Real-world retrospective study of early-stage prostate cancer at a Portuguese Comprehensive Cancer Centre: The PEarlC study

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Abstract. Despite the high prevalence of localised prostate cancer (LPC) and locally advanced prostate cancer (LAPC), evidence on the characteristics of patients, treatments and clinical outcomes stratified by disease risk is limited. The PEarlC study was conducted to characterise a cohort of patients with early-stage prostate cancer that included real-world clinical outcomes. Retrospective data from a cohort of patients diagnosed with LPC/LAPC between 2015 and 2017 and followed up until December 2020 at a Portuguese comprehensive cancer centre (IPO Porto) was analysed. Patients were classified as LPC (high- or non-high-risk) or LAPC according to European Association of Urology guidelines, were eligible if diagnosed at stage I-III and followed up in Urology, Medical Oncology or Radiation Oncology outpatient clinics of IPO Porto. Data was collected from the medical/administrative records database. Clinical outcomes included prostate-specific antigen (PSA) progression-free survival, metastasis-free survival, disease-free survival, progression-free survival, overall survival (OS), PSA response (palliative) and no evidence of residual tumour (prostatectomy). Time-to-event outcomes were compared between subgroups using the log-rank test. A total of 790 patients were included (54.8% non-high-risk LPC, 30.9% high-risk LPC, 14.3% LAPC) and the median follow-up was 46.7 months. Patients had a median age of 68.0 years. The majority of patients were stage II (52.9%) and Eastern Cooperative Oncology Group 0-1 (99.9%) and received treatment with curative intent (85.4%). The median was only achieved in progression-free survival (29.9 months; 95% CI, 26.5-41.0 months), as evaluated in palliative patients. At year 5, 82.9% were free of PSA progression (curative), 87.5% were metastasis-free, 83.7% were disease-free, all patients in palliative treatment progressed and the 5-year OS rate was 92.9% (CI 95%, 90.2-95.7%). Among patients with LPC, OS was worse in high-risk vs. non-high-risk patients (5-year OS rate, 88.8% vs. 96.8%; hazard ratio=3.34, CI 95%, 1.64-7.05; P=0.001). PSA response rate was 81.4% in the palliative setting. There was no evidence of residual tumour in 61.6% of patients who underwent prostatectomy. Although most patients with early-stage prostate cancer treated at IPO Porto showed positive 5-year real-world outcomes, patients with high-risk LPC showed worse OS

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compared with patients with non-high-risk LPC and therefore a poorer prognosis. The present large-sample real-world study is an important contribution to reducing the evidence gap on prostate cancer.

Introduction

In Europe, prostate cancer ranks first among the most frequently diagnosed cancers in men (1). It is more common in men aged >65 years (2), however studies have documented an age-migratory pattern towards an increase in prostate cancer cases in younger age groups (50-59 years) (3). As in other developed countries, prostate cancer incidence has been rising in Portugal since 1998 (4). This cancer was the most common among Portuguese men with 7,529 new diagnoses in 2022 (19.9% of all new cases of malignancy in men) and an age-standardized incidence rate of 62.6 cases/100,000 men (vs. 59.9/100,000 men in Europe) (1). Prostate cancer mortality has declined in most high-income countries since the mid-1990s, including in Portugal (4), likely reflecting advances in treatment and earlier detection with the increased use of prostate-specific antigen (PSA) testing (5-7). In Portugal, there were 2,083 prostate cancer-related deaths in 2022 and the age-standardised mortality rate was 11.1 deaths/100,000 men (vs. 11.2 deaths/100,000 men in Europe (1). Localised disease accounts for >80% of prostate cancer diagnoses and of these 15% are at high risk of cancer recurrence (8,9).

Although the aetiology of prostate cancer is not well understood, risk factors such as age, family history, certain genetic mutations, such as BRCA gene mutation (10), and ethnicity may contribute to the development of prostate cancer (11,12). These may influence both genetic and epigenetic factors (13). Of all the men who receive a diagnosis of prostate cancer, 30-50% may not have a life-threatening condition (14). Therefore, choice of treatment may be complex since it must consider tumour staging, risk stratification, comorbidities, life expectancy, potential side effects of the different treatments and the preference of the patient (14).

