Original Study

Influence of Tumor Characteristics and Time to Metastatic Disease on Oncological Outcomes in Metachronous Metastatic Prostate Cancer Patients

Mike Wenzel,[1] Malin Lutz,[1] Benedikt Hoeh,[1] Florestan Koll,[1] Cristina Cano Garcia,[1] Carolin Siech,[1] Thomas Steuber,[2] Markus Graefen,[2] Derya Tilki,[2,3,4] Luis A. Kluth,[1] Séverine Banek,[1] Felix K.H. Chun,[1] Philipp Mandel[1,2]

Abstract

Onset of metastatic disease for prostate. Cancer (PCa) might be influenced by primary PCa characteristics such as Gleason score (GS) or cancer stage, as well as overall survival (OS) by timing of metastatic onset. We relied on an institutional tertiary-care database and found that timing of smPCa is strongly influenced by GS and pT-stage in real-life setting. OS benefits can be observed with longer time interval between primary PCa diagnosis and onset of smPCa.

Introduction: Metachronous metastatic prostate cancer (mmPCa) patients harbor different characteristics and outcomes, relative to DeNovo metastatic PCa patients. Onset of metastatic disease might be influenced by primary PCa characteristics such as Gleason score (GS) or cancer stage, as well as overall survival (OS) by timing of metastatic onset. **Patients and Methods:** We relied on an institutional tertiary-care database to identify mmPCa patients. Kaplan Meier and Cox Regression models tested for onset of metastases and OS, stratified according to GS, pathological stage and time to mmPCa. **Results:** Of 341 mmPCa patients, 8% harbored GS6 versus 41% versus 51% GS7 and GS8-10. Median time to onset of metastatic disease was 79 versus 54 versus 41 months for GS6 versus GS7 versus GS8-10 ($P = .01$). Moreover, median time to onset of metastases was 64 versus 44 months for pT1-2 versus pT3-4 mmPCa patients undergoing radical prostatectomy ($P = .027$). In multivariable Cox regression models, higher GS and pT-stage was associated with earlier onset of metastases. Additionally, significant OS differences could be observed for time interval of < 24 versus 24-60 versus 60-120 versus ≥ 120 months between primary PCa diagnosis and onset of mmPCa. Specifically, median OS was 56 versus 69 versus 97 months versus not reached ($P < .01$) for these categories. In multivariable Cox regression, shorter time to metastatic onset was associated with shorter OS. **Conclusion:** Timing of mmPCa is strongly influenced by grading and pT-stage in real-life setting. OS benefits can be observed with longer time interval between primary PCa diagnosis and onset of mmPCa.

Clinical Genitourinary Cancer, Vol. 22, No. 5, 102158
Keywords: mHSPC, mCRPC, Recurrent, Metachron, Oligometastatic

Introduction

Metachronous metastatic prostate cancer (mmPCa) patients harbor different patient and tumor characteristics then primary De Novo metastatic prostate cancer patients. In consequence, prognosis such as overall survival (OS) is different between both groups.[1,2] However, the approval of systemic therapies for metastatic prostate cancer often does not stratify according to time point of metastatic disease occurrence (with exception of abiraterone), since most phase III trials included both primary De Novo and secondary recurrent metastatic prostate cancer patients.[3-10]

[1]Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Theodor Stern Kai 7, 60596, Frankfurt, Germany
[2]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Martini Street 52, 20251, Hamburg, Germany
[3]Department of Urology, University Hospital Hamburg-Eppendorf, Martini Street 52, 20251, Hamburg, Germany
[4]Department of Urology, Koc University Hospital, Davutpasa No 4, 34010, Istanbul, Turkey

Submitted: May 12, 2024; Revised: Jul 3, 2024; Accepted: Jul 4, 2024; Epub: 10 July 2024

Address for correspondence: Mike Wenzel, MD, BSc, Department of Urology, Goethe University Hospital Frankfurt, Frankfurt/Main, Germany.
E-mail contact: Mikewenzel91@aol.com

1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2024.102158

Characteristics of mmPCa

MmPCa patients may be a heterogeneous cohort with some patients experiencing onset of metastatic disease after primary local therapy at stage of metastatic hormone-sensitive prostate cancer (mHSPC). Other patients with for example adverse characteristics after local therapy, such as high Gleason score, might receive adjuvant radiation (RT) combined with long-term androgen deprivation therapy (ADT) or long-term ADT without local therapy only. This may be leading to progression to nonmetastatic castration-resistant prostate cancer (nmCRPC) and subsequently with an onset of metastases at the stage of metastatic castration-resistant prostate cancer (mCRPC).[11] However, neither is known on how tumor characteristics such as the Gleason score or pathological stage influences the time to onset of secondary metastases, since most studies focused solely on OS.[12] Moreover, few if any is known about the time interval between local therapy to the primary prostate tumor and development of mmPCa.

