Genomic profiles and clinical outcomes in primary versus secondary metastatic hormone-sensitive prostate cancer

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Abstract

Background: Clinical outcomes may differ among patients presenting with primary (de novo) metastatic hormone-sensitive prostate cancer (mHSPC) versus secondary (metachronous) mHSPC occurring after local therapy. It is unknown what molecular features distinguish these potentially distinct presentations.

Methods: A single-center retrospective study of mHSPC patients classified as primary mHSPC (n = 121) or secondary mHSPC (n = 106). A targeted set of genes was analyzed: BRCA2, PTEN, RB1, TP53, SPOP, CDK12, any two out of PTEN/RB1/TP53 alterations, and homologous recombination deficiency mutations. TP53 mutations were categorized as loss-of-function (LOF) versus dominant-negative (DN). The impacts of genetic features on progression-free survival (PFS) and overall survival (OS) were assessed using univariate and multivariate Cox proportional hazards regression.

Results: Median PFS was 15 and 30 months for men with primary and secondary mHSPC, respectively (hazard ratio: 0.57, 95% confidence interval: 0.41–0.78; p < .01). OS did not show a significant difference between groups. There were more men with Gleason 8–10 disease in the primary versus secondary mHSPC groups (83% vs. 68%; p < .01). In univariate and multivariate analyses, TP53 DN mutations showed a statistically significant association with OS for the entire mHSPC population. Conversely, SPOP mutations were associated with improved OS. Additionally, TP53 mutations (DN and LOF) were associated with worse OS for secondary mHSPC. A combination of PTEN/RB1/TP53 alterations was associated with worse OS and PFS for secondary mHSPC, while no genomic alteration affected outcomes for primary mHSPC.

Conclusions: TP53 DN mutations, but not all TP53 alterations, were the strongest predictor of negative outcomes in men with mHSPC, while SPOP mutations were associated with improved outcomes. In subgroup analyses, specific alterations were prognostic of outcomes in secondary, but not primary, mHSPC.
INTRODUCTION

Metastatic hormone-sensitive prostate cancer (mHSPC) is a diverse group of diseases with a large variation in survival. A potential influence on disease severity is the timing of the development of metastatic disease. Primary (de novo) mHSPC is a subset of metastatic prostate cancer characterized by metastatic disease at presentation, compared to secondary (metachronous) mHSPC which is a progressive disease following prior treatment of localized cancer. Primary mHSPC represents ~5% of prostate cancer diagnoses. Men presenting with primary mHSPC potentially have worse overall survival (OS) and worse progression-free survival (PFS). Additionally, specific genetic alterations in the tumor are known to be associated with differences in prognosis in mHSPC patients. Mutations in SPOP have been associated with favorable prognosis. Alternately, mutations in CDK12 are associated with more aggressive cancer. Alterations in TP53, RB1, and PTEN are associated with poor outcomes, exacerbated when more than one of these genes are mutated. TP53 is the most frequently mutated gene in cancer and is mutated in up to 50% metastatic prostate cancer. The genomic landscape of mHSPC, and particularly primary metastatic disease, has not been well characterized. In one recent study AR, SPOP, and cell cycle alterations were linked to differences in OS in mHSPC.

TP53 is a crucial tumor suppressor gene that can be altered through multiple mechanisms including genomic deletion, loss-of-function (LOF) mutations, and dominant-negative (DN) mutations. TP53 DN mutations inhibit the tumor suppressor function of TP53 and confer multiple neoplastic phenotypes including resistance to apoptosis and increased cellular invasion/migration. In a number of tumor types including lung, ovarian, and colon, specific types of TP53 mutations have been associated with worse outcomes. In patients with metastatic castration-resistant prostate cancer, TP53 DN mutations have been associated with prior enzalutamide/abiraterone.

