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ARTICLE

Clinical Research

The prognostic value of pain in castration-sensitive prostate cancer

Roberto Iacovelli[1] · Chiara Ciccarese[1] · Orazio Caffo[2] · Ugo De Giorgi[3] · Marcello Tucci[4] · Claudia Mosillo[5] · Davide Bimbatti[6] · Francesco Pierantoni[6] · Francesca Maines[2] · Chiara Casadei[3] · Consuelo Buttigliero[7] · Michele Milella[8] · Giampaolo Tortora[1]

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Abstract

Background Cancer-related pain, usually associated with bone metastases, is a frequent and debilitating morbidity in patients with prostate cancer. To date there are only limited data regarding the prognostic role of pain in men with metastatic castration-sensitive prostate cancer (mCSPC). The objective of our analysis was to assess if the presence of pain can be considered an independent prognostic factor in mCSPC patients.

Methods A retrospective analysis was performed on patients with mCSPC referring to six oncology centers in Italy. Clinical and pathological features were recorded. Patients were considered to have pain if this was reported within the patient's file or in case of a chronic analgesic therapy was found among the concomitant medications. Survivals were estimated by the Kaplan–Meier method, and compared across groups using the log-rank test. Cox proportional hazard models, stratified according to the baseline characteristics, were used to estimate hazard ratios for overall survival (OS). All the variables were significant if $p < 0.05$.

Results Data about pain were available for 365 cases and pain was present in 34.8% of patients. Pain was mainly associated with high value of prostate-specific antigen, metastatic bone extension regardless of the site, and lymph node involvement. mCSPC patients with pain had in most of the cases high-volume or Hr disease, and significant shorter OS (27.0 vs. 58.2 months, $p < 0.001$) and PFS (10.1 vs. 17.4 months, $p < 0.001$) compared to those without pain. The negative impact of pain on OS remained significant even if adjusted for CHAARTED or LATITUDE classification, and other significant baseline prognostic factors.

Conclusions This analysis supports the poor prognostic role of cancer-related pain in the setting of mCSPC patients. A prospective validation is required.

Introduction

Prostate cancer (PC) is one of the most frequently diagnosed solid tumors worldwide, and a major leading cause of cancer-related deaths in men in Western societies [1]. Based on the sensitivity to androgen-deprivation therapy (ADT), which is the cornerstone of PC systemic therapy, metastatic PC is commonly classified into castration-sensitive (CSPC) or castration-resistant (CRPC) disease. Metastatic castration-sensitive prostate cancer (mCSPC) includes an heterogeneous spectrum of diverse conditions that differ in terms of clinical presentation, tumor biology, and patients' prognosis. Metastases in CSPC can be present at time of

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✉ Roberto Iacovelli
roberto.iacovelli@policlinicogemelli.it

[1] Medical Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[2] Department of Medical Oncology, Santa Chiara Hospital, 38112 Trento, Italy

[3] Department of Medical Oncology, Scientific Institute Romagnolo for the Study and Treatment of Cancer (IRST) IRCCS, Meldola, Italy

[4] SC Oncologia, Ospedale Cardinal Massaia, Asti, Italy

[5] Medical Oncology Unit, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy

[6] Medical Oncology Unit 1, Istituto Oncologico Veneto IOV IRCCS, Padua, Italy

[7] Department of Oncology, University of Turin, San Luigi Gonzaga Hospital, Turin, Italy

[8] Medical Oncology Unit, Azienda Ospedaliera Universitaria Integrata (AOUI), Verona, Italy

diagnosis (de novo CSPC—~4–5% of all PC diagnosed in developed countries) [2], but can also represent the progression of a localized PC. Clinically, aggressive forms (symptomatic patients with visceral metastases and/or extensive bone involvement mainly associated with undifferentiated tumors of high Gleason score) coexist with more indolent cases (asymptomatic, oligometastatic patients, with well differentiated tumors), explaining the wide range of patients' prognosis with median survivals going from just over 2 years to over 6 years [3].

