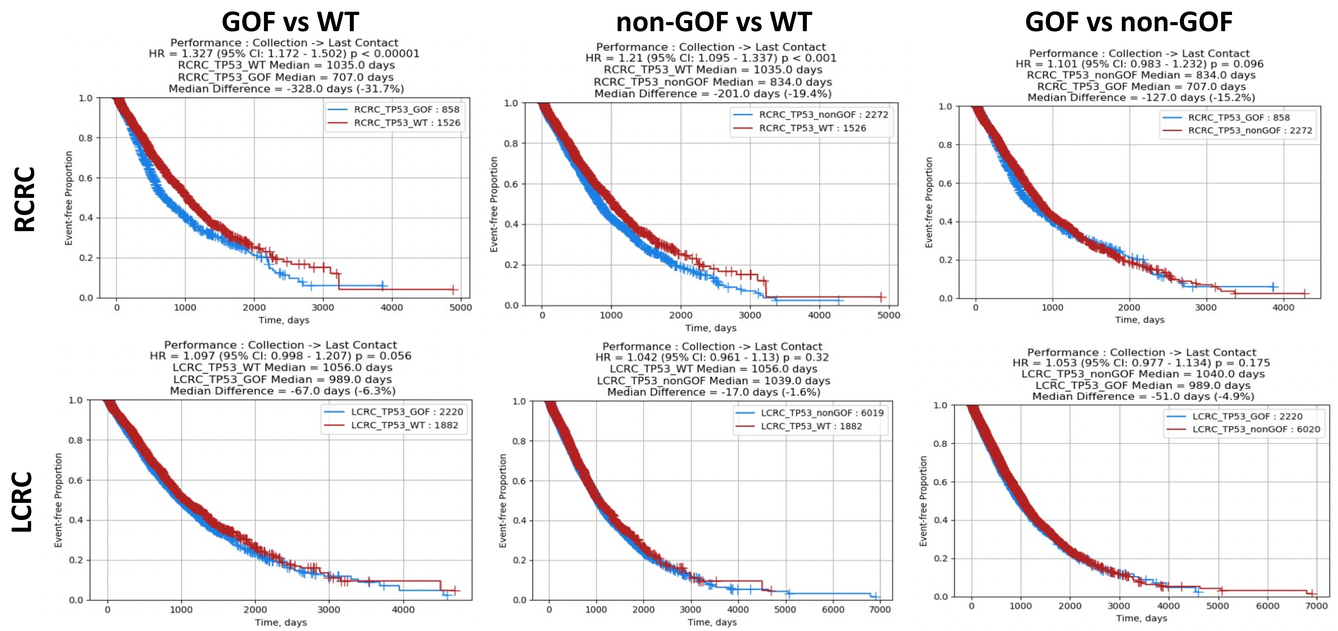
- CRC specimens (6,248 RCRCs and 14,215 LCRCs) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing (NGS) of DNA (592-gene panel or whole- exome sequencing).
- RCRC were defined as arising from the cecum to the hepatic flexure and LCRC from the splenic flexure to the rectum. Tumors of the transverse colon were deemed neither right- nor left- sided and were excluded from analysis
- *R175H*, *R248W*, *R248Q*, *R249S*, *R273H*, *R273L*, and *R282W* were defined as GOF *mTP53* and all other *mTP53* were defined as non-GOF *mTP53*.
- MSI-H/dMMR status was determined by immunohistochemistry (IHC) of MMR proteins and/or NGS. Real-world median overall survival (mOS) was obtained from insurance claims data and calculated from tissue collection to last contact using Kaplan-Meier estimates.

Figure 1: Consort Diagram



Results

Figure 2: Prognostic impact of the type of TP53 mutations on RCRC and LCRC



In RCRC, the mOS for patients with GOF *mTP53 vs. wtTP53* was 23months(m) vs. 34m ($p < 0.00001$), non-GOF *mTP53* vs. *wtTP53* was 27m vs. 34m ($p < 0.001$) and GOF *mTP53 vs.* non-GOF *mTP53* was 23m vs. 27m (p=0.096). In LCRC, the mOS for patients with GOF *mTP53 vs. wtTP53* was 32m vs. 35m (p=0.056), non-GOF *mTP53* vs. *wtTP53* was 34m vs. 35m (p=0.32) and GOF *mTP53 vs.* non-GOF *mTP53* was 32m vs. 34m (p=0.175).

