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WNT pathway mutations in metachronous oligometastatic castration-sensitive prostate cancer

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Abstract

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Background—WNT signaling is a cellular pathway that has been implicated in the development and progression of prostate cancer. Oligometastatic castration-sensitive prostate cancer (omCSPC) represents a unique state of disease in which metastasis-directed therapy (MDT) has demonstrated improvement in progression-free survival. Herein, we investigate the clinical implications of genomic alterations in the WNT signaling cascade in men with omCSPC.

Methods—We performed an international multi-institutional retrospective study of 277 men with metachronous omCSPC who underwent targeted DNA sequencing of their primary/metastatic tumor. Patients were classified by presence or absence of pathogenic WNT pathway mutations (in the genes *APC*, *RNF43,* and *CTNNB1)*. Pearson's χ^2 and Mann-Whitney U were used to determine differences in clinical factors between genomic strata. Kaplan-Meier survival curves were generated for radiographic progression-free survival (rPFS) and overall survival (OS), stratified according to WNT pathway mutation status.

Results—A pathogenic WNT pathway mutation was detected in 11.2% of patients. Patients with WNT pathway mutations were more likely to have visceral metastases (22.6% vs 2.8%; p<0.01) and less likely to have regional lymph node metastases (29.0% vs 50.4%; p=0.02). At time of oligometastasis, these patients were treated with MDT alone (33.9%), MDT + limited course of systemic therapy (20.6%), systemic therapy alone (22.4%), or observation (defined as no treatment for ≥6 months following metastatic diagnosis). Multivariable cox regression demonstrated WNT pathway mutations associated with significantly worse OS (HR=3.87, 95%CI 1.25–12.00).

Conclusion—Somatic WNT pathway alterations are present in approximately 11% of patients with omCSPC and are associated with an increased likelihood of visceral metastases. While these patients have a worse natural history, they may benefit from MDT.

Introduction

Within the United States, prostate cancer represents the most common malignancy in men with nearly 250,000 new cases accounting for 34,000 deaths in 2021[1]. Although the majority of patients with prostate cancer have an indolent clinical course, there is a subset with more aggressive disease with progression to metastatic disease and ultimately lethal castration-resistance. Within castrate-resistant prostate-cancer (CRPC), genomic alterations have been extensively examined[2–5].

Mutations within the WNT signaling pathway have been identified in up to 20% of patients with CRPC[6,7]. The canonical WNT pathway is a evolutionarily conserved embryonic pathway that regulates key aspects of cell fate, cell-cycle progression, proliferation, and migration[8,9] and has been implicated in the pathogenesis of therapeutic resistance in several malignancies [10–12] . Within prostate cancer, WNT pathway activating genomic alterations are associated with inferior outcomes with androgen deprivation[13] possibly due to an androgen receptor independent proliferation through increased canonical WNT/β-catenin signaling[14]. Despite emerging evidence of the role of WNT pathway activating mutations within CRPC, significantly less is understood within castration-sensitive prostate cancer (CSPC)[15].

Within metastatic CSPC, there is a state of limited metastatic disease, termed oligometastasis (omCSPC) in which metastasis-directed therapy (MDT) may play an

integral role in therapy. Oligometastatic disease, typically defined as no more than 3–5 metastases, has demonstrated improved outcomes with metastasis directed therapy over standard of care in a variety of malignancies[16,17]. Within metachronous (development of metastasis >6 months after initial diagnosis) omCSPC, randomized clinical data has also demonstrated that MDT improves both progression-free and ADT-free survival compared to observation[18–20] . Despite this improvement, there remains heterogeneity of outcomes within this population and tumor genomics may provide crucial information to better understand the disease course. Given the important role of WNT pathway mutations within mCRPC, it is a candidate pathway to evaluate within omCSPC. Herein we aim to describe the incidence and type of WNT pathway mutations observed in patients with omCSPC and evaluate for associations with clinical outcomes.