Being able to distinguish different prognostic "classes" of mCSPC so as to tailor the treatment for each patient is one of the greatest future challenges. Indeed, efforts have been made for classifying mCSPC patients with a different prognosis based on clinical features (mainly on the disease burden). The CHAARTED and LATITUDE trials, which demonstrated the superiority in terms of overall survival (OS) of adding to ADT docetaxel or abiraterone, respectively, classified mCSPC patients based on the presence of visceral metastasis, the extension of bone metastatic involvement, and the Gleason score (only LATITUTE trial). However, the classifications criteria used in these two studies to define patients' prognosis are different and not fully corresponding [3]. Certainly, in the past years the treatment scenario of mCSPC has been consistently enriched by novel life-prolonging options, including docetaxel and the novel generation hormonal therapies abiraterone, enzalutamide, and apalutamide [4–10]. However, the lack of a direct comparisons between these therapeutic options, as well as the absence of a reliable molecular and clinical prognostic stratification of mCSPC make difficult an adequate treatment selection, and underline the urgent need for improving the current state of art. The objective of our analysis was to assess the role of pain as an independent prognostic factor so as to improve the management of mCSPC patients.

Materials and methods

Patients

Patients affected by PC and referred to six hospitals were screened to find those with metastatic disease at diagnosis (i.e., de novo metastatic PC). Baseline characteristics required for the inclusion were: diagnosis of PC with evidence of metastatic spread at bone scan, computed tomography (CT), magnetic resonance imaging, or choline PET/CT at diagnosis, availability of ECOG performance status (PS), the beginning of the ADT (±docetaxel), and at least one follow-up visit after the initial diagnosis. Patients were excluded if baseline characteristics, such as histologic diagnosis, extension of disease, and type of treatment were not available.

The prognosis at baseline was evaluated for each patient using the CHAARTED or LATITUDE prognostic criteria [4, 6]. The CHAARTED criteria classified patients based on the disease volume; the high volume (Hv) was defined by the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis, while low volume (Lv) included patients that did not meet the above criteria. The LATITUDE classification included only patient with high-risk (Hr) disease based on the presence of at least two criteria among presence of visceral metastases, number of bone lesions ≥ 3 or Gleason score ≥ 8. For the purpose of this analysis, patients that did not fulfill the criteria for Hr were defined as low risk (Lr).

Patients were considered to have pain if this was reported within the patient's file or in case of a chronic analgesic therapy was found among the concomitant medications. The periodical assessment of pain during clinical monitoring visits was performed at the discretion of clinicians and according to the policy of each individual Institution. The primary endpoint of the present analysis was to assess the independent prognostic role of pain for OS. The study was approved by the Ethical Committee of the Azienda Ospedaliera Universitaria Integrata of Verona and all alive patients signed the informed consent.

Statistics

Descriptive statistics were used to characterize patients at baseline, defined as the date of ADT beginning. The OS was evaluated from the beginning of ADT to death or last follow-up, whichever occurred first. Disease progression was defined by at least one among clinical deterioration, biochemical, or radiological progression. All survivals were estimated by the Kaplan–Meier method, and compared across groups using the log-rank test. Cox proportional hazard models, stratified according to the baseline characteristics, were used to estimate hazard ratios for OS in univariate- and multivariable-adjusted analysis, using a stepwise selection approach with type I error of 0.05 for model entry and 0.10 for elimination. All the variables were significant if $p < 0.05$. The PASW software (Predictive Analytics SoftWare; v 25; IBM SPSS) was used for the analysis.

Results

Patients

Data ~373 de novo metastatic PC patients have been collected; the median age at the diagnosis was 69.6 years (IQR 63.6–75.8). Patients were classified as Lv and Hv of disease based on CHAARTED criteria in 30.1% and 60.9% of cases, respectively, and as Lr and Hr of disease as per

Table 1 Baseline characteristics of the patients.

Characteristics	Patients *N* (%)	No pain *N* (%)	Pain *N* (%)	Chi^2 *p*-value
Median age (years)	69.6	69.2	70.7	0.10[a]
Median PSA (ng/dl)	58.0	38.5	132.0	0.001[a]
Gleason score ≥ 8 (%)	245 (79.5)	166 (76.9)	79 (85.9)	0.073
Hb < LLN	127 (57.2)	62 (28.8)	65 (51.2)	0.049
Site of metastases (%)				
Bone	311 (85.2)	191 (80.3)	120 (94.5)	<0.001
Pelvis	265 (72.6)	149 (62.6)	116 (91.3)	<0.001
Column	199 (54.5)	105 (44.1)	94 (74.0)	<0.001
Ribs	84 (23.0)	35 (14.7)	49 (38.6)	<0.001
Legs/arms	86 (23.6)	43 (18.1)	43 (33.9)	0.001
>3 lesions	238 (65.2)	130 (54.6)	108 (85.0)	<0.001
Lymph-nodes	163 (44.7)	92 (38.7)	71 (55.9)	0.002
Visceral	56 (15.3)	32 (13.4)	24 (18.9)	0.17
CHAARTED classifications				<0.001
High volume	223 (61.1)	124 (52.1)	99 (78.0)	
Low volume	142 (38.9)	114 (47.9)	28 (22.0)	
LATITUDE classifications				0.005
High risk	196 (53.7)	115 (48.3)	81 (63.8)	
Low risk	169 (46.3)	123 (51.7)	46 (36.2)	
Docetaxel for CSPC	103 (28.2)	69 (29.0)	34 (26.8)	0.65

dl deciliter, *N* number, *ng* nanograms, *PSA* prostate-specific antigen.

