Clinical implications of molecular alterations in intraductal carcinoma of the prostate

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Background

Intraductal carcinoma of the prostate (IDC-P) is a recent addition to the 2016 WHO classification system and little is known about the nature of its true incidence and biology. Clinically, it has been observed to be associated with higher grade group tumors and a more aggressive disease course with a high risk of local recurrence and distant metastasis. However, the molecular underpinnings which define IDC-P are not well elucidated. Initial case series with molecular profiling have suggested an enrichment of alterations in DNA damage/repair (DDR), PI3K, WNT and MAPK pathways. We now present comprehensive molecular profiling data from the largest cohort of IDC-P reported to date in order to better characterize this relatively new histologic entity.

Methods

Eligible patients included those with radical prostatectomy tumor tissue labeled as IDC-P on testing requisition with available tissue-based DNA and RNA sequencing utilizing a commercially available CLIA-certified assay (Caris Life Sciences). Prostatic tumor specimens were analyzed using NextGen DNA sequencing (NextSeq, 592 genes and NovaSeq, WES). Digitized H&E slides underwent central pathological review by a board-certified pathologist (SW) specializing in genitourinary malignancies to confirm presence of intraductal histology according to the 2022 WHO classification[1].

Table 1: Patient Demographics of confirmed IDC-P.

Count (N)	31
Median Age [range]	64 [44 - 79]
Median TMB [range]	2.0 [1.0 - 6.0]

Results

Figure 1: Intraductal carcinoma of the prostate with comedonecrosis, with surrounding dense cribiform glands[1].

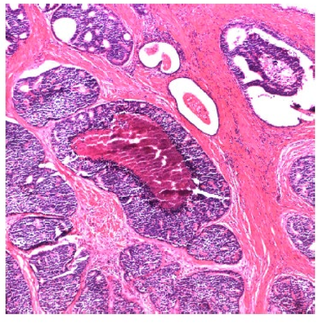

Figure 1: Gleason score distribution for IDC-P.

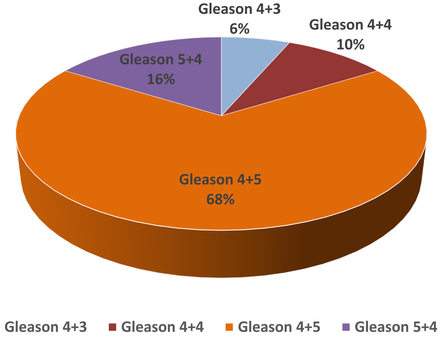

Table 2: Most prevalent alterations in IDC-P.

Pathway Implication	Test	Positive	Negative	Total	% intraductal
Cell cycle	*NGS-TP53*	12	19	31	38.7
	NGS-RB1	1	20	21	4.8
	NGS-PPP2R2A	1	30	31	3.2
	NGS-CDKN1B	1	30	31	3.2
Chromatin remodel	*NGS-SMARCA4*	1	30	31	3.2
	NGS-KMT2D	1	30	31	3.2
	NGS-KDM6A	1	29	30	3.3
	NGS-KMT2A	1	30	31	3.2
	NGS-TET2	1	28	29	3.4
DDR	*NGS-BRCA1*	1	30	31	3.2
	NGS-CDK12	3	28	31	9.7
	NGS-ATM	2	29	31	6.5
	NGS-BRCA2	1	29	30	3.3
Fusions	*Fusion-TMPRSS2*	12	19	31	38.7
	Fusion-SLC45A2	1	30	31	3.2
	Fusion-MAST2	1	30	31	3.2
	Fusion-ETV5	1	30	31	3.2
	Fusion Variant-AR	2	29	31	6.5
PI3K/AKT/MTOR	*NGS-PIK3CA*	3	28	31	9.7
	NGS-PTEN	1	29	30	3.3
	NGS-PIK3R1	1	29	30	3.3
	NGS-AKT1	2	29	31	6.5
WNT	*NGS-RNF43*	1	30	31	3.2
	NGS-CTNNB1	1	30	31	3.2
	NGS-APC	1	30	31	3.2
Other	*NGS-LOH*	1	28	29	3.4
	NGS-SPOP	3	28	31	9.7
	NGS-FOXA1	5	26	31	16.1
	CNA-ARNT	1	30	31	3.2

Figure 2: Oncoprint of 10 most prevalent alterations for IDC-P.

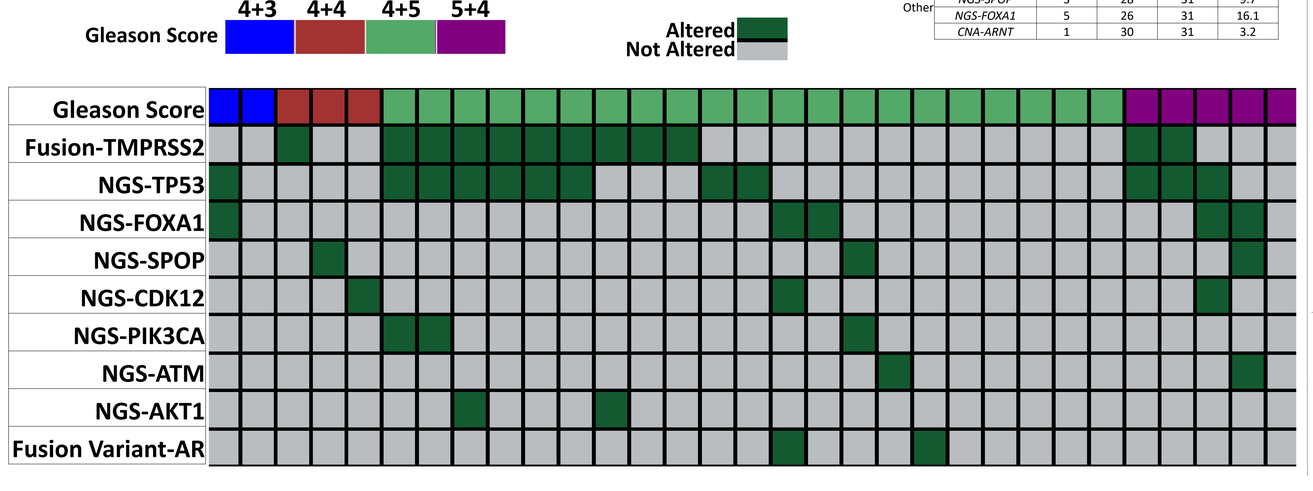

Table 3: FOXA1 pathogenic variants in IDC-P.

Effect	FOXA1 Protein change
CODON_DELETION	N252_G257del
CODON_DELETION	F254_L260del
Missense	G257A
Missense	R261G
Missense	H247Y

Conclusions

- This data suggests that IDC-P harbors targetable molecular alterations in DDR genes (*BRCA1/2* and *CDK12*) with approved targeted agents (e.g. PARP inhibitors).
- We also found enrichment of oncogenic *FOXA1* mutations in IDC-P which are associated with prostate cancer progression, castrate-resistance and an unfavorable prognosis.
- There were no tumors which demonstrated mismatch-repair deficiency (dMMR) or microsatellite instability and none of the profiled tumors had a high tumor mutational burden (> = 10 mutations/megabase).
- Further efforts are ongoing to expand this cohort of IDC-P cases and compare them with a matched cohort of pure adenocarcinoma cases and will include analysis of key RNA expression signatures.

References

1. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. *Eur Urol.* 2016;70(1):106-119. doi:10.1016/j.eururo.2016.02.028