Methods

Following IRB approval, we performed an international multi-institutional retrospective review of men with metachronous omCSPC who underwent next generation sequencing (NGS) of either their primary tumor or metastatic site. NGS was performed either through Foundation One CDx (324-gene panel), Personal Genome Diagnostics CancerSELECT 125 (125-gene panel), or Tempus xT tissue assay (648-gene panel) platforms. Patients included those treated at Johns Hopkins Hospital and Ghent Hospital receiving standard of care therapy (SOC) as well as those enrolled on the STOMP[18] and ORIOLE[19] clinical trials. Both clinical trials had IRB approval and all participants provided informed consent. All patients on STOMP and ORIOLE trials were evaluated for NGS however 14 patients had unavailable tissue (supplemental Figure 1). Patients treated as SOC underwent NGS at the discretion of their treating physician. Patients with samples that underwent NGS but failed were excluded from analysis. For this study, omCSPC was defined as ≤ 5 lesions on conventional imaging (CT/radionuclide bone scan) or enhanced (PET) imaging.

Patients were stratified according to presence of WNT pathway mutation status. Initial treatments included MDT alone (SABR or metastasectomy), MDT + limited course of systemic therapy, systemic therapy alone (ADT, androgen receptor signaling inhibitors or docetaxel), or observation defined as no therapy ≥ 6 months after diagnoses of omCSPC. Patients treated with MDT were required to have receive local therapy to all sites of conventional imaging detected metastases. WNT pathway mutations included pathogenic mutations of *APC*, *RNF43*, or *CTNNB1*. Available follow-up data from serial physical examinations, imaging, and prostate-specific antigen (PSA) measurements were obtained.

The primary endpoint of interest was to describe the frequency and type as well as identify clinical features associated with WNT pathway mutations. Clinical features were compared with a t-test or Mann-Whitney U test and Pearson's $\chi 2$ test or Fisher's exact test for continuous and categorical variables, respectively. Our secondary endpoints included overall survival (OS) and radiographic progression-free survival (rPFS). OS was defined as time from oligometastasis to death of any cause. rPFS was defined as time from oligometastasis to development of new or enlarging metastasis on conventional (per RECIST criteria[21]) or enhanced imaging (per radiologist discretion). Patients underwent imaging at time of PSA or symptomatic progression. Patients were censored at last follow-up. Survival analyses

were performed with the Kaplan-Meier Method. A backward conditional multivariable cox regression model was built using statistically significant variables on univariable regression. For all analyses, a *p*-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics, version 25.

Results

A total of 277 patients with metachronous omCSPC who underwent NGS were included with a median follow-up of 37.2 (IQR 20.2–57.1) months. Baseline tumor characteristics can be found in Table 1. At time of oligometastatic recurrence, median PSA was 3.8 ng/mL (IQR 1.2–11.1), the majority of patients had either one (46.6%) or two (29.2%) metastases, most commonly in either pelvic lymph nodes (47.7%) or bone (42.2%) with a minority presenting with visceral metastases (5.1%).

Within the entire cohort 11.2% (n=31) of tumors harbored pathogenic WNT pathway mutations which included mutations in *APC* (5.4%, n=15), *RNF43* (2.9%, n=8), and *CTNNB1* (4.7%, n=13) (Table 2). 1.4% of patients had more than one WNT pathway alteration in the same tumor. A complete list of specific mutations can be found in supplemental Table 1. Patients with WNT pathway mutations were found to have a faster time to oligometastasis (42.1 vs 54.0 months, p=0.05), less likely to present with pelvic lymph nodes at time of oligometastatic recurrence (29.0% vs 50.4%; p=0.02) and more likely to present with both visceral (22.6% vs 2.8%; p<0.01) and more specifically lung (16.1% vs 1.6%; p<0.01) metastases (Figure 1). No differences in Gleason score, PSA, number of metastases, or frequency of distant lymph node or bone metastses were identified (Supplemental Table 2). Patient samples with WNT pathway mutations were found to be enriched for *SPOP* mutations (22.6% vs 9.3%, p=0.03) but not significantly associated with mutations in *TP53, Rb1,* homologous recombination deficiency genes, or PI3K pathway genes (supplemental Table 2, supplemental Figure 2).

