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Clinical Characterization of Patients Diagnosed with Prostate Cancer and Undergoing Conservative Management: A PIONEER Analysis Based on Big Data

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Abstract

Background: Conservative management is an option for prostate cancer (PCa) patients either with the objective of delaying or even avoiding curative therapy, or to wait until palliative treatment is needed. PIONEER, funded by the European Commission Innovative Medicines Initiative, aims at improving PCa care across Europe through the application of big data analytics.
Objective: To describe the clinical characteristics and long-term outcomes of PCa patients on conservative management by using an international large network of real-world data.
Design, setting, and participants: From an initial cohort of >100 000 000 adult individuals included in eight databases evaluated during a virtual study-a-thon hosted by PIONEER, we identified newly diagnosed PCa cases (n = 527 311). Among those, we selected patients who did not receive curative or palliative treatment within 6 mo from diagnosis (n = 123 146).
Outcome measurements and statistical analysis: Patient and disease characteristics were reported. The number of patients who experienced the main study outcomes was quantified for each stratum and the overall cohort. Kaplan-Meier analyses were used to estimate the distribution of time to event data.
Results and limitations: The most common comorbidities were hypertension (35–73%), obesity (9.2–54%), and type 2 diabetes (11–28%). The rate of PCa-related symptomatic progression ranged between 2.6% and 6.2%. Hospitalization (12–25%) and emergency department visits (10–14%) were common events during the 1st year of follow-up. The probability of being free from both palliative and curative treatments decreased during follow-up. Limitations include a lack of information on patients and disease characteristics and on treatment intent.
Conclusions: Our results allow us to better understand the current landscape of patients with PCa managed with conservative treatment. PIONEER offers a unique opportunity to characterize the baseline features and outcomes of PCa patients managed conservatively using real-world data.
Patient summary: Up to 25% of men with prostate cancer (PCa) managed conservatively experienced hospitalization and emergency department visits within the 1st year after diagnosis; 6% experienced PCa-related symptoms. The probability of receiving therapies for PCa decreased according to time elapsed after the diagnosis.

1. Introduction

Prostate cancer (PCa) is the second leading cause of male cancer death worldwide [1]. Despite high incidence rates, 5-yr disease-specific survival improved significantly from 73% to 82% over the past decade, partly due to widespread availability of prostate-specific antigen (PSA) testing [2]. Although curative-intent therapies are available for men with nonmetastatic disease and life expectancy of ≥10 yr, conservative approaches have been introduced >20 yr ago [3] and are now popular thanks to the availability of long-term data and recommendations by international guidelines [4,5]. The definition of "conservative management" includes both active surveillance (AS) and watchful waiting (WW), which are options recommended by the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines for selected men with PCa [4,5]. Despite this, patients undergoing conservative management have poorly been characterized so far using real-world data [6–8]. This is key since guidelines recommendations, which are based on level 1 evidence coming from randomized controlled trials (RCTs) [4], could not reflect the real-life scenario. Therefore, these might be less generalizable at a population level, where <40% of cancer patients would be eligible in RCTs [9]. For example, older patients or the ones with serious comorbidities are typically under-represented in prospective trials. Moreover, RCTs typically include men managed at high-volume centers, which might not reflect what is happening in the daily clinical practice [10–13]. Although real-world data typically do not provide information on treatment intent or detailed disease features, the availability of these data sources describing the characteristics and outcomes of PCa patients managed conservatively represents a unique opportunity to fill knowledge gaps and complement the evidence coming from randomized studies.

PIONEER is a European network of excellence for big data in PCa that is part of the Innovative Medicine Initiative's (IMI's) "Big Data for Better Outcomes" program [14]. The overall aim of PIONEER is to improve PCa care across Europe

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through the application of big data analytics. Through a broad stakeholder prioritization exercise including healthcare professionals, pharmaceutical companies, and PCa patients, the PIONEER consortium identified this PCa knowledge gap as a priority for all stakeholders. The aim of this study is to describe the clinical characteristics and long-term outcomes of PCa patients on conservative management by using an international large network of real-world data.