Recently, homologous recombination deficiency (HRD) alterations have become important for understanding treatment options in metastatic prostate cancer. Poly (ADP-ribose) polymerase inhibitors are a potential therapeutic agent for patients that harbor an HRD gene alteration and are thought to work through synthetic lethality in this context. Approximately 15%–25% of metastatic prostate cancers harbor an HRD alteration. Consequently, it is important to understand both the patient population which harbors HRD alterations and the potential impact on outcomes.

In this study, we examined genetic alterations in mHSPC patients presenting with primary versus secondary mHSPC. To help guide clinical decision-making, genes thought to influence prognosis and possibly treatment options were the focus of this study.

MATERIALS AND METHODS

2.1 Patient population

This is a single-institution retrospective study of patients seen at Johns Hopkins with available genomic data. Patients were selected who had available tumor somatic sequencing data from the primary tumor, metastatic site, or blood (circulating tumor DNA). Somatic genomic data are housed in our institutional clinicogenomic database, as previously described. Patients with adenocarcinoma histology and hormone-sensitive metastatic disease were eligible for further review and classified as presenting with de novo metastatic disease (primary mHSPC) versus presenting with the localized disease with subsequent development of metastasis (secondary mHSPC). Additional clinical characteristics were collected when available including age at diagnosis of metastatic disease, Gleason score, the volume of disease at diagnosis of metastatic disease, combination therapy for metastatic disease (including chemotherapy and second-generation anti-hormonal agents), and location of metastatic disease. Data were obtained from the medical record, pathology, and obituary data and entered into a database with the data updated as of July 1, 2020. The research database and this study were approved by the Johns Hopkins University institutional review board.

2.2 Clinical outcomes

We estimated the time to progression on androgen deprivation therapy (ADT) given for metastatic disease (termed PFS) as well as OS. PFS was defined as either prostate-specific antigen (PSA) progression or radiographic progression or death, whichever occurred first, starting at the time of ADT initiation (not starting from the time of first metastatic occurrence). OS was defined as the time from the date of diagnosis of metastatic disease until death from any cause. With both endpoints, patients were censored on July 1, 2020 if they had not developed progression or death, respectively.

2.3 Genomic analysis

Mutation status was recorded for BRCA2, PTEN, RB1, TP53, SPOP, CDK12, combined PTEN/RB1/TP53 alterations (two out of three), and a composite of any HRD mutation. HRD genes were classified as a mutation in one of the following genes: BRCA1, BRCA2, ATM, FANCA, PALB2, RAD50, RAD51, MRE11, BLM, ATR, BARD1, BRIP1, CDK12, or...
CHEK2. Mutations were defined as deleterious based on both reported data from the mutation panel and the cBioPortal/COSMIC classifications. TP53 mutations were further classified as DN or LOF, based on previous data. TP53 DN mutations included point mutations at codons R175, R248, R273, R282, and G245. TP53 LOF mutations were those resulting in truncation or loss of TP53 through genomic deletion, frameshift, nonsense, or splicing mutations previously reported in genomic databases (i.e., cBioPortal; COSMIC) as pathogenic.

2.4 | Statistical analysis

Hazard ratios (HRs) were used to quantify the difference of PFS and OS between primary and secondary mHSPC and the significance of the difference in survival between them was determined by the log-rank test. Differences between groups for clinicopathologic variables were determined using Fisher’s exact test or chi-squared test. The association between each genetic alteration and PFS and OS was assessed using a univariate Cox regression analysis and multivariate Cox regression analysis adjusted for age at first metastasis, Gleason sum, PSA at diagnosis of metastatic disease, initial combination therapy for metastatic disease (chemotherapy or novel anti-androgen therapy), and volume of disease (high vs. low). All tests were two-sided and p ≤ .05 were considered to indicate statistical significance.