Within the entire cohort, median and 5-yr OS were not met and 89%, respectively. Multivariable analysis demonstrated number of metastases (HR=1.83, 95%CI 1.26–2.67; p<0.01) and WNT pathway mutation (HR=3.87, 95%CI 1.25–12.00; p=0.02) (Table 3, Figure 2a) associated with inferior OS. Patients with WNT pathway mutations also experienced worse prostate-cancer specific survival (5-yr PCSM 59% vs 95%, p<0.01) from oligometastsis and median OS from time of initial prostate cancer diagnosis (172.9 months vs not reached, p=0.01; supplemental Figure 3).

Within the entire cohort, median and 5-year rPFS were 29.9 (95%CI 24.5–35.2) months and 25% respectively. Multivariable cox regression was not performed as number of metastases was the only variable significantly associated with rPFS on univariable analysis (HR = 1.26, 95%CI 1.08–1.48; p<0.01). On univariable analysis, WNT pathway mutation status was not associated with rPFS (HR=1.01, 95%CI 0.59–1.73; p=0.53) (Table 3, Figure 2b).

We then compared outcomes stratified by whether patients received MDT. Patients who received MDT were found to have significantly lower Gleason scores (p=0.05) and PSA at oligometastasis (2.5 vs 7.4, p<0.01) however there were no differences in any other

clinical or genomic features (supplemental Table 3). Among patients who received MDT, pathogenic WNT pathway mutations were not associated with worse 5-year OS (100% vs 91%, p=0.60) (Figure 3a). Conversely, among patients who did not receive MDT, patients with WNT pathway mutations exhibited significantly worse OS (46% vs 93%, p<0.001) (Figure 3b). Similar results were observed for rPFS however did not reach statistical significance (supplemental Figure 4). Further, MDT demonstrated an improvement in 5-yr OS (100% vs 48%, p=0.03) in WNT pathway mutated patients however had no significant effect on 5-yr OS among patients without a WNT pathway mutation (91% vs 93%, p=0.90) (supplemental Figure 5). A detailed list of clinical and genomic characteristics comparing patients treated with and without MDT among patients with WNT pathway mutations can be found in supplemental Figure 4.

Discussion

We report the incidence and type of WNT pathway mutations within metachronous omCSPC and their association with clinical outcomes. Specifically, we have demonstrated WNT activating mutations are present in approximately 11% of patients with omCSPC which is concordant with prior work[22,23], demonstrating increasing gene mutational burden in the WNT pathway with more advanced disease[24]. Additionally, WNT pathway mutations are associated increased likelihood of visceral metastases and decreased likelihood of regional lymph nodes metastases. Finally, we have identified WNT pathway mutations to be associated with worse overall survival in omCSPC and that outcomes may be improved if men receive MDT.

The WNT pathway has been previously implicated as a driver of visceral metastases in several primary malignancies through a variety of cellular mechanisms[22]. Most notably, both canonical and non-canonical WNT signaling has been implicated in the epithelial-mesenchymal transition (EMT) [25,26]. The sEMT allows for enhanced migratory capacity and invasiveness of epithelial cells and is widely realized as a cellular mechanism for the development of metastasis[27,28]. We and others have shown that similar epithelial plasticity programs are sufficient and seem to be important clinically for prostate cancer metastasis[29–32] and may serve as a mechanism by which omCSPC harboring WNT pathway activating mutations have a significantly higher incidence of visceral metastases.

The findings presented above are partially concordant with those observed in CRPC. Velho et al. demonstrated activating WNT pathway mutations were associated with inferior PFS (6.5 vs 9.6 months) and OS (23.6 vs 27.7 months) in patients with CRPC treated with first line abiraterone/enzaluatimde[13]. The authors hypothesize the differential outcomes may be related to an underlying WNT pathway induced androgen-independent growth and resistance to androgen receptor antagonism[14,33]. However, other studies in CRPC have not demonstrated significant differences in disease progression according to WNT pathway status (by cell-free DNA)[34].