We addressed this knowledge gap and relied on our institutional metastatic prostate cancer database to investigate the impact of the Gleason score and pathological stage on time to onset of metastases in mmPCa patients. We hypothesized that differences in time to metastatic onset may be attributable to the aggressiveness and extend of the primary prostate cancer tumor. Moreover, we also hypothesized that the time interval between primary prostate cancer and occurrence of secondary recurrent metastatic stage influences OS.

Patients and Methods

Study Population

Following approval from the local ethics committee (reference number: SUG-5-2018) and adhering to the tenets of the Declaration of Helsinki, we retrospectively identified all patients with metastatic prostate cancer who were treated and discussed in a multidisciplinary board at the Department of Urology, University Hospital Frankfurt, Germany since 2014 (n = 1066). Exclusion criteria consisted of patients with primary De Novo metastatic prostate cancer (n = 645), unknown Gleason score (n = 45) and unknown date of prostate cancer diagnosis or date of metastatic onset (n = 34). Metastatic disease was defined according to TNM classification as either metastatic lymph nodes above aortic bifurcation, bone or visceral metastasis.[13] Patients with initial nmHSPC and nmCRPC and subsequent mHSPC and mCRPC status were both included since in real-world setting both patient groups are frequently seen and counseled regarding risk of secondary/metachronous metastatic disease. These criteria yielded to 341 mmPCa patients for further analyses.

Statistical Analysis

Descriptive statistics involved analyzing the frequencies and proportions of categorical variables used in the study. Median values and interquartile ranges (IQR) were presented for all continuously-coded variables. The Chi-square test was employed to evaluate the statistical significance of proportion differences, while differences in distributions were assessed using the *t*-test and Kruskal-Wallis test.

Time to onset of metastasis was defined as time point since primary prostate cancer diagnosis and time of occurrence of first metastasis, regardless of local therapies or local recurrences.

For time to metastatic onset analyses, Gleason score was distinguished into Gleason score 6 versus Gleason score 7 versus Gleason score 8-10, according to common distinction for D'Amico risk categories.[13,14] Gleason score from radical prostatectomy specimen was used, if available. Otherwise, biopsy Gleason score was used.

Kaplan Meier curve estimates graphically depicted time until onset of metastatic disease. Moreover, univariable, as well as multivariable Cox regression models were applied for prediction of onset of metastatic disease. Adjustment in multivariable Cox regression models were performed for significant variables used in the univariable model (displayed in Table 2). Despite Gleason score subgroups, we additionally performed similar analyses for pathological stage after radical prostatectomy, stratified according to pT1-2 versus pT3-4. To account for possible differences in mHSPC/mCRPC status, all multivariable Cox regression models were additionally adjusted for mHSPC status.

In the second step of analyses, the effect of time interval between primary prostate cancer diagnosis and mmPCa (interval of time to metastatic onset) on OS was explored. Specifically, time interval was grouped as $<$ 24 months versus 24-60 months versus 60-120 months versus $\geq$ 120 months. Since OS outcomes are mainly influenced by status of hormone sensitivity or castration resistance, in these analyses only mHSPC patients were included. Additionally, also multivariable Cox regression models were applied (Table 2).

All tests were 2 sided with a level of significance set at $P <$ .05. R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.

Results

Overall, 341 mmPCa patients were eligible for analyses. Of these patients, 27 (7.9%) harbored Gleason score 6 versus 141 (41%) versus 173 (51%) Gleason score 7 versus Gleason score 8-10 (Table 1). Overall, 67% of included patients were classified as mHSPC stage at onset of metastatic disease, while 33% were mCRPC with previous nmCRPC status.

Patients with Gleason score 6 were significantly younger at prostate cancer diagnosis (median 62 years, IQR: 58-68) than Gleason score 7 (median 66 years, IQR: 60-70) and Gleason score 8-10 counterparts (median 67 years, IQR: 62-73, $P = .02$). Conversely, median age at metastatic disease did not differ between all 3 groups (medians 72-73 years, $P = .5$).

Patients with Gleason score 8-10 harbored the highest rate of local therapy with RP or RT (73%) compared to Gleason score 7 (71%) and Gleason score 6 patients (48%, $P = .028$). Similarly, unfavorable postsurgical pathological features were significantly more frequently present in Gleason score 8-10 patients than in Gleason score 7 and Gleason score 6 patients, such as pT3-4 disease (78% vs. 59% vs. 41%, $P < .01$), lymph node involvement (30% vs. 7.8% vs. 0%), or positive surgical margins (24% vs. 17% vs. 11%, $P = .1$).