Tables 1 & 2: Impact of TP53 mutants on CRC prognosis in the presence of specific oncogenic alterations

RCRC				
Oncogenic Drivers/MSS-MMR Status		TP53 Status		
		GOF vs WT	non-GOF vs WT	GOF vs non-GOF
		Hazard Ratio		
KRAS	WT	**1.235**	1.125	1.102
	MT	**1.373**	**1.251**	1.105
BRAF	WT	**1.232**	**1.127**	1.095
	MT	**1.78**	**1.474**	1.227
PIK3CA	WT	**1.293**	**1.173**	1.102
	MT	**1.505**	**1.274**	1.185
MSS/MMR	Stable/Proficient	**1.219**	**1.126**	1.083
	Instability-High/Deficient	1.538	**1.359**	1.111

LCRC				
Oncogenic Drivers/MSS-MMR Status		TP53 Status		
		GOF vs WT	non-GOF vs WT	GOF vs non-GOF
		Hazard Ratio		
KRAS	WT	0.903	0.926	0.976
	MT	**1.371**	**1.172**	**1.169**
BRAF	WT	1.091	1.034	1.054
	MT	1.192	1.144	1.065
PIK3CA	WT	1.036	0.986	1.05
	MT	**1.326**	**1.326**	1.029
MSS/MMR	Stable/Proficient	1.097	1.039	1.055
	Instability-High/Deficient	0.84	1.284	0.671

The hazard ratio (HR) to ascertain the impact of *TP53* mutants in the presence of oncogenic drivers and MSS-MMR status are listed for RCRC and LCRC respectively. Compared to wt*TP53* the worse prognosis associated with *mTP53* in RCC was seen in all comparisons, except in GOF *mTP53*/MSI- H/dMMR, and non-GOF *mTP53*/*wtKRAS* subgroups. Similarly, in patients with LCRC, worse prognosis associated with GOF *mTP53* and non-GOF *mTP53* was only noticeable in *KRAS* and *PIK3CA* mutant subgroups. HRs colored in red font reflect comparisons that are statistically significant (p<0.05)

- GOF *mTP53* and non-GOF *mTP53* were identified in 15% and 39% respectively, in RCRC and 17% and 46% respectively, in LCRC.
- The prognostic value of GOF *mTP53* and non-GOF *mTP53* was further explored in relation to MSI-H/dMMR, *RAS*, *BRAF,* and *PIK3CA* mutation status.
- The worse prognosis associated with *mTP53* in RCRC was seen in all comparisons, except in GOF *mTP53*/MSI-H/dMMR, and non-GOF *mTP53*/*wtKRAS* subgroups.
- In patients with LCRC, worse prognosis associated with GOF *mTP53* and non-GOF *mTP53* was only noticeable in *KRAS* and *PIK3CA* mutant subgroups.

Summary and Conclusion

- This is the largest study to explore *TP53* mutations and their prognostic significance in patients with RCRC and LCRC.
- The prevalence of GOF *mTP53* and non-GOF *mTP53* was higher in LCRC compared to RCRC.
- However, both GOF *mTP53* and non-GOF *mTP53* were associated with worse mOS for patients with RCRC, but not LCRC.
- Our study validates the sidedness-dependent prognostic significance of *TP53* mutations.
- It also shows that the worse prognosis of *mTP53* is independent of the approach of collectively classifying *TP53* mutations into GOF *vs.* non-GOF.
- Given the sheer extent and diversity of *TP53* mutations, a more nuanced approach towards re-classification of GOF *mTP53* is warranted.
- Detailed information on p53 mutations will be crucial for the interpretation of future clinical trials and for the design of novel therapeutic strategies.

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