Within CSPC treated with ADT, Geng et al. demonstrated single nucleotide polymorphisms (SNPs) associated with decreased *APC* expression was associated with more advanced stage cancer. Further, patients with SNPs associated with increased *APC* mRNA expression

seemed protective with improved PFS[35]. Interestingly, although the results presented here demonstrate inferior OS, counterintuitively, no difference in rPFS was observed. This may be a result of WNT pathway mutations exerting its effect on OS through propensity to spread to viscera rather than rate of progression or anti-androgen resistance. Importantly, the patient population included here is distinctly different from that in prior reports, as over 50% of the population presented here was treated with consolidative metastasis-directed therapy (MDT) which may limit interpretation of androgen-resistance within these patients.

Another particularly interesting finding of this study is the frequency of concurrent WNT pathway and *SPOP* mutations. As we have demonstrated, patients with WNT pathway mutations appear to experience worse outcomes with increased visceral metastasis. Conversely, mutations in *SPOP* have demonstrated improved time to castration resistance and overall survival in synchronous mCSPC when treated with androgen receptor axis targeted therapies[36]. Interestingly, this work by Swami et al[36]. as well as work by Nakazawa et al.[37] have similarly observed an association between WNT and *SPOP* mutations. It is possible these mutations represent a spectrum of clinical outcomes with concurrent mutations experiencing an intermediate prognosis between the unfavorable WNT pathway mutations alone and favorable *SPOP* mutations alone. Unfortunately, our study and others do not have sufficient numbers to fully characterize this spectrum of concurrent mutations however future work should aim to clarify this finding.

This present study further adds to prior work evaluating for potential prognostic and predictive biomarkers in omCSPC treated with MDT. Deek et al. recently reported on a high-risk mutational signature consisting of *TP53, ATM, Rb1, BRCA1/2,* which demonstrated significantly worse PFS and rPFS in a combined analysis of the STOMP and ORIOLE clinical trials[20]. Further, this work identified a potential greater PFS benefit with MDT over observation in patients with a high-risk mutation (p-interaction of 0.12). Given small numbers of WNT pathway aberrations in this cohort we were unable to evaluate the effect of concurrent high-risk mutations. Importantly, however there was no significant association of WNT pathway mutations with mutations in *TP53, RB1,* or homologous recombination deficiency (HRD - *ATM, BRCA1/2, CHEK2)* indicating the results observed here are unlikely confounded by an enrichment of other high-risk mutations within the WNT mutated subgroup.

Our study has several limitations. First, while the majority of patients included were from 2 randomized clinical trials, this was a retrospective non-pre-specified analysis and also included patients managed off these trials. Additionally, although all patients had metachronous omCSPC there was significant heterogeneity in how these patients were managed ranging from observation, anti-androgen monotherapy, MDT monotherapy, or combination therapy. Second, the genomic profiling was performed through multiple vendors which may have affected how pathogenic mutations were determined. Genomic profiling was also primarily from the primary tumor rather than the metastatic sites which may underestimate mutations acquired during disease progression. Further limitations related to primary prostate cancer multifocality and sampling of tissue via biopsies may have led to missing of relevant clonal alterations. Third, our definition of a WNT pathway mutation was not comprehensive; rather it focused on 3 specific genes (*APC, RNF* and

CTNNB1) that have been implicated in an activated WNT pathway phenotype. Finally, our results of WNT pathway mutations as a prognostic variable of OS but not rPFS should be interpreted cautiously. Although, this may have been a result of the association of WNT pathway mutations with visceral metastases, the lack of difference in rPFS does raise the possibility this could represent a Type I statistical error.

Conclusion

Within metachronous omCSPC, WNT pathway activating mutations are present in approximately 11% of patients and are significantly associated with the presence of visceral metastases. Our data suggest that mutations within this pathway may be negatively prognostic for overall survival similar to observations in CRPC, however MDT in the omCSPC state may improve these outcomes. This work underscores the influence of genomics on the disease course of patients with omCSPC receiving MDT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

Emmanuel Antonarakis : Patent holder/licenser for Qiagen; Consultant for Amgen, Astellas, AstraZeneca, Bayer, Clovis, Dendreon, Eli Lilly and Co. ESSA, GlaxoSmithKline, Jannsen, Medivation, Merck, and Sanofi; Research grant recipient from AstraZeneca, Bristol Myers-Squibb, Celgene, Clovis, Dendreon, Genentech, Janssen, Johnson & Johnson, Merck, Novartis, Sanofi, Tokai

Piet Ost: Consultant for Bayer, Janssen, Curium; Research grant recipient from Varian, Bayer

Phuoc Tran: Consultant for Natsar Pharm, Janssen-Taris Biomedical and RefleXion Medical, Personal fees from Noxopharm, Janssen-Taris Biomedical, Myovant and AstraZeneca; Holds a patent 9114158- Compounds and Methods of Use in Ablative Radiotherapy licensed to Natsar Pharm.