2. Patients and methods

2.1. Study design, setting, and data sources

A retrospective cohort study based on eight electronic healthcare data sources across Europe and the USA, including electronic health records (EHRs), population-based registries, and insurance claims data, was conducted. Full details about included data sources are provided in the Supplementary material. This study was initiated during a dedicated PIONEER study-a-thon (March 8–12, 2021) in collaboration with the IMI European Health Data & Evidence Network (EHDEN) and the global Observational Health Data Sciences and Informatics (OHDSI) community using the OHDSI open science approach [15]. The aims of the study-a-thon were to design a study protocol to characterize PCa patients undergoing conservative management and to evaluate the preliminary results. Clinicians, patients, data scientists, and researchers converted data to the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM), ensuring consistent representation of clinical terms across multiple coding systems and allowing for conducting analyses through a federated model. The study group regularly met every week after the study-a-thon to finalize the study protocol, which was then released on the May 28, 2021 [16]. Prior to the analysis, all data partners obtained institutional review board or equivalent governance approval. Reproducibility between data partners was ensured by the development of a core analytical package used uniformly across datasets. Only aggregated, population-level (ie, not patient-level) results from each data source were shared publicly, and all data partners consented to the external sharing of the result set on data.ohdsi.org.

2.2. Data sources

We performed the analyses across a network of observational EHRs (MAITT [University of Tartu and STACC], Optum deidentified Electronic Health Record Dataset, and Tufts Medical Center [TMC]) and population-based registries based on insurance claims data (Columbia University Irving Medical Center [CUIMC], IQVIA AmbulatoryEMR, IQVIA OncoEMR, IQVIA PharMetricsPlus, and MarketScan), which were standardized into the OMOP CDM, version 5.3.1, and included records for >100 000 000 individuals. Among those, we identified newly diagnosed PCa cases (n = 527 311). The complete specification for the OMOP CDM is available at https://ohdsi.github.io/CommonDataModel/cdm531.html. Dataset characteristics are reported in Supplementary Table 1. Each data source custodian used deidentified data, and thus the analysis was determined not to be research on humans and informed consent was not deemed necessary at any site.

2.3. Study population and follow-up

During the PIONEER study-a-thon, three cohorts of patients were built. More detailed cohort definitions and inclusion criteria are available in the Supplementary material and the published protocol. In cohort 1, adult men with newly diagnosed PCa were identified based on the first diagnosis of PCa in their record (index date). Men had to have undergone a prostate biopsy or a PSA test with a value of ≥50 ng/ml within 30 d of the diagnosis. Men with a prior PCa diagnosis, a prostate dysplasia diagnosis, or prior exposure to PCa-specific drugs (androgen deprivation therapy [ADT] and androgen agonist/inhibitor) within 365 d prior to the index date were excluded. Men from cohort 1 who received curative or palliative treatment for their PCa within 6 mo from the initial diagnosis were included in cohort 2 "immediate management". Those who did not receive the treatment were included in cohort 3 "conservative management." The index date for cohorts 2 and 3 was set at 6 mo after diagnosis. All cohorts were generated with a requirement of at least a 365 d of lookback period prior to the PCa initial diagnosis date. Cohorts were followed from their specific cohort index date to the earliest of death, diagnosis with another malignancy (except for nonmelanoma skin cancer), or end of observation.

2.4. Covariates and outcomes of interest

Information on patient demographics and disease characteristics was collected from 1 to 365 d prior to the index date. The data collected at the index date included age, year, and country of diagnosis. The main outcomes of our study were as follows: (1) "symptomatic progression," which included PCa-specific events that were defined during the PIONEER study-a-thon and included skeletal-related event, urinary retention, hydronephrosis or acute kidney failure, bowel obstruction, or fatigue (European Organisation for Research and Treatment of Cancer score >2); and (2) initiation of "palliative treatments" such as hormonal manipulation, systemic therapy, surgical treatments, and palliative radiotherapy following symptoms. We also assessed the distribution of emergency department (ED) visits and hospitalizations as secondary outcomes. Patients are followed up from the index date until death, diagnosis with another malignancy (except for nonmelanoma skin cancer), or end of observation period.

2.5. Statistical analysis

Baseline patient demographics and disease characteristics at the time of diagnosis were reported using medians and proportions for continuous variables and categorical variables, respectively. The number of patients who experienced the main study outcomes was quantified for each stratum and the overall cohort. Kaplan-Meier analyses were used to estimate the distribution of time to event data, namely, overall survival, time to treatment initiation, time to symptomatic progression, hospitalization, and ED visit from the index date.