[a]*t*-Test.

LATITUDE criteria in 46.4% and 53.6% of cases. All patients received ADT; early docetaxel was administered in 28.2% of cases. Other baseline characteristics of the included patients are reported in the Table 1.

Data about pain were available for 365 cases and pain was present in 34.8% of patients (Supplementary Fig. 1). Pain was mainly associated with high value of prostate-specific antigen (PSA), greater bone extension of disease in any site, lymph node involvement, but not with visceral metastases. Patients with pain have in most of the cases Hv or Hr of disease based on CHAARTED and LATITUDE classification (Table 1).

Effect of pain on OS

After a median follow-up of 38.9 months 43.7% of patients died, the median OS in the whole cohort was 45.2 months (95% CI, 39.2–51.6). Based on CHAARTED classification, the median OS was 62.5 and 35.7 months in patients with Lv and Hv, respectively ($p < 0.001$). When the LATITUDE classification was used the median OS was 58.2 and 41.9 months for Lr and Hr, respectively ($p = 0.005$). These differences remained significant when adjusted for the use of docetaxel in both classifications ($p < 0.01$).

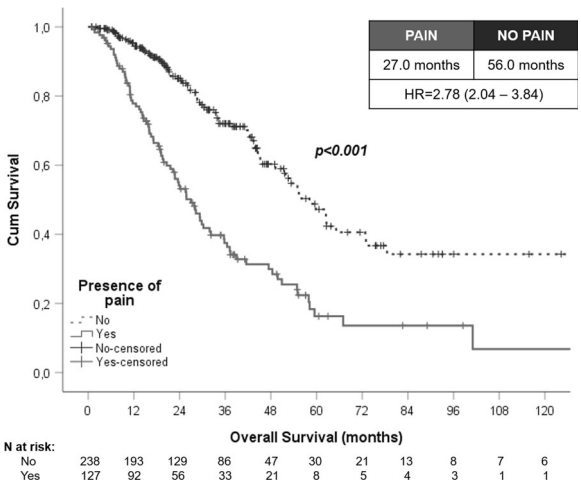

Fig. 1 Overall survival by the presence of pain (red) or not (blue). HR hazard ratio, N number.

In the overall population patients with pain had significant decreased OS compared to those who did not (27.0 vs. 56.0 months, $p < 0.001$ (Fig. 1). This data remained significant even if adjusted for the age, the Gleason's score, the early use of docetaxel, the value of hemoglobin at baseline, and CHAARTED or LATITUDE classification (Table 2).

Table 2 Multivariable analysis for OS using CHAARTED or LATITUDE prognostic classification.

Univariable analysis				Multivariable analysis			
Variable	HR	95% CI	*p*-Value	Variable	HR	95% CI	*p*-Value
Age (cont)	1.04	1.02–1.06	<0.001	Age (cont)	1.01	1.01–1.07	0.003
Gleason ≥ 8 (Y/N)	1.97	1.20–3.21	0.007	Gleason ≥ 8 (Y/N)	1.48	0.75–2.94	0.26
Pain (Y/N)	2.78	2.04–3.84	<0.001	Pain (Y/N)	2.01	1.26–3.19	0.003
Docetaxel (Y/N)	0.65	0.45–0.94	0.024	Docetaxel (Y/N)	0.65	0.35–1.20	0.17
CHAARTED (Hv/Lv)	2.27	1.61–3.23	<0.001	CHAARTED (Hv/Lv)	1.67	0.98–2.84	0.059
Hb < LLN (Y/N)	1.81	1.20–2.70	0.004	Hb < LLN (Y/N)	1.27	0.80–2.01	0.31
Age (cont)	1.04	1.02–1.06	<0.001	Age (cont)	1.05	1.03–1.08	<0.001
Pain (Y/N)	2.78	2.04–3.84	<0.001	Pain (Y/N)	2.34	1.55–3.53	<0.001
Docetaxel (Y/N)	0.65	0.45–0.94	0.024	Docetaxel (N/Y)	0.75	0.44–1.31	0.32
LATITUDE (Hr/Lr)	1.56	1.13–2.12	0.006	LATITUDE (Hr/Lr)	1.25	0.82–1.90	0.29
Hb < LLN (Y/N)	1.81	1.20–2.70	0.004	Hb<LLN (Y/N)	1.52	1.01–2.31	0.045