3 | RESULTS

3.1 | Clinical characteristics of patients with primary versus secondary mHSPC

Our cohort is comprised of 121 patients with primary mHSPC and 106 patients with secondary mHSPC. Median follow-up time was 28.44 months for primary mHSPC and 40.08 months for secondary mHSPC, or 32.92 months in the overall mHSPC population. The mean age for the groups at first metastasis was similar, at 66.0 years for primary mHSPC and 65.4 years for secondary mHSPC (Table 1). Time to progression between initial diagnosis and development of metastatic disease for secondary mHSPC was a mean of 52.7 months. Patients with primary mHSPC were more likely to have a higher Gleason score, with 83% of patients having a Gleason grade of 8–10 compared to 68% of patients with secondary mHSPC (p < .01). The median PFS from initiation of ADT was 15.0 months (95% confidence interval [CI]: 13.9–21.1) for primary mHSPC patients versus 30.0 (95% CI: 25.7–38.1) for secondary mHSPC. The PFS was significantly shorter for primary versus secondary mHSPC, with an HR of 0.57 (95% CI: 0.41–0.78; p < .01; Figure 1A). The OS was 68.5 months (95% CI: 45.9–NA) for primary mHSPC and 76.7 months (95% CI: 69.9–91.9) for secondary mHSPC, which was not significantly different between the two groups (Figure 1B).

3.2 | Genomic features associated with primary and secondary mHSPC

Among the 227 mHSPC patients with available somatic tumor DNA data, 157 cases (69%) were from primary prostatic tumor biopsies or prostatectomies, 49 cases (22%) were from metastatic biopsies, and 19 cases (8%) were from circulating tumor DNA analysis. If prostatic tissue was available for DNA sequencing, this was preferentially used in the analysis. Table S1 shows the distribution of tissue types utilized for genomic which were broadly similar between the two groups.

The frequency of genomic alterations was not significantly different between primary and secondary mHSPC groups (Table 2).

| TABLE 1 | Clinicopathologic characteristics of patients with primary and secondary mHSPC |
| Primary mHSPC, N (%) | Secondary mHSPC, N (%) |
|-----------------------|------------------------|
| Age at first metastasis, mean (SD) | 66 (8.7) | 65.4 (7.5) |
| Caucasian N (%) | 88 (73) | 94 (89) |
| African American N (%) | 22 (18) | 8 (7.5) |
| Other/unknown N (%) | 11 (9) | 4 (4) |
| PSA at diagnosis of metastatic disease, mean (SD) | 290.7 (678.6) | 30.2 (76.9) |
| Time from date of diagnosis to tissue collection for NGS, mean (SD) | 8.2 (26.2) | 34.2 (58.8) |
| Gleason grade group 1, N (%) | 2 (1.7) | 4 (3.8) |
| Gleason grade group 2, N (%) | 1 (0.83) | 10 (9.4) |
| Gleason grade group 3, N (%) | 5 (4.1) | 20 (18.9) |
| Gleason grade group 4, N (%) | 24 (19.8) | 21 (19.8) |
| Gleason grade group 5, N (%) | 76 (62.8) | 51 (48.1) |
| Known | 121 | 106 |
| Unknown | 13 (10.7) | 0 |
| Combination novel anti-androgen therapy, N (%) | 9 (7.4) | 11 (10.4) |
| Combination chemotherapy, N (%) | 26 (21.5) | 10 (9.4) |
| Neither, N (%) | 84 (69.4) | 85 (80.2) |
| Unknown, N (%) | 2 (1.7) | 0 |

Abbreviations: mHSPC, metastatic hormone-sensitive prostate cancer; NGS, next-generation sequencing.
A trend towards an increase was observed in PTEN (28.1% primary mHSPC vs. 18.9% secondary mHSPC; \( p = .12 \)) and CDK12 (6.6% primary mHSPC vs. 3.8% secondary mHSPC; \( p = .39 \)) mutations in primary mHSPC compared to secondary mHSPC. Conversely, BRCA2 mutations were numerically more frequent in secondary mHSPC compared to primary mHSPC (10.4% secondary mHSPC vs. 5.0% primary mHSPC; \( p = .14 \)). Of note, a significant \( p \)-value for such comparisons would be <.005 after Bonferroni correction for multiple testing. There were no other broad differences in genomic profiles between the two groups.