2.6. Stratifications

Men within cohort 3 were stratified based on preindex characteristics determined a priori during the PIONEER study-a-thon based on their clinical relevance and detailed in the study protocol.

3. Results

3.1. Baseline characteristics

Overall, 527 311 men with PCa (cohort 1) across eight datasets including records from >100 000,000 adult individuals were identified. Among these, 123 146 were managed with conservative treatment and included in cohort 3. Table 1 summarizes clinical characteristics of men in cohort 3. The median age at diagnosis ranged from 63 to 73 yr across the eight datasets evaluated. Comorbidity prevalence was heterogeneous among men included in cohort 3. The most common comorbidities were hypertension (35–73%), obe-

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Table 1 – Characteristics and baseline comorbidities (1 yr prior to index) of prostate cancer patients managed conservatively (conservative management) after diagnosis in a network of databases across the USA and Europe

	CUIMC (*n* = 1743)	IQVIA AmbulatoryEMR (*n* = 17 834)	IQVIA OncoEMR (*n* = 207)	MAITT (*n* = 163)	Marketscan (*n* = 40 049)	Optum (*n* = 27 525)	IQVIA PharMetricsPlus (*n* = 35 482)	TMC (*n* = 143)
Year of diagnosis[a]	2013 (2001–2018)	2017 (2014–2019)	2018 (2016–2019)	2017 (2015–2018)	2012 (2009–2016)	2017 (2013–2019)	2018 (2016–2019)	2016 (2015–2019)
Age at diagnosis	68 (62–74)	68 (63–74)	73 (65–79)	70 (65–76)	63 (59–72)	69 (63–74)	63 (58–67)	64 (59–72)
Comorbidities								
Total CVD events	56 (3.2)	NR	NR	11 (6.7)	1028 (2.6)	934 (3.4)	607 (1.7)	NR
Type 2 diabetes	272 (16)	1925 (11)	36 (18)	29 (18)	8339 (21)	7651 (28)	6150 (17)	24 (20)
Hypertension	883 (51)	6254 (35)	97 (49)	119 (73)	23 028 (57)	19 223 (70)	21 387 (60)	89 (73)
Obesity	311 (18)	6404 (36)	33 (17)	15 (9.2)	4363 (11)	5814 (21)	7729 (22)	66 (54)
Anxiety	49 (2.8)	265 (1.5)	11 (5.5)	13 (8)	1492 (3.7)	1865 (6.8)	2753 (7.8)	14 (11)
Respiratory disease[b]	227 (13)	1376 (7.7)	28 (14)	24 (15)	6598 (16)	5360 (19)	4474 (13)	21 (17)
Other malignancies	231 (13)	532 (3)	39 (20)	9 (5.5)	5077 (13)	3312 (12)	1985 (5.6)	16 (13)
Stroke	16 (0.9)	NR	NR	NR	311 (0.8)	269 (1)	168 (0.5)	NR
VTE	22 (1.3)	139 (0.8)	5 (2.5)	NR	595 (1.5)	548 (2)	510 (1.4)	NR
Family history[c]	56 (3.2)	1767 (9.9)	9 (4.5)	NR	2286 (5.7)	2342 (8.5)	4138 (12)	NR
PSA at diagnosis	4.2 (0.6–8)	NR	7.6 (0.7–148.9)	6.0 (1.6–9.4)	NR	NR	NR	4.5 (1.6–8.9)
cT stage								
cT1	NR	NR	NR	25 (15)	NR	NR	NR	NR
cT2	NR	NR	NR	15 (9.2)	NR	NR	NR	NR
cT3–4	NR	NR	NR	6 (3.7)	NR	NR	NR	NR
Grade group (Gleason score)								
GG 1	NR	NR	NR	11 (6.7)	NR	NR	NR	NR
GG 2	NR	NR	NR	5 (3.1)	NR	NR	NR	NR
GG 3	NR	NR	NR	NR	NR	NR	NR	NR
GG 4	NR	NR	NR	NR	NR	NR	NR	NR
GG 5	NR	NR	NR	NR	NR	NR	NR	NR
EAU risk category								
Low risk	NR	NR	NR	NR	NR	NR	NR	NR
Intermediate risk	NR	NR	NR	11 (6.7)	NR	NR	NR	NR
High risk	NR	NR	NR	20 (12)	NR	NR	NR	NR