Localized prostate cancer has often an indolent course but disease progression and metastases can develop in the long-term (15), thus reinforcing the importance of early diagnosis and adequate clinical management. Nevertheless, the clinical approach to patients with early-stage prostate cancer remains controversial (16). Active surveillance is considered appropriate for selected patients, namely for those with a clinically low-risk and for some with an (favourable) intermediate-risk. Remaining patients (intermediate- and high-risk) may undergo radical prostatectomy, radiotherapy including external beam radiotherapy (EBRT) or brachytherapy, or even experimental focal therapies, including high-intensity focused ultrasound, cryotherapy or laser ablation therapy (17).

The natural course of prostate cancer, the time of diagnosis and the available treatment options make the characterisation of patients at the time of diagnosis extremely relevant. Portuguese Oncology Institute of Porto (IPO Porto; Porto, Portugal) is a Portuguese comprehensive cancer centre with integrated oncology and palliative care that serves a large population region. It includes multidisciplinary clinical units, termed the Pathology Clinics, which ensure, in the same physical space, that all the needs of healthcare patients are met according to their diagnosis. Each case is evaluated by different medical specialists, and decision-making occurs through knowledge and expertise, whilst taking into account the preferences, values and priorities of the patients (18).

It is of utmost importance to understand current multidisciplinary clinical practice in the management of these patients and the clinical outcomes resulting from this practice in a real-world setting outside of clinical trials. In this context, the Prostate Early Cancer (PEarlC) study was conducted primarily to investigate real-world characteristics and treatment patterns of a retrospective cohort of patients with early-stage prostate cancer followed up at IPO Porto and to evaluate the response to treatment by clinical outcomes commonly used in real-world practice. As a secondary objective, the present study compared clinical outcomes between different disease risk subgroups.

Materials and methods

Study design. The present study was a retrospective, non-interventional, single-centre cohort study of patients with early-stage prostate cancer diagnosed between January 2015 and December 2017 (index date). For each patient, all available data between the index date and end of clinical activity, end of follow-up (December 2020) or death (whichever occurred first) were retrospectively collected. The data set for the statistical analysis was prepared between July and December 2021, and the final study report was released in May 2022.

This study was approved by The Board of Administration (Contract number 1604247; 21 May 2021) and Ethics Committee of IPO Porto (approval no. CES126/021; 6 May 2021; Porto, Portugal) and by the Data Protector Officer of IPO Porto (DPO Opinion 47/2021; 16 April 2021) before data collection. Patient informed consent was exempt due to the retrospective observational nature of the study and data anonymization. The reporting of the present study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement (19).

Patient selection. The study inclusion criteria was as follows: i) Male patients aged ≥18 years; ii) topographic location (ICD-O-3) C61 (malignant neoplasm of prostate); iii) histologically confirmed prostate adenocarcinoma (ICD-O-3) 8140-8480 (20); iv) diagnosed between 1 January 2015 and 31 December 2017 at IPO Porto; v) disease stage I-III (21); vi) tumour behaviour 3 (malignant); vii) and start of treatment or active surveillance at IPO Porto.

Exclusion criteria included: i) Distant metastasis (clinical stage M1); ii) continuation of prostate cancer treatment in another hospital following admission to IPO Porto; iii) no follow-up in IPO outpatient clinics (urology, medical oncology, radiation oncology and multidisciplinary tumour board); iv) other malignancies in the 5 years before or during the study (except basal/squamous cell carcinoma); v) and participation in clinical trials.

The cohort was stratified into non-high-risk localised prostate cancer (LPC), high-risk LPC and locally advanced prostate cancer (LAPC), based on criteria defined by the guidelines of The European Association of Urology (Table I) (22).

Data. Demographic and disease characteristics, prostate cancer treatment and healthcare resource utilization data were

Table I. EAU risk groups for biochemical recurrence of LPC and LAPC (22).

Low risk	Intermediate-risk	High-risk	
PSA <10 ng/ml and GS <7 (ISUP grade 1) and cT1-2a Localized	PSA 10-20 ng/ml or GS 7 (ISUP grade 2/3) or cT2b	PSA >20 ng/ml or GS >7 (ISUP grade 4/5) or cT2c	Any PSA Any GS (any ISUP grade) cT3-4 or cN+ Locally advanced

GS, Gleason score; ISUP, International Society for Urological Pathology; PSA, prostate-specific antigen.

abstracted from electronic medical and administrative records from IPO Porto. Retrieved data were subject to rigorous quality-control procedures. Confidentiality and anonymization of data for analysis were ensured. Data sources were linked by the IPO Porto internal unique patient identifier.