After onset of metastatic disease, patients with Gleason score 8-10 received significantly more systemic therapy lines (median 3 vs. 2 vs. 2, $P < .01$) than Gleason score 7 and 6 counterparts. Conversely, highest rate of metastases-directive therapy was in Gleason score 6 patients, followed by Gleason score 7 and 8-10 patients (39% vs. 22% vs. 22%, $P = .01$).

Table 1 Patient and Tumor Characteristics of Metachronous Metastatic Prostate Cancer Patients Stratified According to Gleason Score at Prostate Cancer Diagnosis

Characteristic	N	Overall, N = 341[a]	Gleason 6, N = 27 (7.9%)[a]	Gleason 7, N = 141 (41%)[a]	Gleason 8-10, N = 173 (51%)[a]	*P*-Value[b]
Age at PCa diagnosis	341	66 (60, 72)	62 (58, 68)	66 (60, 70)	67 (62, 73)	.02
Age at metastatic PCa	337	72 (66, 77)	73 (70, 75)	72 (66, 76)	73 (66, 78)	.5
PSA at PCa diagnosis	267	10 (7, 24)	8 (7, 22)	9 (6, 16)	14 (8, 36)	< .01
PSA at metastatic PCa	138	9 (2, 26)	43 (8, 211)	6 (1, 17)	10 (2, 24)	.026
PSA nadir mHSPC	101	0.17 (0.01, 0.83)	0.30 (0.13, 0.67)	0.12 (0.04, 0.60)	0.21 (0.01, 1.18)	.8
Decline ≥ 90%		63 (77%)	6 (100%)	23 (68%)	34 (81%)	.2
PSA at mCRPC	133	10 (3, 54)	33 (8, 92)	12 (4, 64)	10 (3, 40)	.5
Therapy lines for metastatic PCa	335	2.00 (2.00, 4.00)	2.00 (2.00, 4.00)	2.00 (2.00, 3.00)	3.00 (2.00, 4.00)	.001
ECOG ≥ 2	238	11 (4.6%)	2 (14%)	2 (1.9%)	7 (5.8%)	.2
Local therapy RP/RT	341	240 (70%)	13 (48%)	100 (71%)	127 (73%)	.028
pT3-4	251	170 (68%)	7 (41%)	61 (59%)	102 (78%)	< .001
pN1	341	63 (18%)	0 (0%)	11 (7.8%)	52 (30%)	< .001
PSM	34	69 (20%)	3 (11%)	24 (17%)	42 (24%)	.13
MDT	280	83 (30%)	48 (39%)	30 (22%)	5 (22%)	.01
High volume	189	39 (21%)	8 (53%)	15 (17%)	16 (19%)	< .01
High risk	189	44 (23%)	5 (33%)	10 (11%)	29 (34%)	< .001

Abbreviations: ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; ECOG = eastern cooperative oncology group; MDT = metastasis-directed therapy; NA = Unknown; PCa = prostate cancer; PSA = prostate-specific antigen; PSM = positive surgical margin; RP = radical prostatectomy; RT = radiation therapy.
[a] Median (IQR); n (%).
[b] Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's chi-square test.

Metastatic Onset According to Gleason Score 6 versus 7 versus 8-10

In time to metastatic onset analyses, significant median time differences were observed for Gleason score 6 versus Gleason score 7 vs. Gleason score 8-10 patients, namely 79 versus 54 versus 41 months ($P = .01$, Figure 1). 5-year MFS rates were 70% versus 44% versus 36% for respectively for Gleason score 6 versus 7 versus 8-10.

In univariable Cox regression models (Table 2A), Gleason score 7 (Hazard Ratio [HR]: 1.63, $P = .02$) and Gleason score 8-10 (HR: 1.84, $P < .01$) were associated with higher risk of metastases, relative to Gleason score 6. After multivariable adjustment, both Gleason 7 (HR: 2.21, $P = .02$) and Gleason 8-10 (2.52, $P < .01$) harbored an interpedently higher risk of metastases over time than Gleason score 6 patients.

Metastatic Onset According to Pathological Stage

In subgroup analyses stratified according to pathological stage after radical prostatectomy, significant median time differences were observed for pT1-2 versus pT3-4, namely 44 versus 64 months ($P = .027$, Figure 2). Five-year MFS rates were 51.9% versus 37.6% for respectively for pT1-2 versus pT3-4.

In univariable Cox regression models, pT3-4 (HR: 1.35) was associated with higher risk of metastases, relative to Gleason score pT1-2. After multivariable adjustment, pT3-4 was still an independent predictor of higher risk of metastases over time than pT1-2 (HR: 1.42, $P = .03$, Table 2B).

OS According to Time to Metastatic Onset

In our third set of analyses, we distinguished secondary mHSPC according to the time interval between primary prostate cancer diagnosis and secondary metastatic onset. Here, significant OS differences were observed between all 4 mHSPC groups (Figure 3, $P < .01$). Specifically, median OS was 56 versus 69 versus 97 versus not reached months for time interval < 24 versus 24-60 versus 60-120 ≥ 120 months.

