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TOPIC PAPER

Importance of metastatic volume in prognostic models to predict survival in newly diagnosed metastatic prostate cancer

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Abstract

Purpose To explore the prognostic importance of metastatic volume in a contemporary daily practice cohort of patients with newly diagnosed metastatic hormone-naive prostate cancer (mHNPC) and to develop a pragmatic prognostic model to predict survival for these patients.

Methods Since 2014, 113 patients with newly diagnosed mHNPC were prospectively registered. Statistical analysis was performed using SPSS 25.0™ with two-sided p value < 0.05 indicating statistical significance. Univariate and multivariate cox regression analyses were performed to identify prognostic risk factors. Kaplan–Meier method with log-rank statistics was constructed to analyze difference in survival in the prognostic groups. Model performance was assessed using the Concordance-index (C-index) and cross-validated in R v3.4.1. High-volume mHNPC (HVD) was defined as the presence of visceral metastasis or ≥ 4 bone metastases with ≥ 1 appendicular lesion.

Results Multivariate analysis identified HVD ($p = 0.047$) and elevated alkaline phosphatase (ALP) ($p = 0.018$) as independent prognostic risk factors for overall survival (OS). Consequently, three prognostic groups were created: a good (no risk factors), intermediate (1 risk factor) and poor prognosis group (2 risk factors). Median OS for the good, intermediate and poor prognosis group was not reached, 73 and 20 months (95% CI 9–31 months with $p < 0.001$ and Correspondence-index of 0.78), respectively.

Conclusions We developed a pragmatic and qualitative prognostic model consisting of three prognostic risk groups for OS in a daily practice cohort of patients with newly diagnosed mHNPC. Independent prognostic risk factors included in the model were HVD and abnormal ALP.

Keywords Alkaline phosphatase · Hormone-sensitive · Metastatic volume · Overall survival · Predictive model · Prostate cancer

Introduction

Treatment of patients with metastatic hormone-naive prostate cancer (mHNPC) has changed substantially in recent years. Since 1940, androgen deprivation therapy (ADT) has been the cornerstone in the treatment of mHNPC [1, 2]. Unfortunately,

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response to ADT is only temporary after which patients develop castration-resistant prostate cancer (CRPC). Even with the novel second-line treatments, overall survival (OS) is still limited (median 42 months) [3]. Therefore, emerging interest is given towards the upfront concomitant administration of previously used second-line treatments with ADT.

In 2015, the CHAARTED trial was a pioneer after proving a benefit on both CRPC-free survival (CRPC-FS) and OS in patients treated with combined docetaxel and ADT versus only ADT [4]. A year later, the STAMPEDE trial confirmed these positive results [5]. Subsequently in 2017, the LATITUDE trial [6] and the STAMPEDE trial [7] demonstrated better outcomes when concomitantly administering abiraterone acetate to ADT. Consequently, mHNPC is becoming increasingly important.

Contrary to the CRPC stage [8–11], little is known about prognostic risk factors in the setting of mHNPC. In 2003, Glass et al. were the first to publish a prognostic model for OS based on a retrospective analysis of patients enrolled in the SWOG 8894 trial [12]. They created a rather complex model comprising three prognostic groups (good, intermediate, poor prognosis) according to four risk factors: performance status, prostate-specific antigen (PSA), Gleason score and appendicular bone metastasis. In 2014, Gravis et al. retrospectively validated this, by then outdated, prognostic model using the patient cohort of the GETUG-15 phase-3 trial [13]. The discriminatory value of the model by Glass et al. turned out low with no significant difference in the intermediate and poor prognosis group. Next, Gravis et al. developed a new simple prognostic model, essentially underlying the role of alkaline phosphatase (ALP). However, the performance of the model remained rather low. A major limitation was the lack of information regarding the number and location of the bone metastases, both important known prognostic parameters [12, 14, 15]. Moreover, since great deal has been changing in the management of these patients, these data from 10 to 15 years ago might be currently outdated. All the above-mentioned facts urge the need for a novel prognostic model.