### Impact of genomic features on clinical outcomes

For all patients, PTEN alterations (HR: 1.51, CI: 1.05–2.18; \( p = .03 \)), TP53 DN mutations (HR: 1.91, CI: 1.02–3.60; \( p = .04 \)) were associated with shorter PFS (Figure 2). Interestingly, TP53 mutations overall, and TP53 LOF mutations, did not significantly alter PFS. Similarly, OS was worse for patients with TP53 DN mutations (HR: 2.77, CI: 1.28–5.97; \( p = .01 \)), but TP53 mutations overall and LOF mutations were also associated with worse OS (all TP53 muts: HR: 1.80, CI: 1.15–2.80; \( p = .01 \); TP53 LOF muts: HR: 1.66, CI: 1.04–2.65; \( p = .03 \)). Additionally, combined PTEN/RB1/TP53 alterations (at least two out of three) were associated with a worse OS (HR: 1.89, CI: 1.07–3.32; \( p = .03 \); Figure 2). PTEN alterations alone were not significantly associated with worse OS.

In multivariate analysis of OS, TP53 DN mutations (HR: 2.63, CI: 1.15–6.02; \( p = .02 \)) were associated with worse OS, but not TP53 LOF mutations (HR: 1.36, CI: 0.83–2.24; \( p = .23 \)). Additionally, SPOP mutations were associated with an improved OS (HR: 0.34, CI: 0.13–0.89; Figure 3B). No alterations were associated with statistically significant differences in PFS in the multivariate analysis, although TP53 DN mutations showed a strong trend towards worse PFS (HR: 1.91, CI: 0.98–3.70; \( p = .06 \)).

Interestingly, for the primary mHSPC subset, no genetic alteration significantly influenced PFS or OS (Table S2). For secondary mHSPC, the combination group of PTEN/RB1/TP53 mutations was associated with shorter PFS (HR: 2.12, CI: 1.15–3.91; \( p = .02 \)) and shorter OS (HR: 2.67, CI: 1.26–5.69; \( p = .01 \); Table S3). Additionally, TP53 DN and LOF alterations were both associated with worse OS (TP53 LOF: HR: 2.08, CI: 1.04–4.15; \( p = .04 \); TP53 DN: HR: 3.20, CI: 1.17–8.78; \( p = .02 \)) in the secondary mHSPC group.
3.4 | Genomic landscape of mHSPC with TP53 DN versus LOF mutations

To explore the TP53-related genomic landscape further, we compared concurrent genomic alterations and clinical characteristics among mHSPC patients with TP53 DN versus LOF mutations. In doing so, we found that there was a trend towards a higher Gleason sum associated with DN mutations (92%) compared to LOF mutations (71%). Importantly, there were no differences in the distribution of mutations derived from the primary prostate tissue versus a metastatic site (Table 3). Additionally, no other alteration co-occurred more frequently with one type of TP53 mutation versus another (Table S4). This suggests that the type of TP53 mutations itself rather than the co-occurrence with additional alterations results in differences in patient outcomes. Alternatively, a genomic alteration not analyzed in this study could be co-occurring with a specific type of TP53 alteration.

4 | DISCUSSION

In this study, primary mHSPC progressed more rapidly than secondary mHSPC and was associated with higher Gleason scores and worse PFS as well as a trend towards worse OS which is consistent with findings from the CHAARTED trial. Shorter PFS and worse OS has also been noted for primary mHSPC in a previous smaller study of 38 patients with de novo mHSPC and 52 patients with secondary HSPC. However, another study of 275 patients with primary
TABLE 3 Clinicopathological characteristics of patients with TP53 DN mutations and TP53 LOF mutation