Definition of clinical outcomes. The following clinical outcomes were calculated based on extracted data: i) PSA progression-free survival (evaluated in patients treated with curative intent). If submitted to surgery, defined as time from radical prostatectomy to first PSA >0.2 ng/ml over baseline. If treated with radiation therapy (EBRT or brachytherapy) (23), defined as time from the initial treatment to first PSA level according to the Phoenix Criteria (23). If treated with systemic therapy (24), defined as time from systemic treatment initiation to first PSA level according to the Phoenix Criteria; ii) metastasis-free survival (evaluated in patients treated with curative or palliative intent) defined as time from treatment start to diagnosis of first metastasis; iii) disease-free survival (evaluated in patients in curative treatment) defined as time from treatment start to first relapse; iv) progression-free survival (evaluated in patients in palliative treatment) defined as time from start of palliative treatment to progression or death in the hospital, whichever occurred first. Progression was evaluated considering PSA level progression, clinical progression or radiographic progression (bone scintigraphy or CT-scan); v) overall survival (OS; evaluated in all patients) defined as time from date of diagnosis to death by any cause; vi) PSA response rate (evaluated in patients in palliative treatment after PSA progression) defined as the percentage of patients with a decline of at least 50% in the PSA level. Patients with death due to disease progression or without any evaluation during follow-up were excluded; and vii) no evidence of residual tumour rate (evaluated in patients who underwent radical prostatectomy) defined as the percentage of patients who had an anatomopathological result of no residual tumour (R0) or microscopic residual tumour (R1).

Statistical analysis. Data was summarized using descriptive statistics for the overall sample and stratified by study subgroups. The characteristics of the patients at diagnosis were compared between LPC and LAPC subgroups using non-parametric statistical tests for independent samples [Mann-Whitney test for age, Chi-square test for age groups and Fisher's exact test for disease stage and Eastern Cooperative Oncology Group (ECOG)]. The Kaplan-Meier method was used to analyse time-to-event variables and to estimate the median, corresponding 95% confidence intervals (CI), and 1- and 5-year rates. If the event of interest was not observed, time was censored at the end of the follow-up (except progression-free survival, where time was censored at the end of the follow-up or death outside the hospital, whichever occurred first). Survival curves were compared between subgroups using the log-rank test. Cox proportional-hazards regression analysis was used to compute hazard ratios (HR) and 95% CI. Missing data was not replaced. A two-sided $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using R software version 4.1.0 (R Foundation for Statistical Computing) (25).

Results

Number of patients. In the present retrospective cohort study, a total of 1,414 patients were assessed for eligibility and 601 were excluded, including 259 who continued treatment in another hospital following admission to IPO Porto, 181 who had no follow-up visits in IPO outpatient clinics, 158 who had multiple primary tumours (within 5 years before or within the follow-up period) and 3 who were enrolled in clinical trials. Of the 813 eligible patients, 23 were lost to follow-up during the study period and excluded from statistical analysis (n=790; Fig. 1).

Demographic and clinical characteristics. Table II describes the characteristics at diagnosis and vital status of patients at the end of the follow-up. Overall, the median age was 68.0 years. The majority of patients had LPC (85.7%), of whom ~1/3 (36.0%) were high-risk. Only 1.1% had a ECOG performance status ≥2. The majority of the patients had been diagnosed with stage II (52.9%) or stage III (30.1%). The median follow-up was 46.7 months and was similar between subgroups. There were ~94.8% patients alive at the end of the follow-up. There were significant statistical differences in age ($P=0.001$) and disease stage ($P<0.001$) of LPC vs. LAPC patients but not in ECOG ($P=0.627$).

First treatment characterization. The majority of the patients received treatment with curative intent (EBRT, brachytherapy or radical prostatectomy; Table III). Only 4.3% received palliative treatment (androgen deprivation therapy) and 10.3% (n=81) had no treatment until the end of the follow-up period (in active surveillance or watch-and-wait; Table III). The majority of the untreated patients had a short life expectancy, comorbidities or a poor performance status (data not shown). The percentage of patients in palliative treatment was higher in high-risk (10.2%) than in non-high-risk (1.2%) LPC and LAPC (3.5%)