The primary objectives of this study were to explore the prognostic importance of metastatic volume in an up-to-date, daily practice cohort of patients with newly diagnosed mHNPC and to develop a pragmatic prognostic model to predict survival. Secondly, we aim to verify previous prognostic models using our patient cohort.

Materials and methods

Trial design and patients

Between May 2014 and January 2018, patients with newly diagnosed mHNPC were offered to sign an informed consent for prospective registration (B670201420709). Metastatic prostate cancer was defined as histologically confirmed prostate cancer with at least one metastatic lesion after staging by thoraco-abdominopelvic computed tomography (CT) and bone scintigraphy at time of initial diagnosis. In case of equivocal findings, additional investigations were performed: magnetic resonance imaging (MRI) of the full spine, choline/PSMA positron emission tomography (PET-)CT and/or biopsy of the lesion if technically feasible. Exclusion criteria were metastatic recurrence after prior local curative treatment, previous local or systemic treatment for prostate cancer, N1M0-stage and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 ($n = 6$). Digital rectal examination, transrectal ultrasound $\pm$ multiparametric MRI of the prostate were utilized for local staging (T stage). The 2014 International Society of Urologic Pathology grading system was used to assess the tumor grade group [16]. Systemic therapy was offered in accordance with the multidisciplinary oncologic discussion and European Association of Urology (EAU) guidelines [17], further taking into account the patient's health status and preference. From 2016, docetaxel could be added to ADT in high-volume disease (HVD) which was defined as the presence of visceral metastasis or ≥ 4 bone metastases with ≥ 1 beyond the vertebral bodies and pelvis [4]. Accessible systemic CRPC treatments, defined according to EAU guidelines [2], were abiraterone acetate, enzalutamide, docetaxel, cabazitaxel and radium-223. Patients were evaluated every 3 months through medical history, physical examination and PSA. In case of clinical symptoms development, clinical deterioration and/or PSA progression, restaging was performed.

Statistical analysis

Descriptive statistics were used to characterize the study population. Time to death was calculated starting from the date of histological diagnosis of prostate cancer. Univariate Cox regression analyses were performed to identify prognostic risk factors. Next, all significant parameters were included in a backwards multivariate Cox regression model calculating p values based on likelihood ratio's. Subsequently, Kaplan–Meier method with log-rank statistics was used to analyze difference in survival in the prognostic groups. Two-sided p values < 0.05 indicated statistical significance (SPSS 25.0™). Model performance was assessed using the Concordance-index (C-index) and cross-validated (R v3.4.1) [18].

Results

In total, 113 patients with newly diagnosed mHNPC were included in our contemporary daily practice cohort. Baseline patient and tumor characteristics are presented in

Table 1 and systemic prostate cancer treatment in Supplementary Table 1. After a median follow-up of 20 months (IQR 11–36), 52/113 (46%) patients reached CRPC stage and 23/113 (20%) died [20/23 (87%) of prostate cancer]. Median CRPC-FS was 27 months (95% CI 19–35) with 5-year CRPC-FS estimate of 14% (95% CI 1–28). Median OS was 73 months (95% CI 49–97) with 5-year OS estimate of 62% (95% CI 44–79).

Prognostic risk factors

Univariate analyses identified ECOG performance status of 2 ($p=0.002$), HVD ($p<0.001$) and elevated ALP ($p<0.001$) as prognostic risk factors of shorter OS (Table 2). Taking into account the limited number of deceases, only HVD was included in our multivariate model. This definition encompasses all remaining significant risk factors describing metastatic volume (visceral disease, ≥4 bone metastases and appendicular disease). ECOG of 2, HVD and elevated ALP were included in the multivariate analysis which identified HVD (HR 4.15, $p=0.047$) and elevated ALP (HR 3.31, $p=0.018$) as independent prognostic risk factors (Table 2).