In univariable Cox regression models, HRs were 0.58 ($P = .12$) for 24-60 months, HR: 0.59 ($P = .13$) for 60-120 months and HR: 0.17 ($P < .01$) for ≥ 120 months mHSPC patients. After multivariable adjustment, time interval 24-60 months (HR: 0.23, $P < .01$), 60-120 months (HR: 0.36, $P = .043$) and ≥ 120 months (HR: 0.12, $P = .01$) were independent predictors for better OS in mHSPC, relative to time interval < 24 months (Table 2C).

Discussion

We hypothesized that differences in time to metastatic onset of mmPCa may be attributable to the aggressiveness and extend of the primary prostate cancer tumor. Moreover, we also hypothesized that the time interval between primary prostate cancer and occurrence of secondary recurrent metastatic stage also influences OS. We tested these hypotheses by relying on our institutional metastatic prostate cancer database and made several important observations.

First, we observed that only a minority of 7% of patients with Gleason score 6 at diagnosis harbored mmPCa. Moreover, we observed that patients with Gleason score 8-10 also harbored signif-

Figure 1 Metastatic onset stratified according to Gleason score (GS) in secondary/metachronous metastatic prostate cancer patients (smPCa).

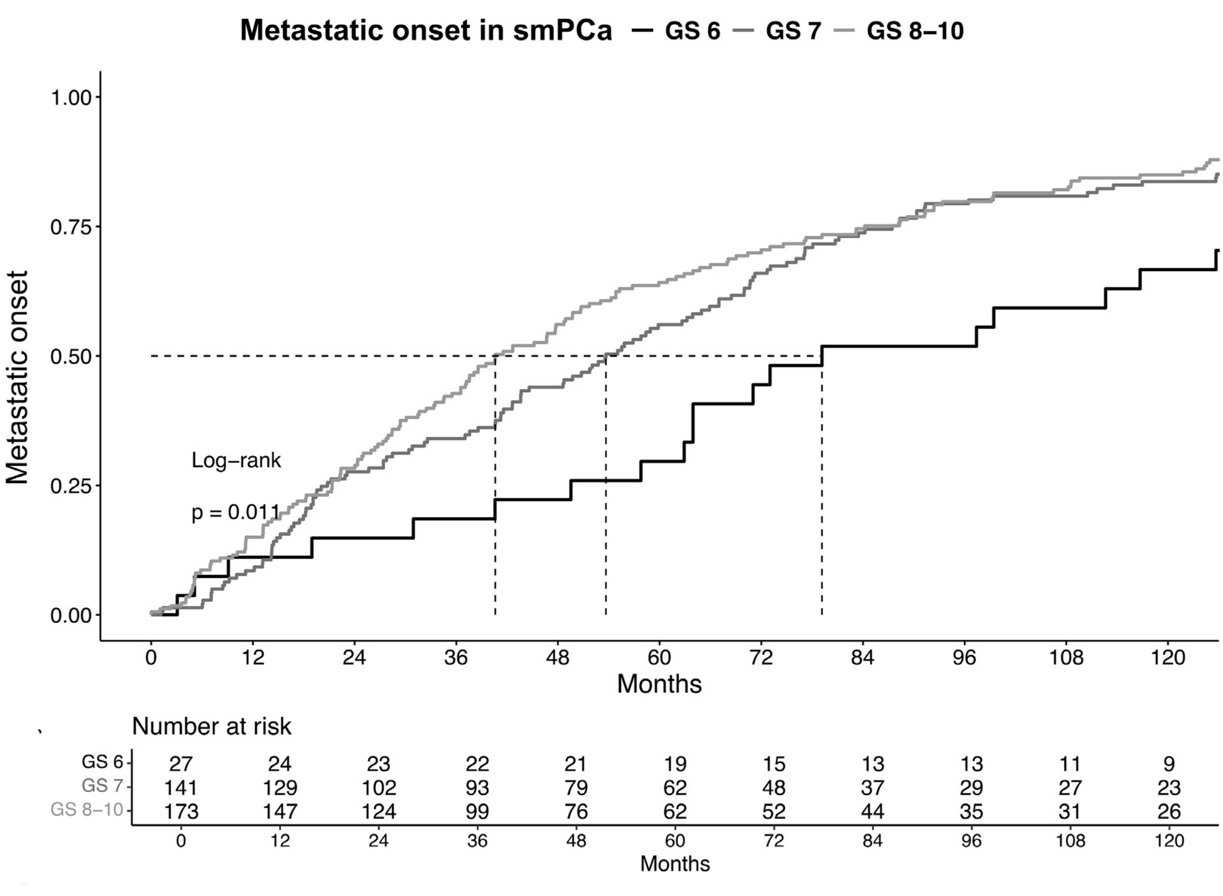
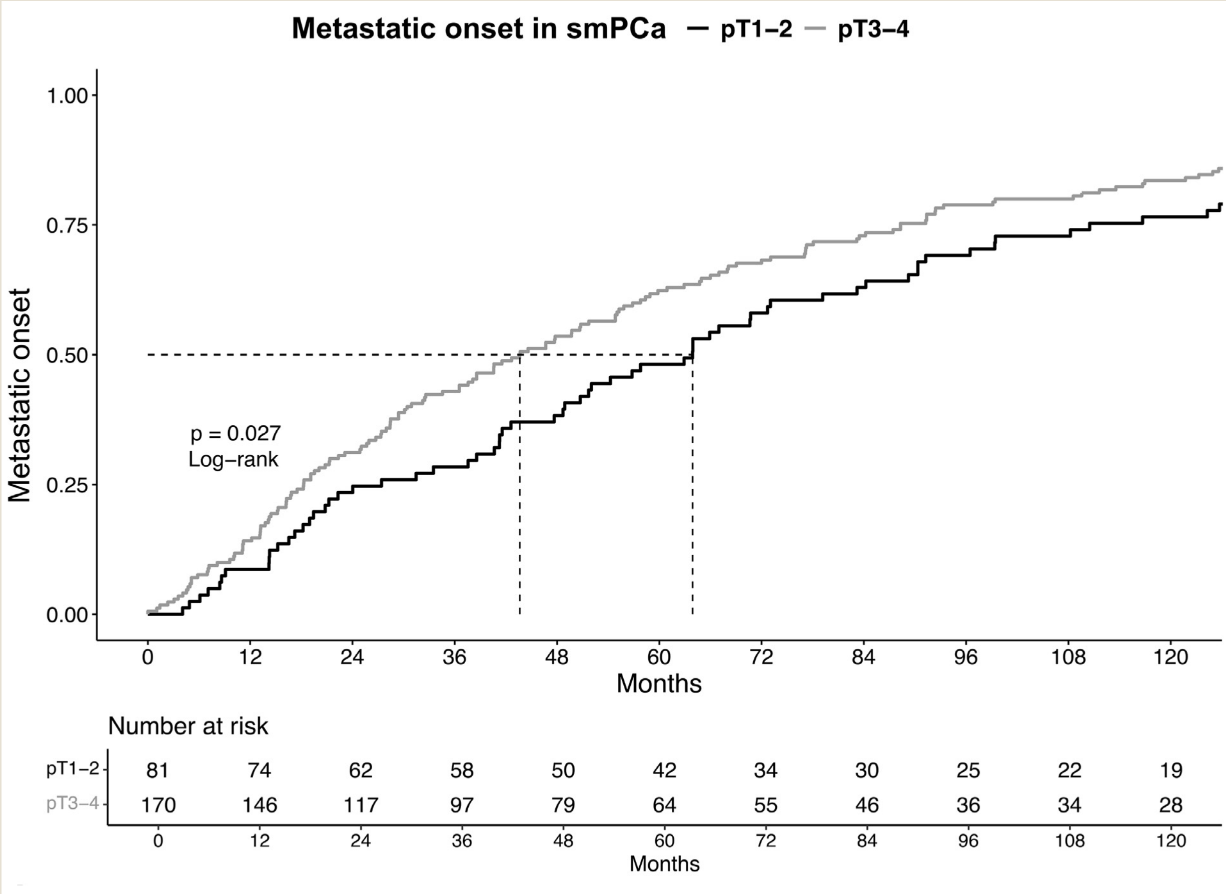