CUIMC = Columbia University Irving Medical Center; CVD = cardiovascular disease; EAU = European Association of Urology; GG = grade group; MAITT = University of Tartu and STACC; NR = data not available or not reported by the data partner; Optum = Optum Clinformatics; PSA = prostate-specific antigen; TMC = Tufts Medical Center; VTE = venous thromboembolism.
Data are reported as median (interquartile range) and *n* (%).
[a] Median (range).
[b] Prevalent asthma or chronic obstructive pulmonary disease.
[c] Family history of prostate cancer or history of selected germline mutations.

sity (9.2–54%), and type 2 diabetes (11–28%). Overall, hypertension was the most common comorbidity in all age groups (Supplementary Table 2). Moreover, the prevalence of all comorbidities increased with age, except anxiety and obesity, which instead had a negative trend. PSA values were reported by four datasets (CUIMC, IQVIA OncoEMR, MAITT, and TMC), and the median PSA varied between 3.9 and 7.6 ng/ml across datasets. Of men, <12% had a positive family history for PCa. Information on disease characteristics were available only for those in the MAITT dataset, where the rates of cT2, grade group 1, and high-risk PCa, according to the EAU risk classification, were 9%, 7%, and 12%, respectively.

3.2. Outcomes

Table 2 depicts the number of patients who experienced symptomatic progression, ED visits, and hospitalization, and received palliative and curative-intent treatments. Table 3 describes the number of patients who did not experience the event at different time points for all datasets. Figure 1 shows the free-to-outcome probability. The free-to-

Table 2 – Number of patients with prostate cancer who were managed with conservative management experiencing outcomes during the follow-up

	Curative treatment	Palliative treatment	Symptomatic progression	ED visit	Hospitalization
CUIMC	205	151	275	424	487
IQVIA AmbulatoryEMR	370	1341	1366	NR	47
IQVIA OncoEMR	NR	34	16	NR	NR
MAITT	18	40	11	NR	74
MarketScan	9822	5322	5642	13 305	11 377
Optum	6701	4401	3834	7090	8507
IQVIA PharMetricsPlus	8808	3819	3902	8303	8728
TMC	12	5	25	32	37

CUIMC = Columbia University Irving Medical Center; ED = emergency department; MAITT = University of Tartu and STACC; NR = data not available or not reported by the data partner; Optum = Optum Clinformatics; TMC = Tufts Medical Center.

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Table 3 – Number of patients followed without an event at different time points

