Molecular characterization of appendiceal goblet cell carcinoid

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Introduction

- Goblet cell carcinoid (GCC) is a very rare malignant neoplasm, almost exclusively seen in the appendix, with an incidence of approximately 0.01-0.05/100,000/year[1)].
- According to the SEER database, 3-year overall survival (OS) rate of appendiceal GCC is 96.6%, 91.7%, 65.3% and 32.9% for stage I, II, III and IV diseases, respectively[2)].
- Due to their rarity, data on GCC are scarce and the ENETs Consensus Guidelines includes the minimal consensus statement on the treatment of GCC[3)].
- While GCC have both glandular and neuroendocrine morphology, it exhibits distinct clinical behavior compared to both appendiceal adenocarcinoma and neuroendocrine tumor (NET)[4)].
- There are very few genetic studies focusing on the molecular differences between GCC and other appendiceal tumors[5)].

Methods

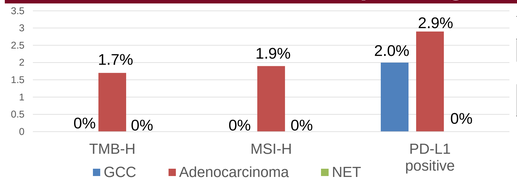
- Samples submitted to a commercial CLIA-certified laboratory (CARIS Life Sciences) from April 2015 to September 2019 were retrospectively analyzed for their molecular alteration. FFPE samples were sent for analysis from clinical physicians around the world. A total of 495 appendiceal tumor samples (53 GCCs, 428 adenocarcinomas and 14 NETs) were analyzed. Molecular characteristics of GCCs are compared with those of adenocarcinomas and NETs.
- Next-Generation Sequencing (NGS) was performed on genomic DNA isolated from FFPE samples using the NextSeq platform (Illumina, Inc.). A custom-designed SureSelect XT assay was used to enrich 592 whole-gene targets (Agilent Technologies).
- Microsatellite instability (MSI) / mismatch repair (MMR) status was tested with a combination of NGS, immunohistochemistry (IHC) and fragment analysis.
- Tumor mutational burden (TMB) was measured by counting all nonsynonymous missense mutations found per tumor [592 genes and 1.4 megabases (MB) sequenced/tumor]. The threshold to define TMB-high (TMB-H) was ≥17 mutations/MB. This threshold was established by comparing TMB with MSI by fragment analysis in colorectal cancer cases, based on reports of TMB having high concordance with MSI-H in colorectal cancer.
- PD-L1 was tested by IHC (using SP142 antibody) and tumor proportion score ≥5% was regarded as PD-L1 positive.

Results

Patient characteristics

Characteristics		GCC (N = 53)	Adenocarcinoma (N = 428)	NET (N = 14)	*P*-value	
Age	Average	57.6	58.2	44.4	GCC vs Adeno GCC vs NET	0.75 <0.01
Sex	Male (%) Female (%)	25 (47) 28 (53)	193 (45) 235 (55)	7 (50) 7 (50)	GCC vs Adeno GCC vs NET	0.77 0.85