Prognostic model

Three prognostic groups were created according to the number of risk factors as identified in the multivariate model: a good (no HVD and normal ALP), intermediate (HVD or elevated ALP) and poor prognosis group (HVD and elevated ALP). The median OS for the good ($n=55$), intermediate ($n=37$) and poor prognosis group ($n=21$) was not reached, 73 and 20 months (95% CI 9–31), with 5-year OS estimates of 91% (95% CI 81–100), 66% (95% CI 38–94) and 23% (95% CI 0–57%, $p<0.001$), respectively (Fig. 1). The C-index was 0.78 with cross-validated C-index of 0.78.

Validation previous prognostic models for overall survival

The median OS for the good ($n=64$), intermediate ($n=29$) and poor prognosis group ($n=15$) according to the model of Glass et al. was not reached, 51 (95% CI 33–69) and 56 months (95% CI 0–117) with 5-year OS estimates of 87%, 46% and 38% ($p=0.004$), respectively. The C-index was 0.71 with cross-validated C-index of 0.70.

The median OS for the normal ($n=66$) and abnormal ALP group ($n=23$) according to the model of Gravis et al. was 73 and 23 months with 5-year OS estimates of 80% and 26% ($p<0.001$), respectively. The C-index was 0.75 with cross-validated C-index of 0.75.

Discussion

The introduction of docetaxel and abiraterone in patients with mHNPC is leading to a revolutionary shift in the treatment sequence of metastatic prostate cancer. Consequently, mHNPC is becoming increasingly important. However, not that much is known about prognostic risk factors for these patients.

Currently, there are only two prognostic models for survival in patients with mHNPC with some important limitations [12, 13]. Both models used data of patients included in clinical trials which may not be fully representative for daily practice. Moreover, since great deal has been changing in the management of these patients, the data might be currently outdated. Additionally, Glass et al. used a complex recursive partitioning method not easily applicable in practice [12]. The discriminatory value of this model after external validation by Gravis et al. was low with no significant difference in the intermediate and poor prognosis group (C-index 0.59) [13]. Although Gravis et al. developed a simplified prognostic model, the performance of the model remained rather low (C-index 0.64) [13]. This model only differentiated two prognostic risk groups with very different prognosis. Distinction of an intermediate group seems to be preferential for a more accurate OS estimation. Next, a key limitation was the lack of information regarding the metastatic volume, an essential prognostic parameter that could potentially improve model performance [12, 14, 15]. The above-mentioned facts urged the need for a novel prognostic model. The use of one universal prognostic model would allow better comparison of trials with different results.

As a primary endpoint, we wanted to explored the prognostic importance of metastatic volume for patients with newly diagnosed mHNPC since this was absent in the model by Gravis et al. [13]. In our contemporary, daily practice cohort, HVD according to the definition of the CHAARTED trial was the strongest independent risk factor for OS and thus included in the prognostic model. We included this definition since it is easy to use for clinical decision making in daily practice with only two risk factors to consider. We previously proved that there is an excellent agreement between the definition of metastatic volume in the CHAARTED and LATITUDE trial with similar prognostic value in mHNPC [19].

In the pioneering trials substantiating upfront combination therapy, the metastatic volume already played a key role in predicting survival benefit [4, 6]. The subgroup analysis from the CHAARTED trial suggested that only patients with HVD acquire a benefit from concomitant docetaxel and ADT [4]. While the LATITUDE trial only included patients with high-risk disease anticipating their

Table 1 Baseline patient and tumor characteristics in the total cohort and according to our prognostic risk groups