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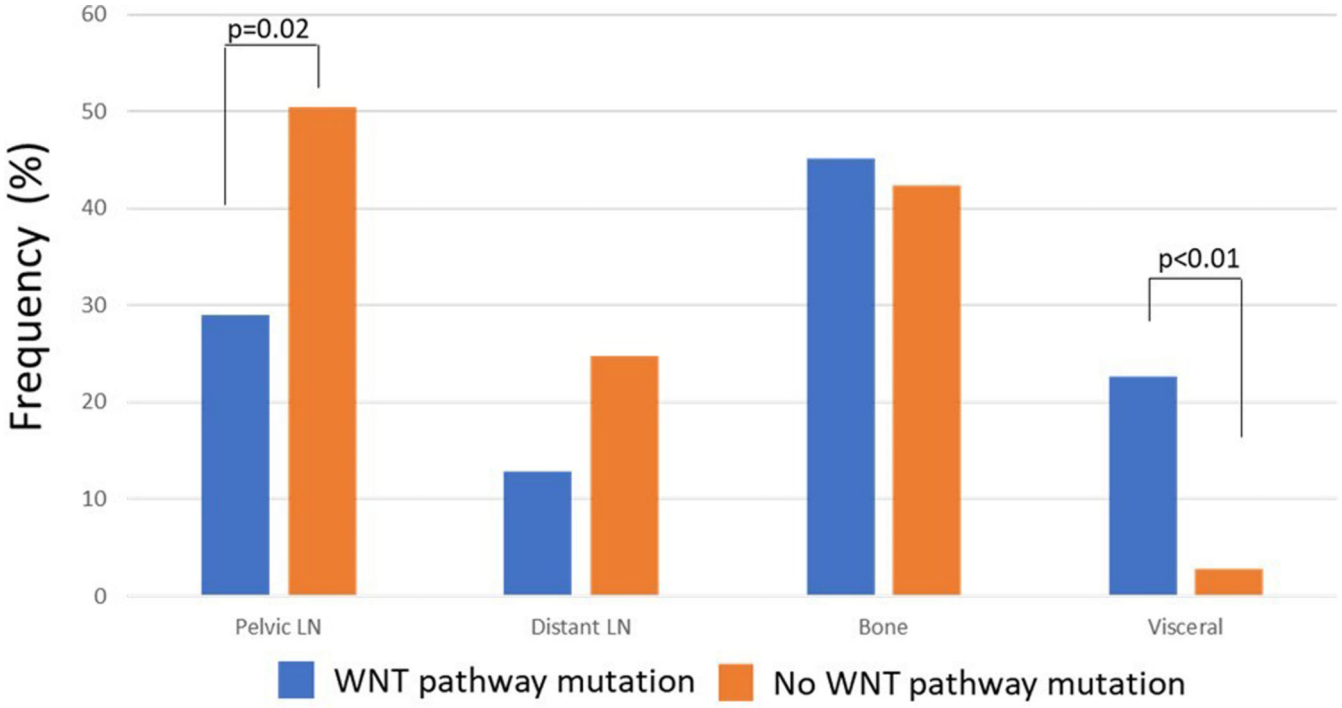

Figure 1.
Frequency of metastatic lesion location at time of oligometastsis stratified by presence or absence of WNT pathway mutation.