|                        | TP53 DN total N = 13, N (%) | TP53 LOF total N = 76, N (%) | p-Value          |
|------------------------|-----------------------------|------------------------------|------------------|
| Metastatic disease site, N (%) |                             |                              |                 |
| Visceral               | 2 (15)                      | 24 (32)                      | .33              |
| Bone                   | 13 (100)                    | 62 (82)                      | .21              |
| Lymph node             | 4 (31)                      | 47 (62)                      | .07              |
| Race, N (%)            |                             |                              |                 |
| Caucasian              | 11 (85)                     | 63 (83)                      | 1.00             |
| African American       | 1 (8)                       | 11 (14)                      | 1.00             |
| Other/unknown          | 1 (8)                       | 2 (3)                        | .38              |
| Gleason sum, N (%)     |                             |                              |                 |
| >7                     | 12 (92)                     | 54 (71)                      |                 |
| ≤7                     | 1 (8)                       | 13 (17)                      | .45              |
| Not available          | 0                           | 9 (12)                       |                 |
| Genomic tissue source, N (%) |                           |                              |                 |
| Prostate               | 10 (77)                     | 47 (62)                      | .36              |
| Plasma (ctDNA)         | 2 (15)                      | 6 (8)                        | .33              |
| Metastatic site        | 1 (8)                       | 21 (28)                      | .17              |
| Multiple               | 0 (0)                       | 2 (3)                        | 1.00             |

Abbreviations: ctDNA, circulating tumor DNA; DN, dominant-negative; LOF, loss-of-function; mHSPC, metastatic hormone-sensitive prostate cancer.

mHSPC and 175 patients with secondary mHSPC did not show a difference in outcomes.9 The disease course for primary and secondary mHSPC is an important question to address given the clinical implications and variety of treatment options available depending on disease severity.

We did not find a statistically significant difference when comparing the mutation spectrum between primary and secondary mHSPC, as we had hypothesized. A trend was noted towards differences in the frequency of PTEN and CDK12 alterations (higher in primary mHSPC), as well as BRCA2 alterations (higher in secondary mHSPC). For gene alterations occurring in a small percentage of patients such as with CDK12 and BRCA2, larger studies may be able to elucidate a statistically significant difference in the frequency of these alterations between groups. We did, however, note that the implication of the genetic alterations on disease outcomes differed depending on disease presentation. In addition, we observed favorable effects of SPOP mutations on OS in multivariate analysis for all mHSPC patients. The notion that SPOP mutations may impart a favorable prognosis to hormonal therapies in the context of mHSPC is supported by prior studies and is thought to be related to decreased proteasomal degradation of the AR protein in SPOP-mutant cancers leading to enhanced AR addiction in these tumors.15,16

Data has been emerging on the importance of combined mutations in RB1, TP53, and PTEN. Previous triple-knockout mouse models showed an aggressive disease variant with ADT resistance and a high potential for metastases.17,18 Recent data on combined mutations in TP53 and RB1 in metastatic prostate cancer demonstrated these tumors had high proliferation rates and patients were androgen-resistant with shortened OS.19 Here, we show in the hormone-sensitive setting that the combination of these alterations is associated with worse OS for patients in the entire cohort. In subgroup analysis, OS and PFS were worse for patients with compound RB1, TP53, and PTEN mutations in the secondary mHSPC group but not in primary mHSPC patients. The differential effect of these tumor suppressor gene mutations on outcomes in primary and secondary mHSPC suggests that a different tumor biology may be driving the primary mHSPC phenotype. Consequently, when evaluating the aggressive nature of prostate cancer, these mutations are important in the setting of secondary mHSPC but may not have the same prognostic implications in primary mHSPC. It will be important to correctly interpret the significance of different mutations in the context of the disease presentation.