	Total	Good	Intermediate	Poor
n	113	55	37	21
Median age, years (IQR)	70 (63–78)	69 (59–74)	74 (66–83)	69 (64–79)
ECOG performance status, *n* (%)				
0–1	106 (94)	53 (96)	35 (95)	18 (86)
2	7 (6)	2 (4)	2 (5)	3 (14)
Metastatic symptoms[a], *n* (%)				
No	94 (83)	53 (96)	29 (78)	12 (57)
Yes	19 (17)	2 (4)	8 (22)	9 (43)
ISUP grade group, *n* (%)				
1	2 (2)	1 (2)	1 (3)	0 (0)
2–3	15 (13)	10 (18)	4 (11)	1 (5)
4–5	93 (82)	43 (78)	31 (84)	19 (91)
Clinical T stage[b], *n* (%)				
1–2	25 (22)	17 (31)	5 (14)	3 (14)
3–4	87 (77)	38 (69)	31 (84)	18 (86)
Clinical N stage[c], *n* (%)				
0	32 (28)	14 (26)	13 (35)	5 (24)
1	81 (72)	41 (75)	24 (65)	16 (76)
Clinical M stage[d], *n* (%)				
1[a]	25 (22)	25 (46)	0 (0)	0 (0)
1[b]	71 (63)	30 (55)	24 (65)	17 (81)
1[c]	17 (15)	0 (0)	13 (35)	4 (19)
Median M1b (IQR)	6 (2–13)	1.5 (1–3)	7 (1–2)	15 (10–20)
Appendicular bone disease, *n* (%)				
No	62 (55)	49 (89)	13 (35)	0 (0)
Yes	51 (45)	6 (11)	24 (65)	21 (100)
Metastatic volume, *n* (%)				
LVD	57 (50)	55 (100)	2 (5)	0 (0)
HVD[e]	56 (50)	0 (0)	35 (95)	21 (100)
Median PSA, ng/mL (IQR)	49 (19–244)	29 (12–88)	5 (23–274)	289 (78–571)
PSA group, *n* (%)				
< 50	59 (52)	37 (67)	18 (49)	4 (19)
> 50	54 (48)	18 (33)	19 (51)	17 (81)
Alkaline phosphatase, *n* (%)				
Normal	66 (74)	41 (75)	25 (68)	0 (0)
Abnormal[f]	23 (26)	0 (0)	2 (5)	21 (100)
Glass prognostic group, *n* (%)				
Good	64 (59)	47 (86)	16 (43)	1 (5)
Intermediate	29 (27)	14 (26)	12 (32)	11 (52)
Poor	15 (14)	0 (0)	7 (19)	8 (38)

HVD high-volume disease, *IQR* interquartile range, *LVD* low-volume disease, *M1b* number of bone metastases, *ISUP* International Society of Urological Pathology, *PSA* prostate-specific antigen

[a]Defined as symptoms related to metastatic disease such as bone pain and lymph edema

[b]63% of patients were staged using multiparametric magnetic resonance imaging

[c]88% of patients were staged using computed tomography, 7% using multiparametric magnetic resonance imaging and 5% using additional positron emission tomography

[d]89% of patients were staged using bone scan, 6% with additional positron emission tomography and 3% using additional multiparametric magnetic resonance imaging

[e]Defined as the presence of visceral metastasis or ≥ 4 bone metastases with ≥ 1 beyond the vertebral bodies and pelvis [4]

[f]Defined as any value exceeding the normal reference upper limit value of 120 U/L