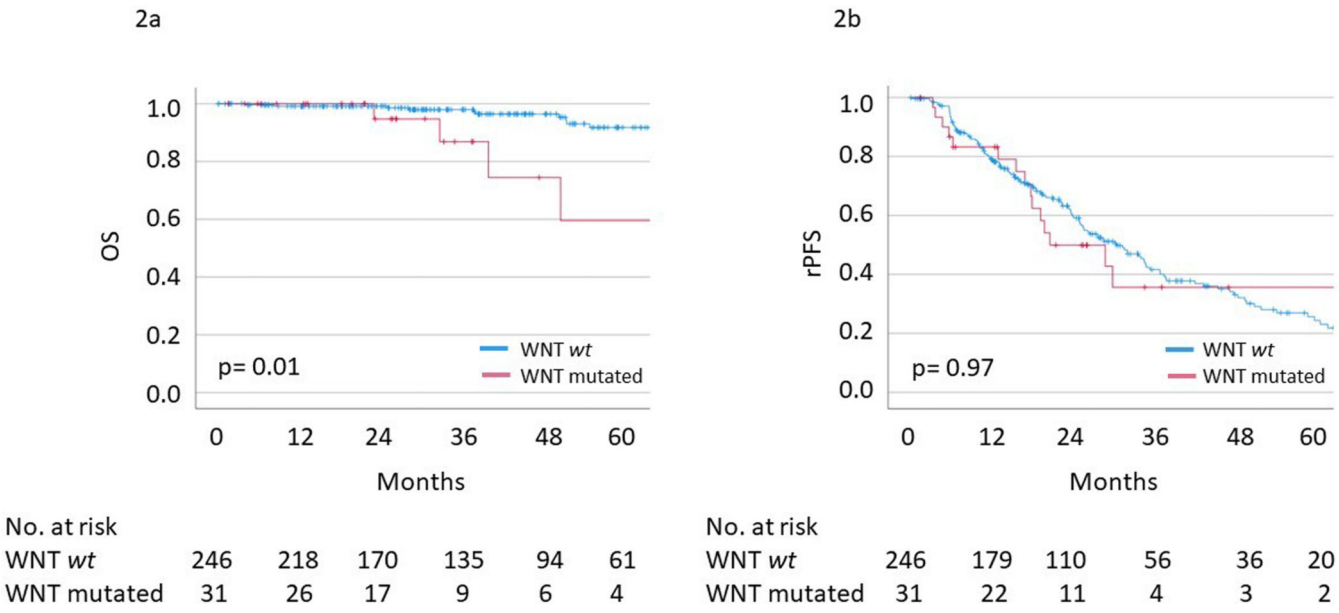

Figure 2.

Kaplan Meier survival curves of (a) overall survival and (b) radiographic progression-free survival stratified by WNT pathway mutational status.