CI confidence interval, *cont* continuous, *HR* hazard ratio, *Hr* high risk, *HV* high volume, *LLN* low limits of normal, *LR* low risk, *LV* low volume, *N* no, *Y* yes.

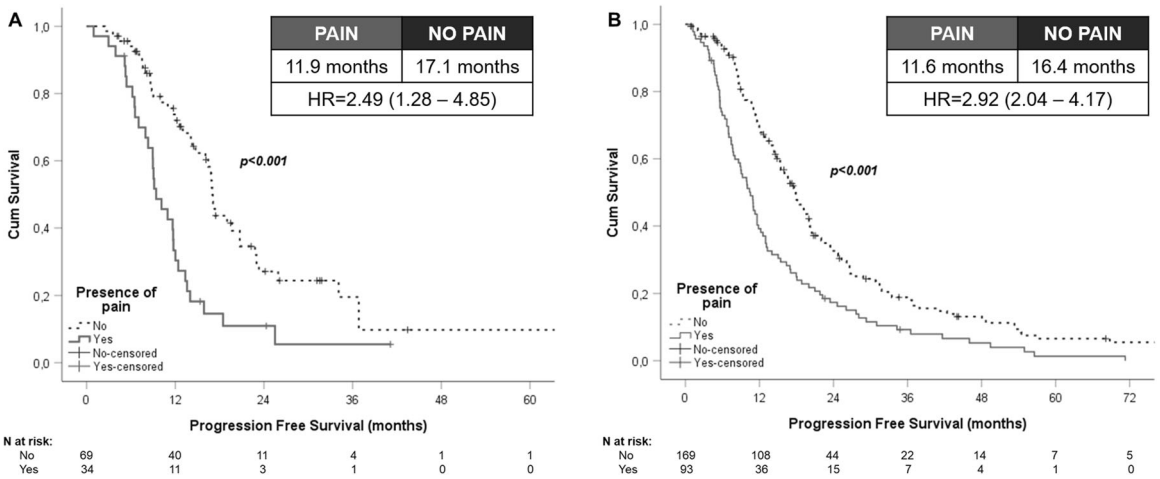

Fig. 2 Progression-free survival to first-line ADT by the presence of pain (red) or not (blue) in patients who received (**a**) or not docetaxel (**b**). HR hazard ratio, N number.

Effect of pain on PFS

Based on CHAARTED classification, the median PFS was 17.6 and 12.0 months in patients with Lv and Hv, respectively ($p < 0.001$). When the LATITUDE classification was used the median PFS was 16.9 and 11.8 months for Lr and Hr, respectively ($p = 0.002$). These differences remained significant when adjusted for the use of early docetaxel in both classifications ($p < 0.01$).

In the overall population patients with pain had significant decreased PFS compared to those who did not (10.1 vs. 17.4 months, $p < 0.001$). This difference remained significant among the patients who received early docetaxel (17.1 vs. 11.9; $p = 0.020$) and those who did not (16.4 vs. 11.6; $p = 0.022$; Fig. 2). Moreover, this data remained significant even if adjusted for CHAARTED or LATITUDE classification ($p < 0.001$).

Discussion

Bone represents the most frequent site of metastasis of PC, usually associated with debilitating pain and functional limitation. Cancer-related pain has been assumed to be an important prognostic factor of adverse clinical outcome in men with CRPC, regardless of treatment as summarized in Table 3 [11]. An important analysis in a wide variety of cancer types demonstrated the prognostic value of patient-reported outcomes (PROs) assessed at baseline in cancer clinical trials [12]. Indeed, debilitating bone pain at baseline

Table 3 Literature evidence about the prognostic role of pain at baseline in prostate cancer.