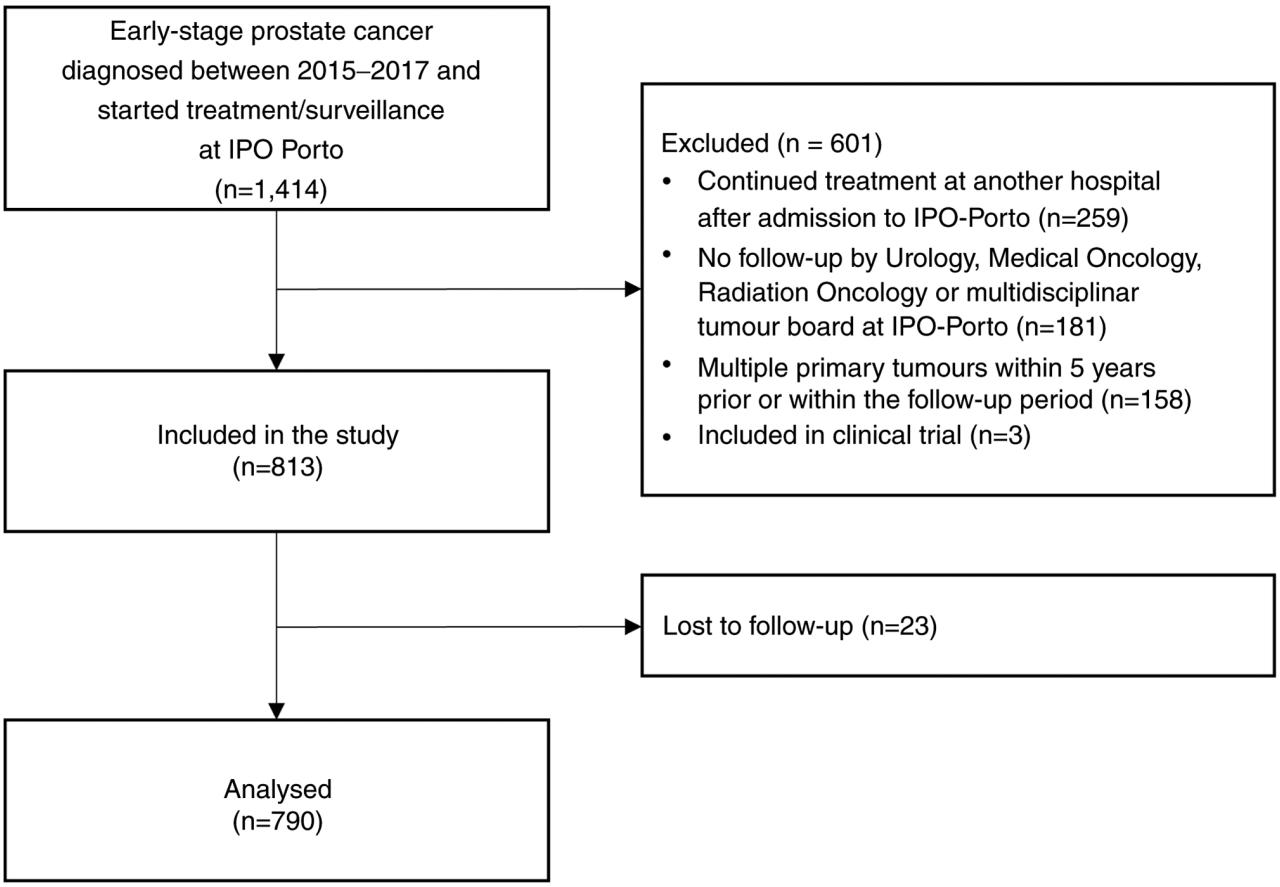

Figure 1. Study diagram flow.

groups. The most common first-line treatment was radical prostatectomy (38.8%) in patients with non-high-risk LPC and radiotherapy plus hormone therapy (HT) both in patients with high-risk LPC (50.6%) and patients with LAPC (89.1%).

Clinical outcomes. After 5 years, the OS rate was 92.9% (95% CI, 90.2-95.7%; all patients), 82.9% (95% CI, 77.3-100.0%) of the patients treated with curative intent were free of PSA progression, 87.5% (95% CI, 82.6-92.7%) of patients with curative/palliative treatment were metastasis-free, 83.7% (95% CI, 78.0-89.8%) of patients treated with curative intent were disease-free. In time-to-event outcomes, the median was only reached in progression-free survival (29.9 months; 95% CI, 26.5-41.0 months) with no patients free of progression after 5 years (Table IV).