Table 2 Univariable and Multivariable Cox Regression Models Predicting Occurrence of Metastasis (A-B) According to Gleason Score And Time to Metastatic Prostate Cancer (PCa) Disease on Overall Survival (OS, C)

	Univariable			Multivariable		
(A) Metastatic Onset	**HR**	**CI**	**P-Value**	**HR**	**CI**	**P-Value**
Gleason score 6[a]	**Ref.**	-	-	**Ref.**	-	-
Gleason score 7[a]	1.63	(1.08-2.48)	.02	2.21	(1.11-4.41)	.02
Gleason score 8-10[a]	1.84	(1.23-2.78)	< .01	2.52	(1.27-5.02)	< .01
(B) Metastatic onset						
pT1-2	**Ref.**	-	-	**Ref.**	-	-
pT3-4[b]	1.35	(1.03-1.77)	.027	1.42	(1.03-1.96)	.03
(C) OS in mHSPC						
Time to metastatic PCa < 24 months[c]	**Ref.**	-	-	**Ref.**	-	-
Time to metastatic PCa 24-60 months[c]	0.58	(0.29-1.14)	.12	0.23	(0.08-0.62)	< .01
Time to metastatic PCa 60-120 months[c]	0.59	(0.30-1.17)	.13	0.36	(0.13-0.97)	.043
Time to metastatic PCa > 120 months[c]	0.17	(0.05-0.60)	< .01	0.12	(0.02-0.66)	.01

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; mHSPC = Metastatic hormone-sensitive prostate cancer.
Adjustment in multivariable Cox regression models was made for:
[a] Age at PCa diagnosis, pT stage, PSA, local therapy, mHSPC status.
[b] Age at PCa diagnosis, Gleason Score, PSA, mHSPC status.
[c] Low versus high volume disease according to CHAARTED criteria, Gleason Score, PSA, amount of therapy lines.