Study [ref]	Type of PC	Cutoff for pain	Effect on OS HR (95% CIs)
TAX327 [13]	mCRPC	<2 vs. ≥2	1.72 (1.50–1.98)
COU-AA-302 [17]	mCRPC	<2 vs. ≥2	1.31 (1.08–1.59)
COU-AA-301 [17]	mCRPC	<0.5 vs. ≥0.5	0.54 (0.43–0.70)
PREVAIL [15]	mCRPC	<2 vs. ≥2	0.77 (0.64–0.92)
TROPIC [16]	mCRPC	Yes vs. no	1.23 (0.80–1.67)
FIRSTANA [18]	mCRPC	Pain-p vs. radio-p vs. PSA-p	18.5 vs. 30.6 vs. 27.2 months

CIs confidence intervals, *HR* hazard ratio, *mCRPC* metastatic castration-resistant PC, *OS* overall survival; *pain-p* pain progression, *PC* prostate cancer, *radio-p* radiographic progression, *PSA-p* PSA progression, *ref* reference.

was significantly associated with worse OS (HR 1.48; 95% CI, 1.23–1.79) in a retrospective analysis from the TAX327 trial in mCRPC men treated with docetaxel [13]. Analogously, a post hoc analysis of the COU-AA-302 study of abiraterone/prednisone compared to placebo/prednisone in chemotherapy-naive mCRPC patients identified tumor-associated pain as a variable that independently impacted OS. It is important to keep in mind that this trial enrolled asymptomatic patients—as assessed by the Brief Pain Inventory-Short Form (BPI-SF) score (0–1), or, at least, mildly symptomatic (BPI-SF score 2–3) mCRPC men. A significant association between the presence of pain (BPI-SF score 2–3), PSA levels ≥ 80 ng/ml at the start of treatment, and a GS ≥ 8 at primary diagnosis with shorter OS, rPFS, and time to chemotherapy and opiate use was observed compared to asymptomatic patients with PSA levels < 80 ng/ml at the start of treatment and GS < 8. Of note, the superiority of abiraterone in prolonging OS was confirmed in both patient groups, regardless of pain [14]. Cancer-related pain (0–1 vs. ≥2 assessed with a linear scale) was found as a strong independent prognostic variable for OS (together with other ten prognostic factors) also in chemotherapy-naive mCRPC men treated with enzalutamide within the PREVAIL trial (enzalutamide vs. placebo) database [15]. The prognostic role of debilitating pain could retain its value also in mCRPC patients who received second-line chemotherapy (cabazitaxel) after progression to first-line docetaxel. An analysis of data from the TROPIC trial (cabazitaxel/prednisone vs. mitoxantrone/prednisone) identified a prognostic model for OS that included (besides ECOG-PS, time since last docetaxel use, measurable disease, presence of visceral disease, duration of hormonal use, hemoglobin, PSA, and alkaline phosphatase) baseline pain defined by a mean pain intensity score of two or greater and mean analgesic score of ten or greater [16].

The key role of cancer-related pain in monitoring and guiding diagnostic, and treatment decisions comes also from the relationship demonstrated between changes in PROs during an active treatment and clinical outcomes (worsening symptom reports were more likely associated with shortened time to progression or death), as assessed with abiraterone in a post hoc analysis of the COU-AA-301 and COU-AA-302 datasets [17]. Likewise, pain progression (defined as mean present pain intensity ≥ 2 and/or mean analgesic score ≥ 10 over the 7 days prior to randomization) at initiation of chemotherapy has been associated with a worse OS in a post hoc analysis of the FIRSTANA trial (comparing docetaxel to cabazitaxel in chemo-naive mCRPC patients) [18].

Contrary to the setting of mCRPC patients, to date there are only limited data regarding the prognostic role of pain in men with mCSPC, moreover long-standing and therefore difficult to translate into daily clinical reality. Glass et al. used the large prospective clinical SWOG 8894 study comparing orchiectomy ± flutamide in mCSPC patients to identify clinical features with a prognostic relevance. He found bone pain, together with PSA value (<65 vs. ≥65 ng/ml), Gleason score (<8 vs. ≥8), patients' PS (0 vs. 1–3), bone metastases (appendicular vs. axial involvement), and previous radical prostatectomy as independent prognostic factors at multivariate analysis (p 0.05). Based on the four risk factors with a major impact on outcomes (bone metastases, PS, PSA value, and Gleason score), three different prognostic groups were identified. Patients at good prognosis (without appendicular disease and without visceral involvement or with appendicular and/or visceral metastases, but with PS of 0 and Gleason < 8), patients at intermediate prognosis (with appendicular and/or visceral metastases and ECOG-PS of 0 with Gleason ≥ 8, or with ECOG-PS ≥ 1 and PSA < 65 ng/ml), and poor prognosis patients (with appendicular bone and/or visceral metastases and PS-ECOG ≥ 1 and PSA ≥ 65 ng/ml), with a 5-year survival rates of 42%, 21%, and 9%, respectively [19]. A subsequent validation of Glass's prognostic system was then performed by Gravis et al. in a more updated patient cohort (using data of the phase 3 GETUG- AFU15 trial) to overcome the bias of the obsolete SWOG 8894 patients population treated >20 years ago. Gravis confirmed the prognostic value of Glass model, identifying a significant OS difference between good (mOS 69.1 months, 95% CI 60.9–NR) and intermediate (mOS 46.5 months, 95% CI 37.7–NR) prognostic groups, and between good and poor