	Index	Year 1	Year 5	Year 10	Year 15	Year 20
Treatment Initiation						
CUIMC	1743 (0)	1271 (170)	576 (273)	232 (297)	102 (310)	48 (310)
IQVIA AmbulatoryEMR	17 834 (0)	12 935 (938)	2652 (1550)	133 (1637)	1 (1640)	0 (1640)
IQVIA OncoEMR	207 (0)	98 (26)	13 (33)	2 (33)	1 (34)	0 (34)
MAITT	163 (0)	100 (31)	19 (54)	1 (54)	0 (54)	0 (54)
MarketScan	40 049 (0)	20 289 (8015)	3266 (10 870)	276 (11 079)	8 (11 091)	1 (11 092)
Optum	27 525 (0)	14 682 (5289)	2466 (7437)	218 (7599)	1 (7605)	0 (7605)
IQVIA PharMetricsPlus	35 482 (0)	17 866 (6776)	1056 (9258)	1 (9296)	0 (9296)	0 (9296)
TMC	143 (0)	108 (9)	46 (15)	2 (15)	1 (15)	0 (15)
Hospitalization						
CUIMC	1743 (1)	1280 (186)	490 (389)	169 (454)	69 (478)	29 (485)
IQVIA AmbulatoryEMR	17 834 (0)	13 691 (27)	3007 (44)	166 (47)	1 (47)	0 (47)
MAITT	163 (0)	97 (37)	14 (74)	1 (74)	0 (74)	0 (74)
MarketScan	40 049 (0)	21 464 (6610)	3100 (10 798)	208 (11 344)	8 (11 376)	1 (11 377)
Optum	27 525 (17)	15 320 (4725)	2264 (8041)	168 (8494)	1 (8507)	0 (8507)
IQVIA PharMetricsPlus	35 482 (0)	18 632 (5653)	972 (8667)	1 (8728)	0 (8728)	0 (8728)
TMC	143 (0)	103 (15)	33 (36)	2 (37)	1 (37)	0 (37)
Symptomatic progression						
CUIMC	1743 (0)	1380 (52)	604 (178)	223 (235)	93 (257)	36 (272)
IQVIA AmbulatoryEMR	17 834 (0)	13 319 (457)	2622 (1233)	122 (1363)	1 (1366)	0 (1366)
IQVIA OncoEMR	207 (0)	105 (12)	13 (15)	2 (16)	1 (16)	0 (16)
MAITT	163 (0)	122 (4)	28 (11)	2 (11)	0 (11)	0 (11)
MarketScan	40 049 (0)	24 673 (2227)	4128 (5042)	282 (5604)	9 (5642)	1 (5642)
Optum	27 525 (7)	17 533 (1632)	3100 (3521)	233 (3827)	1 (3834)	0 (3834)
IQVIA PharMetricsPlus	35 482 (0)	21 348 (1955)	1329 (3859)	1 (3902)	0 (3902)	0 (3902)
TMC	143 (0)	110 (6)	37 (24)	2 (25)	1 (25)	0 (25)
ED visit						
CUIMC	1743 (1)	1281 (175)	493 (346)	169 (401)	63 (416)	21 (422)
MarketScan	40 049 (0)	21 113 (6888)	2498 (12 662)	128 (13 278)	4 (13 305)	1 (13 305)
Optum	27 525 (24)	15 982 (3618)	2423 (6703)	203 (7081)	1 (7090)	0 (7090)
IQVIA PharMetricsPlus	35 482 (0)	19 257 (4718)	946 (8232)	1 (8303)	0 (8303)	0 (8303)
TMC	143 (0)	105 (11)	37 (29)	2 (32)	1 (32)	0 (32)
Death						
CUIMC	1743 (0)	1423 (14)	685 (34)	279 (52)	131 (55)	61 (60)
MAITT	163 (0)	126 (2)	33 (7)	1 (7)	0 (7)	0 (7)
TMC	143 (0)	115 (3)	50 (7)	2 (7)	1 (8)	0 (8)

CUIMC = Columbia University Irving Medical Center; ED = emergency department; MAITT = University of Tartu and STACC; Optum = Optum Clinformatics; PSA = prostate-specific antigen; TMC = Tufts Medical Center.

curative and palliative treatment probabilities decreased during follow-up in all analyzed databases, with the highest rate of change during the first 2–4 yr (up to 38%) and 12–16 yr (up to 42%) for curative and palliative treatment, respectively. The decrease in the free-to-event probability was more consistent for the other outcomes.

The rate of PCa-related symptomatic progression ranged between 2.6% and 6.2% during the 1st year after diagnosis, 1.4% and 8.6% during the 2nd year, and 2.1% and 5.4% thereafter (Table 4). The rate of palliative treatment ranged between 4.1% and 12% during the 1st year of follow-up, 1.9% and 3.7% during the 2nd year, and 3.1% and 14% thereafter. The most common events were hospitalization and ED visit, with large differences between the year of follow-up and database. The percentage of patients hospitalized varied between 12% and 25% and between 12% and 25% during the 1st and the 2nd years of follow-up, respectively. The probability of ED visit ranged between 10% and 14% in the 1st year of follow-up and between 8.2% and 14% in the 2nd year of follow-up. The proportion of men who underwent curative treatment after the first 12 mo from diagnosis decreased during the follow-up in all datasets (from 1.4–19% to 0.3–4.5%).

Owing to the lack of information on disease characteristics in most of the available data sources, we had appropriate data to perform subgroup analyses only for patients stratified according to chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus (T2DM), obesity, and age. Using Kaplan-Meier analyses, PCa patients with COPD (Supplementary Fig. 1B) and T2DM (Supplementary Fig. 1C) had the highest probability of ED visit and hospitalization, whereas obese men had the highest probability of curative treatment and symptomatic progression in one dataset (CUIMC) and of being hospitalized in the MarketScan, Optum, and PharMetricsPlus datasets (Supplementary Fig. 1A). On the contrary, none of these comorbidities were associated with overall survival (Supplementary Fig. 2). Grouping patients by age, we observed that the oldest men had the worst outcomes (palliative treatment, ED visit, hospitalization, symptomatic progression, and overall survival) but the lowest probability of curative treatment (Supplementary Figs. 3 and 4).

