Clinical-Pathologic and Molecular Features of *IDH1*-Mutant Prostate Cancers

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Background

- Prostate cancers with *IDH1* mutations (*IDH1*-mt) represent a rare (<1%), potentially targetable subtype characterized by genome-wide DNA hypermethylation.
- One previous cohort of four *IDH1*-mt tumors identified the presence of psammomatous calcifications and anterior tumor location as pathologic features of these tumors, however clinical follow-up was not available.
- Here, we report the clinical-pathologic and molecular features for 10 *IDH1*-mt prostate tumors from Johns Hopkins (JH) and 35 *IDH1*-mt tumors from Caris, and we examine clinical outcomes in a separate group (n=24) from cBioportal.

Design

- JH cases (n=10) were primary tumors identified by immunohistochemistry specific for the R132H mutation (Clone H09, Dianova) performed on tissue microarrays (n=2) or research-based or clinical next generation sequencing (NGS) assays (n=8). 80% (8/10) had radical prostatectomy tissue available for pathologic re-review, and 6 of these had known ERG and PTEN status based on genetically validated immunohistochemistry.
- Caris cases (n=35) were identified by NGS, including 27 primary/local disease samples and 8 metastatic samples. 89% (24/27) of local samples and 100% (8/8) of metastatic samples had paired H&E images for re-review.
- cBioportal cases (n=24) were compared to *IDH1*-wild type (-wt) cases (n=10,677).

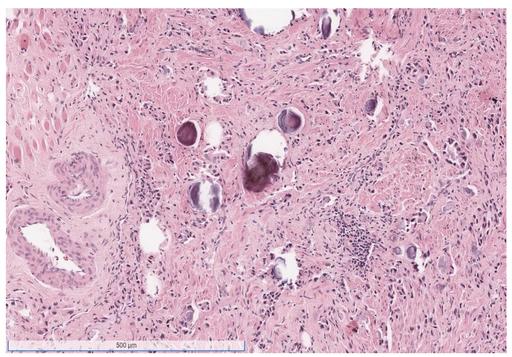

Figure 1. *IDH1*-mt prostatic adenocarcinoma with poorly formed glands, and single cells with scattered intratumoral psammomatous calcification in the anterior apex.

Results

Table 1: Clinical-pathologic features of JH *IDH1*-mt cases

ID	IDH1 mutation	ID'd by	Age at diagnosis	IDH1 mutation	Self-reported Race	Family history	PSA at diagnosis	Gleason at diagnosis	Stage at Diagnosis (TNM)	Risk Group	Psammoma bodies	Anterior tumor
1	R132H	NGS	58	R132H	Unk	None	23.8	5+5=10 (5)	T3bN0M0	Very high	ND	ND
2	R132H	NGS	48	R132H	Asian	Yes	49	4+5=9 (5)	T2cN0M0	High	No	Yes
3	R132C	NGS	61	R132C	Unk	Yes	2.7	4+3=7 (3)	T2bN0M0	Unfavorable intermediate	ND	ND
4	R132C	NGS	67	R132C	White	Yes	6.7	4+5=9 (5)	T3bN0	Very high	No	No
5	R132L	NGS	62	R132L	Black	Unk	Unk	3+4=7 (2)	T3aN0M0	Favorable intermediate	Yes	Yes
6	R132C	NGS	65	R132C	Black	None	5.4	3+4=7 (2)	T3bN0M0	Favorable intermediate	No	No
7	R132C	NGS	40	R132C	Black	None	7.4	5+3=8 (4)	T3aN0M0	Very high	Yes	Yes
8	R132G	NGS	63	R132G	Black	Yes	4	4+3=7 (3)	T2cN0M0	Unfavorable intermediate	No	Yes
9	R132H	IHC	50	R132H	White	Unk	10	4+3=7 (3)	T2N0M0	Unfavorable intermediate	No	Yes
10	R132H	IHC	58	R132H	White	Yes	15.5	3+3=6 (1)	T2N0M0	Favorable intermediate	Yes	Yes

Clinical-pathologic summary of JH and Caris cases:

- JH and Caris *IDH1*-mt cases **commonly had adverse pathologic features** (potentially partly confounded by their selection for NGS).
- JH cases showed a predominance of anterior dominant tumor nodules.
- **Psammoma bodies were present in only a minority** of JH and Caris *IDH1*-mt cases (note that Hopkins cases were entirely re-reviewed for calcifications, while Caris cases had only one representative H&E available for re-review.

Molecular summary of JH and Caris cases:

- ***ETS* family fusions were rare** among the *IDH1*-mt cases ($p<0.05$ in comparison to *IDH1*-wt Caris cases).
- ***FOXA1* mutations were common** in *IDH1*-mt cases ($p<0.05$ in comparison to *IDH1*-wt Caris cases).

Table 2: Clinical-pathologic/molecular features of JH and Caris *IDH1*-mt cases

	JH cases	Caris cases
n	10 primaries	24 primaries, 8 mets
***IDH1* p.R132C, p.R132H, p.R132G**	40%, 40%, 10%	49%, 23%, 20%
Median age	60 years	69 years
Family history	63%	NA
Grade group 4/5	40%	67% primaries
Non-organ confined	50%	NA
Anterior dominant nodule	75%	NA
Psammoma bodies	38%	17% primaries, 13% mets
***ETS* family fusions**	0% (IHC)	4% primaries, 0% mets
***FOXA1* mutations**	33%	33% primaries, 25% mets

Clinical outcomes of JH and cBiorportal cases:

- JH cases: Although 40% (4/10) of *IDH1*-mt patients required radiation and androgen deprivation therapy after prostatectomy, **90% (9/10) had no evidence of disease** with a median follow-up of 15 years.
- cBioportal cases: Compared to *IDH1*-wt cases, *IDH1*-mt prostate cancer cases in cBioportal tended to have higher Grade Group (21% vs 10% with Grade Group 5, $p=0.073$), but longer survival ($p=0.200$).

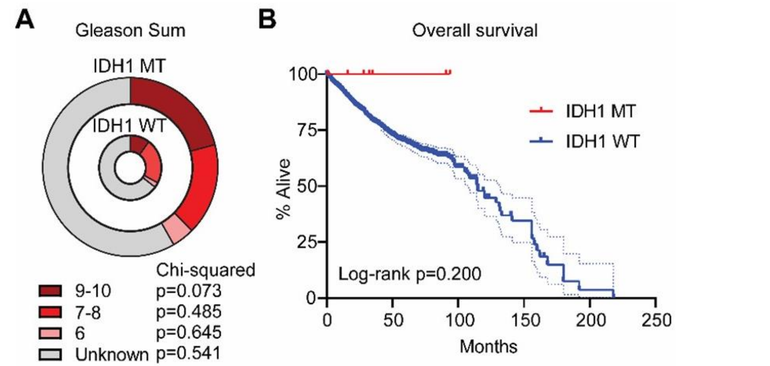

Figure. Comparison of features of pts with *IDH1*-mt PCa (n=24) vs *IDH1*-wt PCa (n=10,677) in cBioPortal database.

Conclusions

Data are limited by the rarity of this subtype, however *IDH1*-mt prostate tumors tend to have high grade and stage and anterior location, but favorable outcomes after radical prostatectomy. Psamommatous calcifications may be enriched but are not a sensitive indicator of this subtype in our cohorts. *FOXA1* mutations are common and *ETS* rearrangements are rare in *IDH1*-mt tumors.

References

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