(mOS 36.6 months, 95% CI 28.5–58.9) prognostic groups. No significant difference emerged between intermediate and poor prognosis patients, but the small sample size of the poor prognosis group (only 83 patients) could have affected these results [20]. Of note, bone pain was not included in these two prognostic models. To further confirm the absence of a unique validated prognostic classification, the two pivotal studies of mCSPC patients—the CHAARTED and LATITUDE—used diverse criteria to stratified patients, both of which based mainly on the disease volume. Hence, the need of identifying clinical and biological features with a clear role in defining the patient's prognosis.

Three more randomized phase III trials reported new evidence in mCSPC. The ARCHES and ENZAMET trials supported the use of enzalutamide, while the TITAN trial supported the use of apalutamide over ADT alone in these patients [8–10]. Only the TITAN trial reported the presence of pain at baseline in ~60% of patients and, this study as well the ARCHES one both failed to show an improvement in the secondary endpoint of time to pain deterioration. The Cancer-related pain is one of the most common and disabling morbidities experienced by metastatic PC men, and, beyond all, there is a strong clinical perception that the presence of pain is linked with a worse patient's prognosis. Our analysis is therefore one of the first to assess the prognostic role of pain in a cohort of >350 mCSPC patients, and to evaluate its correspondence with the CHAARTED and LATITUDE classifications. We found that pain was present in about one third of the overall cohort of patients; it was mainly associated with high value of PSA, metastatic bone extension regardless of the site, lymph node involvement, but not with visceral metastases. mCSPC with pain had in most of the cases Hv or Hr disease, and significant shorter OS (27.0 vs. 58.2 months, $p < 0.001$) and PFS compared to those patients without pain. The negative impact of pain on survival and PFS remained significant even if adjusted for CHAARTED or LATITUDE classification, and the use of early docetaxel. The magnitude of the difference in survival in the presence of pain (more than halved), and how the OS curves separated (see Fig. 1), are a clear sign of the negative impact on patients' prognosis of cancer-related pain. Furthermore, the persistent negative correlation between pain and clinical outcomes, regardless of the early docetaxel therapy (the only possible option in Italy to be associated with ADT in the castration-sensitive setting) reflects the strong independent role of pain on the prognosis of these patients, and suggests its evaluation in the clinical management and treatment selection process.

Our study is not devoid of limitations. Given the retrospective design, all analyses are subject to selection biases and imbalances in unquantified variables. Moreover, the non-utilization of the BPI-SF score (we considered the presence of pain if reported in patient's file, or in case of a reported chronic analgesic therapy) could affect the results. Further research is required to establish whether symptomatic mCSPC patients benefit from a particular kind of systemic treatment.

In conclusion, this analysis supports the poor prognostic role of cancer-related pain in the setting of mCSPC patients. External prospective validation in CSPC patient cohorts is required to establish if cancer-related pain can help in guiding the treatment decision process.

Compliance with ethical standards

Conflict of interest R.I.: advisory board member for Pfizer, Janssen, Sanofi, IPSEN, MSD, and Novartis. O.C.: advisory board member/speaker for Pfizer, Janssen, IPSEN, and Astellas. U.D.G.: advisory board or consultant fees from Merck Sharp & Dohme, Bristol Myers Squibb, Janssen, Astellas, Sanofi, Bayer, Pfizer, Ipsen, Novartis, Pharmamar and Institutional research grant from Astrazeneca, Sanofi, and Roche. C.B.: advisory board member for Janssen. G.T.: advisory board member for BMS and Novartis. Chiara Ciccarese (occasional consultant of IPSEN and Merck), M.T., C.M., D.B., F.P., F.M., Chiara Casadei, and M.M. declare that they have no conflict of interest.

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