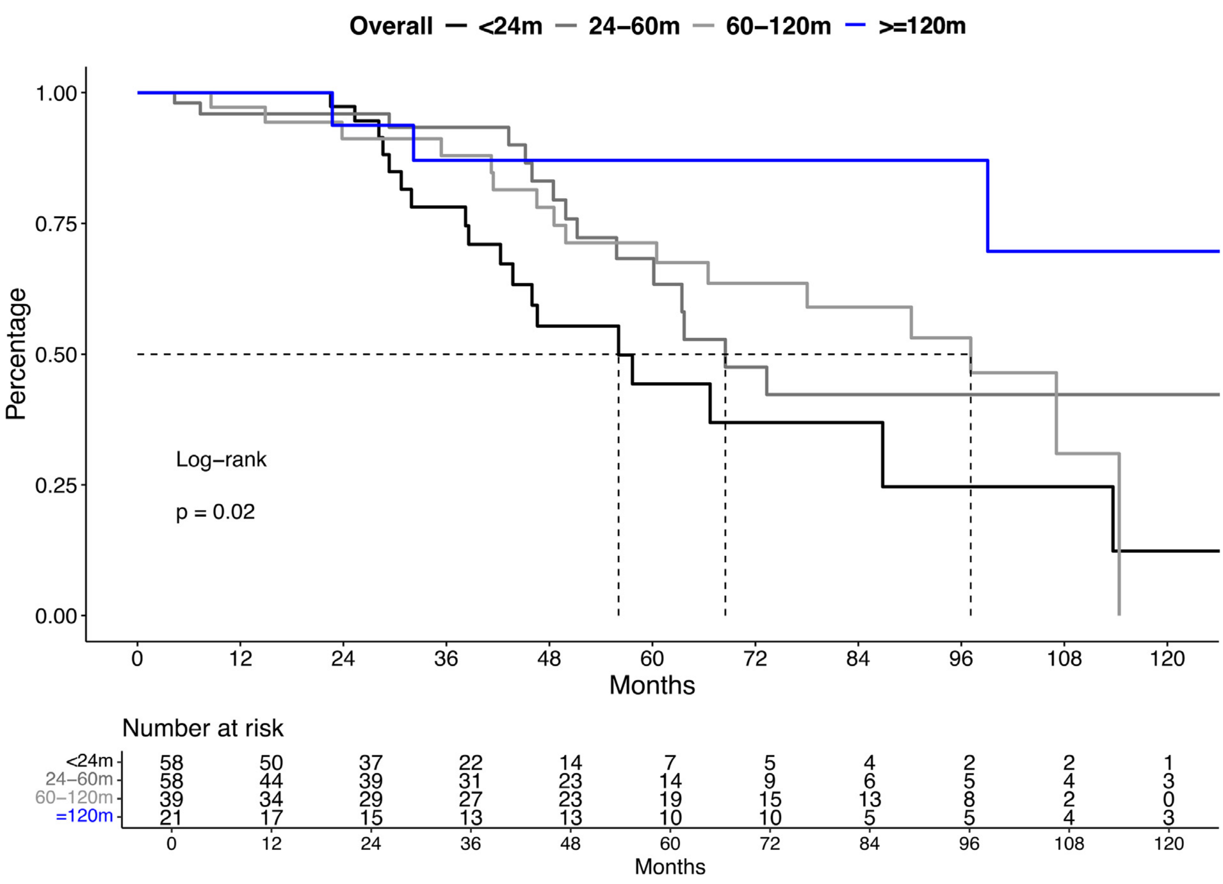
Figure 2 Metastatic onset stratified according to pT1-2 versus pT3-4 in secondary/metachronous metastatic prostate cancer patients (smPCa).



icantly worse pathological features after RP and received more systemic therapy lines than Gleason score 6 and 7 counterparts. These observations are comparable with previous reports. In 2 prospective phase II trials with mmPCa patients, proportions with Gleason score 6 also ranged from 6% to 22%.[15,16] In another analyses by De Bruycker et al., in which all patients received an 18-F PET-CT scan for metastatic recurrence detection, 19% harbored Gleason score 6.[17] Our lower rate of Gleason score 6 patients may be explained by lower rates of PET-CT scan for staging purposes in clinical real-world setting, which is in generally a predictor for lower MFS.[18] However, in general, metastatic progression of Gleason score 6 is a rare event irrespectively of the primary treatment or active surveillance.[19,20]