TP53 mutations are a heterogeneous group of alterations that have different implications on tumor growth. TP53 DN hotspot mutations are of particular interest given their potentially distinct impact on clinical outcomes. In this study, TP53 DN mutations had the most consistent association with worse OS in the entire population in multivariate analyses. Interestingly, TP53 DN mutations were associated with worse outcomes with respect to PFS in univariate analysis, but LOF mutations were not. Thus, in the context of hormone-sensitive disease, the type of TP53 mutation may influence disease severity. These findings may also extend to the castration-resistant disease state, and this hypothesis should be further explored in that setting.

Our study shows that genetic alterations found in mHSPC influence disease severity. More specifically, the association of a genetic alteration with the severity of the disease also depends on the disease presentation. Especially with the growing number of treatment options for mHSPC (ADT alone, ADT plus enhanced hormonal therapy, or ADT plus chemotherapy), it will be important to understand how the genomic landscape of a tumor is associated with disease severity and prognosis. It is also possible that one or more of these genetic alterations may be utilized as treatment-selection markers, to prioritize certain patients for enhanced hormonal therapy while others may benefit more from early chemotherapy, a hypothesis that is ripe for testing in future studies.

This study has several limitations. First, a variety of tissue types were used and the majority were not metastatic site biopsies. Differences may exist between the primary prostate genomic landscape and metastatic disease, especially in secondary mHSPC where there is a longer time between diagnosis and tissue acquisition for next-generation sequencing (NGS) studies. Additionally, for secondary mHSPC, the use of prostate genomic data for inclusion in the study may skew towards a population with more rapid metachronous metastases given that tissue may not be available for patients diagnosed that had a longer time to secondary progression after primary therapy. Also, given that these patients had genomic
sequencing in a clinical context, a variety of platforms were used with a different methodology for mutation calls. The targeted genomic alterations explored in this study are known cancer-related genes and were reported by all NGS platforms. Furthermore, mutation zygosity could not be assessed and consequently, the study cannot distinguish between biallelic and monoallelic TP53 (or other tumor suppressor gene) mutations. Finally, the definition of PFS was imperfect because the interval of PSA testing and imagining as- sessments was not standardized, given that this reflected real-world clinical practice. Further, this study analyzed OS but was unable to distinguish between cancer-related mortality versus mortality from other causes (since the cause of death was not captured in our database).

5 | CONCLUSION

In conclusion, contrary to our initial hypothesis, there were no sig- nificant differences in the mutation spectra of the analyzed genes between primary and secondary mHSPC in our cohort. Nonetheless, we found that TP53 DN mutations were associated with inferior clinical outcomes in the overall mHSPC population and that SPOP mutations were associated with longer survival. The prognostic impact of TP53 DN alterations, rather than overall TP53 mutations, should be further studied both in the hormone-sensitive and the castrate-resistant prostate cancer settings moving forward. The utility of these alterations as a predictive biomarker for use of early chemotherapy in addition to androgen deprivation therapy, as suggested by the CHAARTED trial, should be evaluated.

CONFLICT OF INTERESTS

Dr. Antonarakis reports grants and personal fees from Janssen, per- sonal fees from Astellas, grants and personal fees from Sanofi, grants and personal fees from Dendreon, personal fees from Pfizer, personal fees from Invitae, grants and personal fees from AstraZeneca, grants and personal fees from Clovis, grants and personal fees from Merck, grants from Johnson & Johnson, grants from Genentech, grants from Novartis, grants from Bristol Myers-Squibb; and also has a patent (PCT/US2015/046806; US20170275673A1) on an AR-V7 biomarker technology, licensed to Qiagen. Dr. Isaacsson Velho reports honoraria from Bayer, Astellas Pharma, and AstraZeneca, and on the speakers’ bureau for AstraZeneca, Pfizer, Bristol-Myers Squibb, and Bayer, and research funding from Bristol-Myers Squibb, Bayer, and Pfizer, and expert testimony for Bayer, and travel, accommodations, expenses from AstraZeneca, Astellas Pharma, Pfizer, Merck Serona, and Merck. No disclosures to report for authors Emily Nizialek, Su Jin Lim, Hao Wang, and Srinivasan Yegnasubramanian.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

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