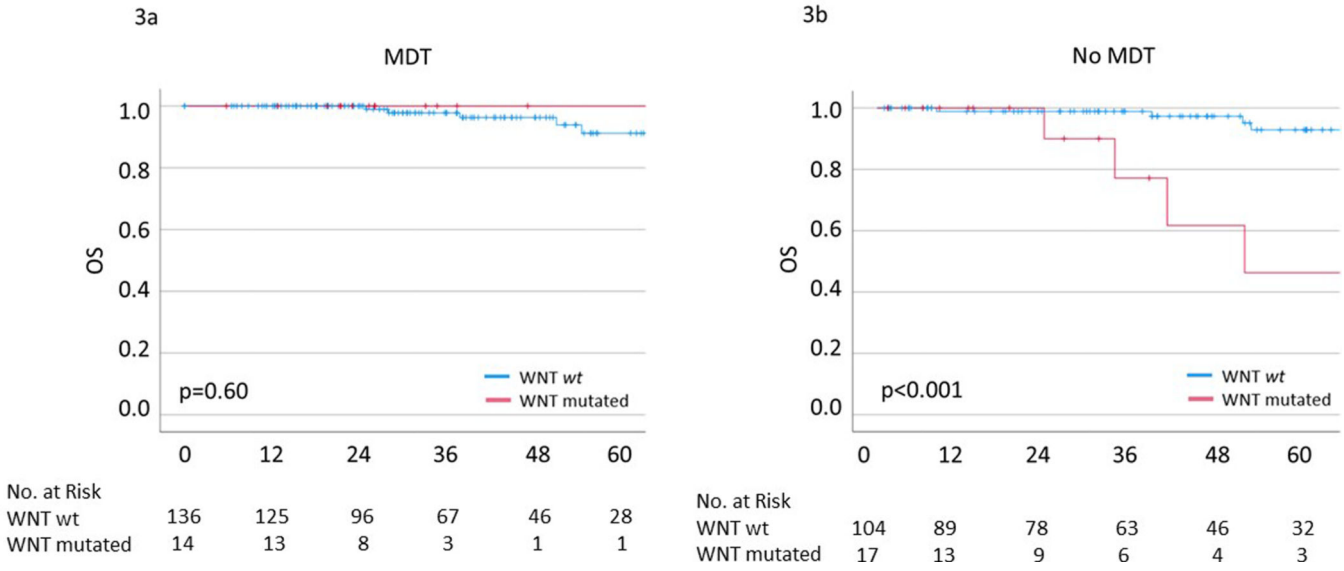

Figure 3.

Kaplan Meier survival curves of overall survival stratified by WNT pathway mutational status in (a) patients treated with metastasis-directed therapy and (b) patients not treated with metastasis directed therapy.

Table 1.

Demographic, tumor, and treatment characteristics of the entire cohort

Characteristic	N=277
Initial Characteristics	
iPSA (IQR)	7.5 (4.6–13.4)
Primary Therapy	236 (85.2%)
Surgery	36 (13.0%)
RT	5 (1.8%)
Unavailable	
T Stage	15 (5.4%)
T1	87 (31.4%)
T2	165 (59.6%)
T3	5 (1.8%)
T4	5 (1.8%)
Unavailable	
N Stage	213 (76.9%)
N0	32 (11.6%)
N1	32 (11.6%)
Nx	
Gleason	14 (5.1%)
6	118 (42.6%)
7	43 (15.5%)
8	92 (33.2%)
9	8 (2.9%)
10	2 (0.7%)
Unavailable	
Characteristics at oligometastasis	
PSA at Oligomet (IQR)	3.8 (1.2–11.1)
Number of Mets	
1	129 (46.6%)
2	81 (29.2%)
3	43 (15.5%)
4	18 (6.5%)
5	6 (2.2%)
Location of Mets	
Pelvic LN	132 (47.7%)
Distant LN	65 (23.5%)
Bone	117 (42.2%)
Visceral	14 (5.1%)
Initial Treatment (First treatment within 6 months oligomet)	
MDT	94 (33.9%)
MDT+ defined course systemic therapy	57(20.6%)

Characteristic	**N=277**
Systemic Therapy	62 (22.4%)
Observation	60 (21.7%)

Table 2.

Frequency of WNT pathway mutations and specific WNT pathway genes

	N=277
WNT Pathway Mutation	
Yes	31 (11.2%)
No	246 (88.8%)
APC	
Yes	15 (5.4%)
No	262 (94.6%)
RNF43	
Yes	8 (2.9%)
No	269 (97.1%)
CTNNB1	
Yes	13 (4.7%)
No	264 (95.3%)

Table 3.

Univariable and Multivariable Cox Regression of characteristics associated with OS and rPFS

	Univariate		Multivariate	
	HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**
OS				
Gleason Grade Group ≥4	1.60(0.62–4.12)	0.33		
iPSA	1.00 (0.99–1.02)	0.54		
PSA at Oligometastasis	1.00 (0.97–1.02)	0.99		
Number of Metastases	1.84 (1.26–2.69)	<0.01	1.83 (1.26–2.67)	<0.01
Visceral metastases	4.35 (1.25–15.13)	0.02	Term removed by model	
WNT Mutation	3.861.26–11.83)	0.02	3.87 (1.25–12.00)	0.02
rPFS				
Gleason Grade Group ≥4	0.98 (0.72–1.35)	0.91		
iPSA	1.00 (1.00–1.01)	0.22		
PSA at Oligometastasis	1.0 (1.00–1.01)	0.60		
Number of Metastases	1.26 (1.08–1.48)	<0.01		
Visceral metastases	0.79 (0.37–1.68)	0.53		
WNT Mutation	1.01 (0.59–1.73)	0.97		

OS: overall survival, rPFS: radiographic progression-free survival