Secondly, we observed that median time to metastatic onset is shortest with higher Gleason score. More specifically, median time to metastatic onset significantly differed between the compared groups (Gleason score 6 vs. 7 vs. 8-10). However, since the above-described differences in unfavorable postsurgical characteristics may have also contributed to the development of mmPCa, we applied multivariable Cox regression models to adjust for those confounding biases and the postsurgical treatment leading to nmHSPC/nmCRPC status. Here we also found that a higher Gleason score is independently associated with shorter time to onset of metastatic disease. Compared to previous reports, our median time of 41 months to the onset of metastases in Gleason score 8-10 patients is at the upper bound to the median MFS of the 3 phase III trials ARAMIS, SPARTAN and PROSPER investigating MFS in nmCRPC patients with high-risk of disease progression (defined as PSA doubling time $\leq$ 10 months; median MFS: 37-41 months).[21-23] However, rates of Gleason score 8-10 were slightly lower in these 3 trials (41%-44%) and only approximately one third of patients in our cohort were classified as nmCRPC. Moreover, our results are also in an agreement with previous reports predicting MFS for localized prostate cancer treated with RP, in which higher Gleason score was associated with shorter MFS.[24,25] However, these MFS rates are not comparable to our study, since we solely included metachronous prostate cancer patients with onset of metastases, while conversely the above studies also included patients which never developed metastatic stage during follow-up. Therefore, the rates of the current study remain higher than the previous reports. Moreover, we also validated our findings in a more heterogeneous cohort using pathological stage after radical prostatectomy. Here,

Figure 3 Overall survival (OS) of metastatic hormone-sensitive prostate cancer patients (mHSPC) stratified according to time since prostate cancer diagnosis and onset of secondary/metachronous metastatic disease.



we also found that locally-advanced stage is independently associated with shorter time to metastatic onset.

Finally, we observed that longer time interval between primary prostate cancer diagnosis and onset of metastases is associated with longer OS in mHSPC patients. Nevertheless, when also including the cohort of patients with mCRPC, the results remained qualitatively the same. These observations seem intuitively on hand, since general life expectancy is shortened when metastatic stage occurred. However, to the best of our knowledge, this phenomenon has never been formally addressed.

Limitations of the current retrospective single-center study include several factors that may affect the interpretation and generalizability of our findings. Firstly, the study's scope is limited to a single institution, which may not accurately represent other patient populations or healthcare settings. Additionally, the retrospective nature of the study introduces selection bias, as data are collected from medical records that may be incomplete or biased towards certain patient groups, such as the primary treatment (radiation therapy vs. radical prostatectomy) to the prostate and/or adjuvant or salvage treatments, ADT treatment for relapse and the stage of patients (nmHSPC vs. nmCRPC before onset of metastases). However, the current study aims to draw conclusions in real-world scenario which is reflected by including both entities with possible differences in disease outcomes. Furthermore, the quality of the data relies heavily on the accuracy and completeness of medical records, which can vary and may impact the validity of the results. Finally, interobserver variability may apply for the pathological reports and the Gleason score grading or pathological stage made for the included mmPCa patients.

Conclusion

Taken together, onset of mmPCa in Gleason score 6 patients is a rare event. However, metastatic onset is strongly influenced by Gleason score and advanced pT-stage in real-life setting, even after controlling for possible unfavorable confounders. Finally, survival may be prolonged with longer time interval between primary prostate cancer diagnosis and onset of metastases. All of these above findings should be used in consideration for clinical follow up and patient counseling after initial local therapy. Specifically, patients with advanced grade or stage should be followed up closely for onset of mmPCa.

Clinical Practice Points

- Onset of smPCa in Gleason score 6 patients is a rare event.
- Metastatic onset is strongly influenced by Gleason score and advanced pT-stage in real-life setting, even after controlling for possible unfavorable confounders.
- OS may be prolonged with longer time interval between primary prostate cancer diagnosis and onset of metastases.

Disclosure

None.

CRediT authorship contribution statement

Mike Wenzel: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Malin Lutz:** Writing – original draft, Investigation, Formal analysis. **Benedikt Hoeh:** Project administration, Methodology, Formal analysis. **Florestan Koll:** Writing – original draft, Validation, Investigation. **Cristina Cano Garcia:** Writing – original draft, Methodology, Formal analysis. **Carolin Siech:** Writing – original draft, Formal analysis. **Thomas Steuber:** Writing – review & editing, Validation, Supervision. **Markus Graefen:** Writing – review & editing, Validation, Supervision. **Derya Tilki:** Writing – original draft, Validation, Supervision. **Luis A. Kluth:** Writing – review & editing, Validation, Supervision. **Séverine Banek:** Validation, Supervision, Investigation. **Felix K.H. Chun:** Writing – review & editing, Validation, Supervision. **Philipp Mandel:** Writing – original draft, Validation, Project administration, Conceptualization.