Immune profiling

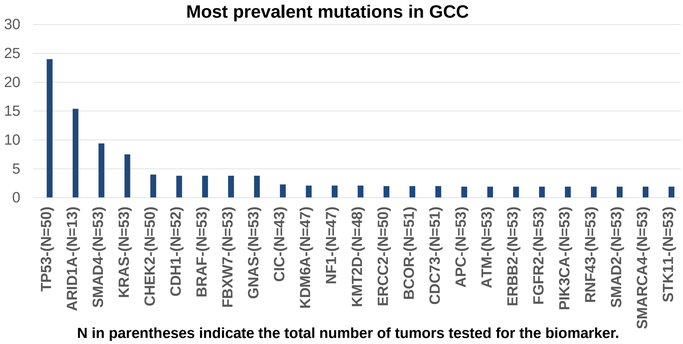


Test	GCC	AC	NET
TMB-H	52	409	14
MSI-H	53	427	14
PD-L1	51	412	14

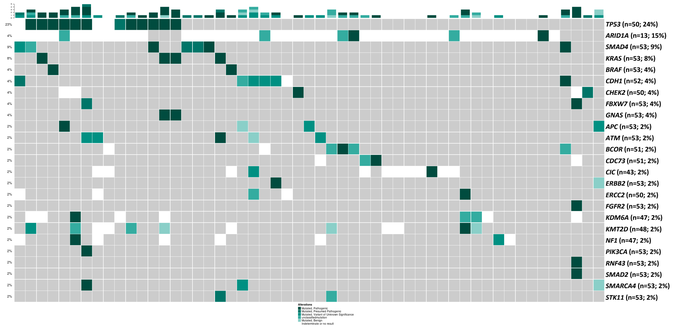
N=Total number of tumors tested

* No significant differences were observed in the immune profiling.

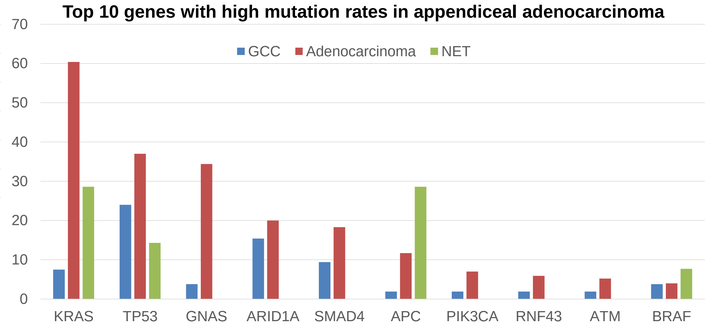
Gene mutations in GCC



N in parentheses indicate the total number of tumors tested for the biomarker.



Comparison of mutation rate



All genes showing significant *p*-value in the comparison of mutation rate

	Mutation rate		*P*-value
	GCC	AC	
KRAS	7.5%	60.4%	<0.01
GNAS	3.8%	34.4%	<0.01
APC	1.9%	11.7%	0.03
CDH1	3.8%	0.7%	0.04
CHEK2	4.0%	0.3%	<0.01
CDC73	2.0%	0.0%	<0.01
ERCC2	2.0%	0.0%	<0.01
FGFR2	1.9%	0.0%	<0.01

	Mutation rate		*P*-value
	GCC	NET	
KRAS	7.5%	28.6%	0.03
APC	1.9%	28.6%	<0.01
BRCA2	0.0%	7.1%	0.05
FANCA	0.0%	7.1%	0.05

Summary

- The age at diagnosis was significantly higher in patients with GCC than in those with NET (average, 57.6 vs 44.4). It was not different between GCC and adenocarcinoma (average, 57.6 vs 58.2).
- A gender preference was not observed for GCC. The proportion of gender did not differ between GCC and adenocarcinoma/NET.
- In GCC, TMB-H, MSI-H and PD-L1-positive were seen in 0.0%, 0.0% and 2.0%, respectively. These immune profiles were not different from those of adenocarcinoma and NET.
- Most prevalent mutations in GCC were observed in *TP53* (24.0%), *ARID1A* (15.4%), *SMAD4* (9.4%), *KRAS* (7.5%) and *CHEK2* (4.0%.)
- Compared to adenocarcinoma, GCC showed significantly lower mutation rate in *KRAS* (7.5% vs 60.4%), *GNAS* (3.8% vs 34.4%) and *APC* (1.9% vs 11.7%), and significantly higher mutation rate in *CDH1* (3.8% vs 0.7%), *CHEK2* (4.0% vs 0.3%), *CDC73* (2.0% vs 0.0%), *ERCC2* (2.0% vs 0.0%) and *FGFR2* (1.9% vs 0.0%).
- Compared to NET, GCC showed significantly lower mutation rate in *KRAS* (7.5% vs 28.6%), *APC* (1.9% vs 28.6%), *BRCA2* (0.0% vs 7.1%) and *FANCA* (0.0% vs 7.1%).

Conclusions

GCC showed considerably distinct mutational profile compared to appendiceal adenocarcinoma and NET. Understanding these molecular characteristics may be critical for a development of effective treatment strategy in GCC.

References

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