Table 2 Univariate and multivariate Cox regression analyses for overall survival

		Raw HR (95% CI)	*p* value
Univariate analyses			
Age (years)		1.02 (0.98–1.06)	0.4
ECOG performance status	< 2 vs. 2	4.28 (1.57–11.6)	0.002*
Metastatic symptoms[a]	No vs. yes	1.63 (0.66–4.03)	0.3
ISUP grade group	< 4 vs. ≥ 4	2.79 (0.37–20.8)	0.3
Clinical T stage	< 3 vs. ≥ 3	1.35 (0.46–3.99)	0.6
Clinical N stage	0 vs. 1	1.47 (0.54–3.99)	0.4
Visceral metastasis	No vs. yes	3.18 (1.16–8.69)	0.017*
Bone metastases	≤ 4 vs. > 4	9.81 (1.31–73.0)	0.006*
Appendicular bone disease	No vs. yes	4.89 (1.65–14.5)	0.002*
Metastatic volume	LVD vs. HVD[b]	7.24 (2.14–24.5)	< 0.001*
PSA group	≤ 50 vs. > 50	2.18 (0.92–5.15)	0.070
Alkaline phosphatase	Normal vs. abnormal[c]	5.72 (2.16–15.1)	< 0.001*
Upfront ADT	No vs. yes	1.43 (0.60–3.41)	0.4
Upfront ADT + docetaxel	No vs. yes	1.73 (0.66-4.54)	0.3
Multivariate analyses			
ECOG	< 2 vs. 2	2.24 (0.71–7.02)	0.2
Metastatic volume[a]	LVD vs. HVD	4.15 (0.84–20.5)	0.047*
Alkaline phosphatase	Normal vs. abnormal	3.31 (1.16–9.44)	0.018*

ADT androgen deprivation therapy, *CI* confidence interval, *CRPC-FS* castration-refractory prostate cancer-free survival, *HR* hazard ratio, *HVD* high-volume disease, *LVD* low-volume disease, *ISUP* International Society of Urological Pathology, *PSA* prostate-specific antigen, *OS*: overall survival, *LVD* low-volume disease

*Significant *p* values

[a]Defined as symptoms related to metastatic disease such as bone pain and lymph edema

[b]Defined as the presence of visceral metastasis or ≥ 4 bone metastases with ≥ 1 beyond the vertebral bodies and pelvis [4]

[c]Defined as any value exceeding the normal reference upper limit value of 120 U/L

poor prognosis [6]. Unfortunately, neither documented ALP levels. Based on our findings and those of Gravis et al. [13], it seems crucial to also include ALP when stratifying patients.

As mentioned above, our prognostic model verified the importance of ALP conform the findings of Gravis et al. However, the metastatic volume was an even more important prognostic risk factor (HR 4.15 vs. 3.31 for ALP). Possibly when only including ALP, a subset of poor prognosis patients is missed such as patients with visceral metastases only and presumably low ALP. The prognosis of patients with numerous bone metastases located in the axial body/pelvis might otherwise be underestimated when only considering ALP since the absence of appendicular bone disease is known to be related to better prognosis [12].

In contrary to Glass and Gravis et al., the tumor aggressiveness (grade group) was not a prognostic risk factor in our population. This can be explained by the observation that the large majority (82%) of patients with newly diagnosed mHNPC harbor high-grade tumors (grade group ≥ 4). The existing models did, however, not only include patients with newly diagnosed mHNPC but also patients who developed metastasis after recurrent prostatic disease. This last cohort logically had a grade group assessment (at prostate cancer diagnosis) in an earlier stage of the disease and presumably a less aggressive disease course compared to patients with metastasis at diagnosis. Moreover, post hoc analysis in the CHAARTED trial showed that concomitant use of ADT and docetaxel was only significant in patients who received no prior treatment for prostate cancer [4]. Inclusion of patients with metastatic recurrent disease results in a much more heterogeneous patient cohort and possibly presence of important (hidden) confounders. This might also explain the improved C-indexes for the model according to Glass et al. and Gravis et al. in our newly diagnosed validation cohort compared to the C-indexes reported by Gravis et al. [13].

Our validation showed overlapping OS for the intermediate and poor prognosis group according to the model of Glass et al. and consequently a lower performance compared to our model (C-index 0.70 vs. 0.78, respectively). The 5-year OS estimates according to the model of Gravis et al. (80% for normal vs. 26% for abnormal ALP) seem to correspond with our combined good/intermediate and poor prognosis group what could explain the (slightly) lower