4. Discussion

Using the largest available patient-level cohort of men with PCa undergoing conservative management, our study provides one of the first real-world evidence resources to improve our understanding of the current landscape of the disease in this setting. In addition, it represents the first major attempt for in-depth characterization of men with PCa undergoing conservative management at a large scale aimed at answering one of the PIONEER research questions

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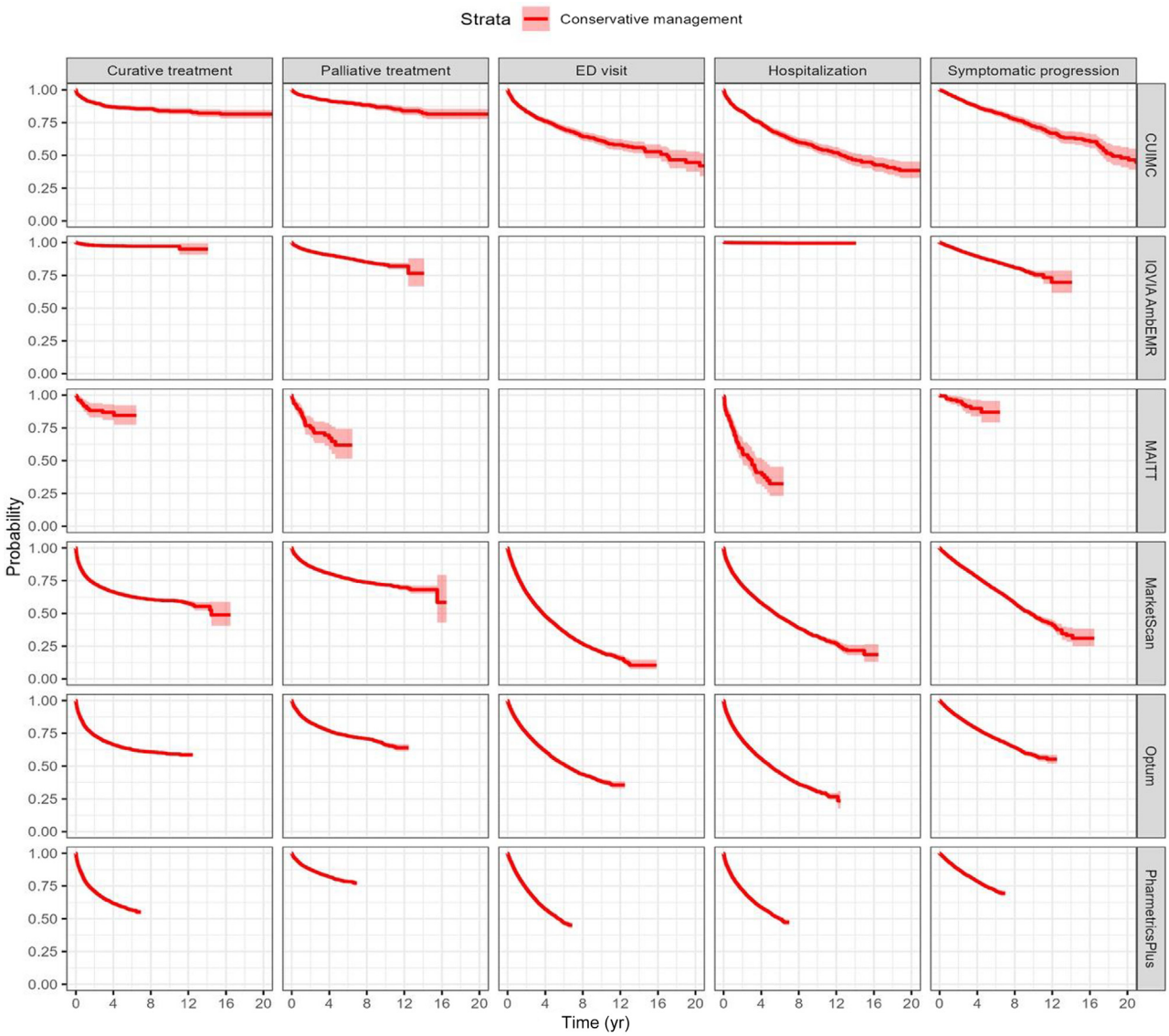