Data Sharing Statement

Data are available for bona fide researchers who request it from the authors.

Acknowledgments

This study was part of the EPIC-REAP project (Enhancing Prostate cancer care In Germany Combining Real-world data And AI for Enhanced Analysis and Precision) supported by the Mildred-Scheel Nachwuchszentrum Frankfurt.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Preisser F, Chun FelixK H, Banek S, et al. Management and treatment options for patients with de novo and recurrent hormone-sensitive oligometastatic prostate cancer. *Prostate Int*. 2021;9(3):113–118. doi:10.1016/j.prnil.2020.12.003.
2. Francini E, Gray KP, Xie W, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). *The Prostate*. 2018;78(12):889–895. doi:10.1002/pros.23645.
3. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(11):1080–1087. doi:10.1200/JCO.2017.75.3657.
4. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13–24. doi:10.1056/NEJMoa1903307.
5. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132–1142. doi:10.1056/NEJMoa2119115.
6. Mandel P, Hoeh B, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer patients: a systematic review and network meta-analysis. *Eur Urol Focus*. 2023;9(1):96–105. doi:10.1016/j.euf.2022.08.007.
7. Wenzel M, Würnschimmel C, Nocera L, et al. Overall survival after systemic treatment in high-volume versus low-volume metastatic hormone-sensitive prostate cancer: systematic review and network meta-analysis. *Eur Urol Focus*. 2022;8(2):399–408. doi:10.1016/j.euf.2021.04.003.
8. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352–360. doi:10.1056/NEJMoa1704174.
9. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121–131. doi:10.1056/NEJMoa1903835.
10. Hoeh B, Garcia CC, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer: updated network meta-analysis stratified by disease volume. *Eur Urol Focus*. 2023;S2405-4569(23):00094–00099. doi:10.1016/j.euf.2023.03.024.
11. Wenzel M, Nocera L, Collà Ruvolo C, et al. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. *Prostate Cancer Prostatic Dis*. 2022;25(2):139–148. doi:10.1038/s41391-021-00395-4.
12. Würnschimmel C, Wenzel M, Chierigo F, et al. Presence of biopsy Gleason pattern 5 + 3 is associated with higher mortality after radical prostatectomy but not after external beam radiotherapy compared to other Gleason Grade Group IV patterns. *The Prostate*. 2021;81(11):778–784. doi:10.1002/pros.24175.
13. Mottet N, van Den Bergh R, Briers E, Cornford P, Santis MD, Fanti S, et al.. *EAU Guidelines on Prostate Cancer*. 2019.
14. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969–974. doi:10.1001/jama.280.11.969.
15. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650–659. doi:10.1001/jamaoncol.2020.0147.
16. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(5):446–453. doi:10.1200/JCO.2017.75.4853.
17. De Bruycker A, Lambert B, Claeys T, et al. Prevalence and prognosis of low-volume, oligorecurrent, hormone-sensitive prostate cancer amenable to lesion ablative therapy. *BJU Int*. 2017;120(6):815–821. doi:10.1111/bju.13938.
18. Wenzel M, Hussein R, Maurer T, et al. PSMA PET predicts metastasis-free survival in the setting of salvage radiotherapy after radical prostatectomy. *Urol Oncol*. 2022;40(1):7.e1–7.e8. doi:10.1016/j.urolonc.2021.06.008.
19. Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2023;388(17):1547–1558. doi:10.1056/NEJMoa2214122.
20. Neal DE, Metcalfe C, Donovan JL, et al. Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the protect randomised controlled trial according to treatment received. *Eur Urol*. 2020;77(3):320–330. doi:10.1016/j.eururo.2019.10.030.
21. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408–1418. doi:10.1056/NEJMoa1715546.
22. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2020;382(23):2197–2206. doi:10.1056/NEJMoa2003892.
23. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235–1246. doi:10.1056/NEJMoa1815671.
24. Würnschimmel C, Wenzel M, Wang N, et al. Radical prostatectomy for localized prostate cancer: 20-year oncological outcomes from a German high-volume center. *Urol Oncol*. 2021;39(12):830.e17–830.e26. doi:10.1016/j.urolonc.2021.04.031.
25. Preisser F, Wang N, Abrams-Pompe RS, et al. Oncologic outcomes of organ-confined Gleason grade group 4-5 prostate cancer after radical prostatectomy. *Urol Oncol*. 2022;40(4):161.e9–161.e14. doi:10.1016/j.urolonc.2021.11.019.