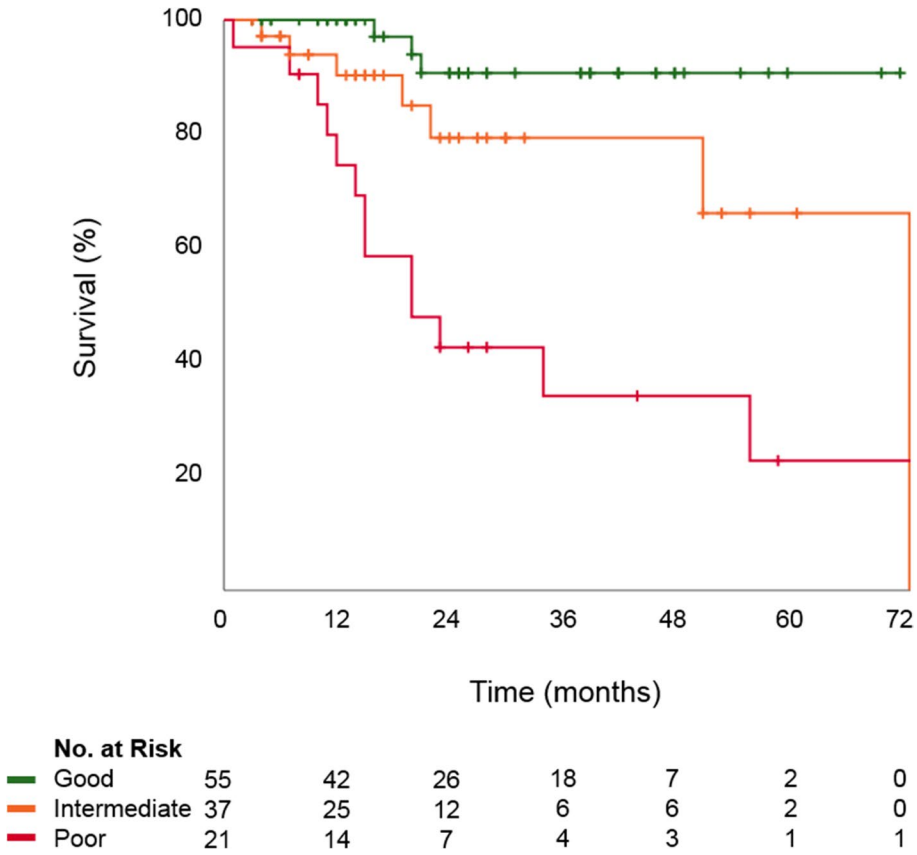

Fig. 1 Prognostic model for overall survival (OS). The median OS for the good, intermediate and poor prognosis group was not reached, 73 and 20 months (95% CI 9–31, $p < 0.001$), respectively

performance compared to our model (C-index 0.75 vs. 0.78, respectively). To our knowledge, this was the first time the model by Gravis et al. was externally validated.

The OS in our patient cohort was notably better compared to previously reported data (median 73 vs. 42 months [3]). This might be due to a subset of patients that received upfront concomitant chemohormonal therapy and the fact that many patients received multiple systemic agents due to the relatively high accessibility in Belgium. Furthermore, in case of equivocal findings on standard imaging, additional investigations were performed resulting in better sensitivity for detecting metastatic lesions. These patients would probably not be defined as metastatic in the setting of a clinical trial. However, this might become the new standard in the future what could lead to the definition of metastatic volume according to the CHAARTED trial becoming outdated. Another explanation might be the high opportunistic PSA screening rates in Belgium, leading to earlier mHNPC diagnosis.

We used a Cox regression based model instead of recursive partitioning method because regression models provide more accurate results and are easier in practice. This was substantiated by good C-indexes and internal statistical validation.

The main limitations of our study were the small sample set, limited follow-up and the heterogeneous therapeutic management. Furthermore, a subset of the ALP values were retrospectively collected resulting in some missings.

Conclusions

We developed a pragmatic and qualitative prognostic model consisting of three prognostic risk groups for OS in a daily practice cohort of patients with newly diagnosed mHNPC. Independent prognostic risk factors included in the model were HVD and abnormal ALP.