Fig. 1 – Outcomes (curative and palliative treatment initiation, emergency department visit, hospitalization, and symptomatic progression) in the conservative management cohort across the PIONEER network. Kaplan-Meier (KM) plots are presented only for databases with available information on conservative management cohort. KM plots are censored at 20 yr. CUIMC = Columbia University Irving Medical Center; ED = emergency department; MAITT = University of Tartu and STACC; Optum = Optum Clinformatics.

prioritized by healthcare professionals, pharmaceutical companies, and PCa patients.

Our findings are several-fold. First, we were able to characterize PCa patients undergoing conservative management, to describe the most common comorbidities and their outcomes at intermediate-term follow-up. Men managed with conservative treatment were in their late 60s or early 70s, and on average, had several relevant comorbidities. This observation might be related to disease management according to the most recent EAU and AUA guidelines [4,5], where conservative management with WW is recommended for men with PCa who have life expectancy shorter than 10 and 5 yr, respectively. Previous studies showed minimal benefit from local treatment in PCa patients with limited life expectancy. Albertsen et al. [17] analyzed 65-yr-old patients with PCa managed with conservative treatment and showed that those with a Charlson comorbidity index score of >2 were most likely to die of other causes than PCa after 10 yr of follow-up. On the contrary, the authors of the SPCG-4 trial focusing on the age at diagnosis reported an unclear advantage of surgery over conservative management in cancer-specific and overall mortality in PCa patients aged 65 yr or older in the pre-PSA era [18]. Their results were also confirmed by Lu-Yao et al. [8] using a population of 31 137 men receiving conservative management for clinically localized (T1 or T2) PCa diagnosed in the PSA-testing era.

Second, our data indicate a high level of heterogeneity in comorbidity prevalence among these patients. Such heterogeneity may partially be explained by different geographic regions data were obtained from and the different distribution of these comorbidities in each region/geography, difference in practice patterns across different regions, and the heterogeneity in the capture of comorbidities in each data-

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Table 4 – Frequency of outcomes during year 1 (0–365 d after index), year 2 (366–730 d after index), and year 3+ (731+ d after index) of follow-up in the conservative management cohort across the PIONEER network

	CUIMC (*N* = 1743)	IQVIA AmbulatoryEMR (*N* = 17 834)	MAITT (*N* = 163)	MarketScan (*N* = 40 049)	Optum (*N* = 27 525)	IQVIA PharMetricsPlus (*N* = 35 482)
0–365 d after index						
Curative treatment (%)	7.2	1.4	7.4	19	18	18
Symptomatic progression (%)	3.4	2.6	NR	6	6.3	5.7
ED visit (%)	11	NR	NR	18	14	14
Hospitalization (%)	12	0.15	25	18	18	16
Palliative treatment (%)	4.1	4.1	12	8.9	11	7.4
366–730 d after index						
Curative treatment (%)	2.2	0.41	NR	4.1	4.5	4.4
Symptomatic progression (%)	1.4	1.6	8.6	3	3.6	2.3
ED visit (%)	8.2	NR	NR	14	9.7	8.7
Hospitalization (%)	7.2	0.1	17	8.8	9.8	7.1
Palliative treatment (%)	2.9	1.9	NR	3.7	3.6	3
731+ d after index						
Curative treatment (%)	4.5	0.26	NR	4.5	4.4	3.1
Symptomatic progression (%)	5.4	2	4.9	4.4	4.6	2.1
ED visit (%)	22	NR	NR	23	16	9
Hospitalization (%)	24	0.1	17	17	17	7
Palliative treatment (%)	15	3.5	3.1	8.7	6.8	3.1

CUIMC = Columbia University Irving Medical Center; ED = emergency department; MAITT = University of Tartu and STACC; NR = data not available; Optum = Optum Clinformatics.

base. Differences in the intent of conservative management can also explain the heterogeneity observed in the distribution of comorbidities observed in our study. That being said, the most common comorbidities were hypertension, obesity, and T2DM, which are some of the most frequent pathologies in western elderly men [19–22].