Author contributions SB: data collection/management, data analysis, manuscript writing; EDB, KD, PO, VF and SR: data collection/management, manuscript editing; BD: data collection/management; WV: data analysis, manuscript editing; KDM and CS: manuscript editing; NL: protocol/project development, data collection/management, data analysis, manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the local ethical committee of Ghent (Belgian registration number B670201420709). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Huggins C (1941) Studies on prostatic cancer. Arch Surg 43(2):209. https://doi.org/10.1001/archsurg.1941.01210140043004
2. Cornford P, Bellmunt J, Bolla M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71(4):630–642. https://doi.org/10.1016/j.eururo.2016.08.002
3. James ND, Spears MR, Clarke NW et al (2015) Survival with newly diagnosed metastatic prostate cancer in the docetaxel era: data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol 67(6):1028–1038. https://doi.org/10.1016/j.eururo.2014.09.032
4. Sweeney CJ, Chen Y-H, Carducci M et al (2015) Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373(8):737–746. https://doi.org/10.1056/NEJMoa1503747
5. James ND, Sydes MR, Clarke NW et al (2016) Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 387(10024):1163–1177. https://doi.org/10.1016/S0140-6736(15)01037-5
6. Fizazi K, Tran N, Fein L et al (2017) Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. https://doi.org/10.1056/nejmoa1704174
7. James ND, de Bono JS, Spears MR et al (2017) Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. https://doi.org/10.1056/nejmoa1702900
8. Halabi S, Lin C-Y, Kelly WK et al (2014) Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 32(7):671–677. https://doi.org/10.1200/JCO.2013.52.3696
9. Van Praet C, Rottey S, Van Hende F et al (2017) Which factors predict overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate post-docetaxel? Clin Genitourin Cancer. https://doi.org/10.1016/j.clgc.2017.01.019
10. Smaletz O, Scher HI, Small EJ et al (2002) Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. J Clin Oncol 20(19):3972–3982. https://doi.org/10.1200/JCO.2002.11.021
11. Armstrong AJ, Garrett-Mayer ES, Yang Y-CO, de Wit R, Tannock IF, Eisenberger M (2007) A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res 13(21):6396–6403. https://doi.org/10.1158/1078-0432.CCR-07-1036
12. Glass TR, Tangen CM, Crawford ED, Thompson I (2003) Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 169(1):164–169. https://doi.org/10.1097/01.ju.0000042482.18153.30
13. Gravis G, Boher J-M, Fizazi K et al (2015) Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. Eur Urol 68(2):196–204. https://doi.org/10.1016/j.eururo.2014.09.022
14. Tait C, Moore D, Hodgson C et al (2014) Quantification of skeletal metastases in castrate-resistant prostate cancer predicts progression-free and overall survival. BJU Int 114(6b):E70–E73. https://doi.org/10.1111/bju.12717
15. Klaff R, Varenhorst E, Berglund A et al (2016) Clinical presentation and predictors of survival related to extent of bone metastasis in 900 prostate cancer patients. Scand J Urol 50(5):352–359. https://doi.org/10.1080/21681805.2016.1209689
16. Epstein JI, Egevad L, Amin MB et al (2015) The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. Am J Surg Pathol 40(2):1. https://doi.org/10.1097/pas.0000000000000530
17. Mottet N, Bellmunt J, Bolla M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 71(4):618–629. https://doi.org/10.1016/j.eururo.2016.08.003
18. Efron B, Tibshirani R (1997) Improvements on cross-validation: the. 632 + Bootstrap method. J Am Stat Assoc 92(438):548–560
19. Buelens S, Poelaert F, Dhondt B et al (2018) Metastatic burden in newly diagnosed hormone-naive metastatic prostate cancer: comparing definitions of CHAARTED and LATITUDE trial. Urol Oncol Semin Orig Investig 36(4):158.e13–158.e20. https://doi.org/10.1016/j.urolonc.2017.12.009