Third, the risk of curative and palliative treatments varied substantially during follow-up and was higher during the first years after diagnosis. By contrast, the event-free rate for PCa-related symptoms and progression, ED visits, and hospitalization decreased consistently over the follow-up. This would provide important information for patient counseling to clinicians who are proposing conservative management as an alternative option to PCa patients. Moreover, our findings highlight that the probability of experiencing PCa-related symptomatic progression is still consistent >5 yr after diagnosis with consequent implications for tailoring follow-up protocols in this setting. Our findings also highlight differences after grouping by age. The frequency of curative and palliative treatment was, respectively, lowest and highest in the oldest patients. In this context, Lu-Yao et al. [8] showed how the risk of treatment varied according to patient age, with lower 15-yr risk of curative treatment for patients ≥75 yr old than for patients aged 65–74 yr. On the contrary, they reported the highest 15-yr risk of ADT in the oldest population.

Finally, we evaluated how long-term outcomes of PCa patients on conservative management vary, according to prespecified individual patients' characteristics. We found that the oldest patients had the highest risks of ED visit, hospitalization, and symptomatic progression, and the worst overall survival. Likewise, our data show that patients with COPD and T2DM had the highest risks of hospitalization and ED visit. It is likely that these results may be explained by the well-known association of these pathologies with the highest risk of complications [21,22]. Taken together, these observations might reflect the clinician choice to offer WW to old and comorbid patients, who therefore would be at a higher risk of symptomatic progression and would be considered for palliative approaches. By contrast, younger men without comorbidities would typically be included in AS programs. These individuals could be considered for curative-intent treatments at the time of disease progression.

Our findings demonstrate for the first time that PIONEER offers a unique opportunity to systematically assess the status of real-world evidence in PCa and that this large project can answer specific research questions prioritized by key stakeholders. Indeed, this represented the first attempt in using large-scale real-world data to gain insight into a clinically important question on the management of PCa. The study provided meaningful insights into the potential value and limitations of real-world data, the importance of an evidence quality framework to ensure generation of reliable and valid evidence that can inform clinical decision-making. The results of the study also highlight the need for an in-depth large-scale assessment of the natural history and treatment pathways of men with PCa. This ongoing effort will complement the findings from the current study, and provide further insights into the patterns of care for PCa across geography and the impact of different treatment strategies in patients' outcomes.

Despite several strengths, there are some limitations that need to be considered. This study has been performed using

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data recorded in a collection of EHRs, claims, and tumor registries. Lack of details for cancer attributes such as PSA levels, Gleason score, and clinical stage at the time of PCa diagnosis precluded us from further investigation of patients' characteristics and outcomes according to disease characteristics. Of note, longitudinal data on PSA level and other disease features are typically available only within EHR systems. Since most of the data in this study are coming from large administrative claims, we were unable to retrieve this information and stratify patients accordingly. Similarly, a lack of information on treatment intent and the difficulty in distinguishing WW from AS represent major limitations of the study. Indeed, due to the retrospective nature of our study design and the use of population-based data, treatment intent upon PCa diagnosis was not generally captured. As such, identification of patients who were initially treated with conservative management (cohort 3) was based on the lack of events (drugs, observations, or procedures indicative of immediate PCa treatment) following PCa diagnosis. Moreover, medical conditions may also be underestimated as these were based on the presence of condition codes, with the absence of such a record taken to indicate the absence of a disease. Finally, due to the nature of the real-world data, we could not describe the follow-up duration for patients without an event.

5. Conclusions

Our results allow us to better understand the current landscape of patients with PCa managed with conservative treatment. PIONEER offers a unique opportunity to characterize for the first time the baseline features and outcomes of PCa patients managed conservatively using real-world data.

Author contributions: Giorgio Gandaglia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing: In the interest of transparency and scientific reproducibility, all study materials including the computer-executable code (which is compatible with any data set in the OMOP common data model) have been made available. Code: https://github.com/ohdsi-studies/PioneerWatchfulWaiting. Analysis apps: https://pioneer-shiny.hzdr.de/PioneerWatchfulWaiting_restricted/. The protocol is available on https://protocolexchange.researchsquare.com/article/pex-1468/v1.

Peer Review Summary

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