Kaplan-Meier curves were not statistically different between patients with LPC vs. LACP patients (Fig. 2A). Within patients with LPC, high-risk patients showed a worse OS in comparison with non-high-risk patients (5-year OS rate, 88.8% vs. 96.8%; HR=3.34, 95% CI, 1.64-7.05, P=0.001; Fig. 2B). The 5-year metastasis-free survival rate was worse in high-risk (78.5%) vs. non-high-risk patients (91.8%), although the difference was not statistically significant (P=0.061; Fig. 2B).

A total of ~84.1% (58/69 patients; CI 95%, 73.3-91.8%) of the patients treated with palliative treatment following PSA progression had a PSA response (Fig. 3). In patients who underwent radical prostatectomy, 61.6% (114/185 patients; 95% CI, 54.2-68.7%) showed no evidence of residual tumour (Fig. 3).

Discussion

It is known that the number of patients in treatment for LPC has been increasing in Portugal (26) likely due to the widespread use of PSA (contributing to an increase in incidence and early cancer detection), improved access to healthcare (mainly hospital specialist consultations) and population aging (26). However, there is still a lack of knowledge on the characteristics and clinical outcomes of these patients with early prostate cancer, namely those with high-risk LPC and LAPC. Real-world data is important to characterise patients treated in clinical practice and measure outcomes outside of the clinical trial setting where highly selected patients are frequently enrolled (27). It can also be of importance to provide insights about health care patterns, including treatments (27). Real-world data is increasingly being used to propose and support decision-making in the clinical management of patients (27).

To the best of our knowledge, the present retrospective study provided the first characterisation of a large cohort of patients with early-stage prostate cancer treated in real-world conditions at a tertiary cancer institute in Portugal, together with an exhaustive set of clinical outcomes. The present study covered the clinical practice at IPO Porto over 6 years (2015-2020). Clinical practice at IPO Porto for early-stage prostate cancer has not suffered major changes since then. Therefore, it is expected that the results presented here are still valid for the present setting. Although this is a single-centre

Table II. Demographic and clinical characteristics at diagnosis and status at end of follow-up.

Characteristic	LPC, n=677		LAPC, n=113	Overall, n=790	P-value, LPC vs. LAPC
	Non-high-risk, n=433	High-risk, n=244			
Median age (range), years	66.0 (44.0-83.0)	71.0 (46.0-89.0)	70.0 (42.0-85.0)	68.0 (42.0-89.0)	0.001
Age group, years (%)					
<60	87 (20.1)	23 (9.4)	5 (4.4)	115 (14.6)	0.001
60-69	211 (48.7)	87 (35.7)	48 (42.5)	346 (43.8)	
>=70	135 (31.2)	134 (54.9)	60 (53.1)	329 (41.6)	
Stage, n (%)					
I	125 (28.9)	6 (2.5)	0 (0)	131 (16.6)	<0.001[a]
II	207 (47.8)	211 (86.5)	0 (0)	418 (52.9)	
III	99 (22.9)	26 (10.7)	113 (100)	238 (30.1)	
Unknown	2 (0.5)	1 (0.4)	0 (0)	3 (0.4)	
ECOG, n (%)					
0-1	419 (96.8)	230 (94.3)	110 (97.3)	759 (96.1)	0.627[a]
2-3	3 (0.7)	4 (1.6)	2 (1.8)	9 (1.1)	
Unknown	11 (2.5)	10 (4.1)	1 (0.9)	22 (2.8)	
Status at end of follow-up, n (%)					-
Dead	11 (2.5)	21 (8.6)	9 (8.0)	41 (5.2)	
With evidence of disease	8 (1.8)	16 (6.6)	4 (3.5)	28 (3.5)	
Without evidence of disease	3 (0.70)	5 (2.00)	5 (4.40)	13 (1.60)	
Alive	422 (97.5)	223 (91.4)	104 (92.0)	749 (94.8)	
With evidence of disease	77 (17.80)	39 (16.00)	10 (8.80)	126 (15.90)	
Without evidence of disease	345 (79.70)	184 (75.40)	94 (83.20)	623 (78.90)	

[a]Statistical test was performed excluding the 'Unknown' category. ECOG, Eastern Cooperative Oncology Group; LPC, localised prostate cancer; LAPC, locally advanced prostate cancer.

study, IPO Porto is one of the most relevant Portuguese centres treating oncologic diseases, including prostate cancer, and is responsible for the management of ~850 new patients with prostate cancer per year, equating to ~11.3% of all new cases in Portugal (1). The present study conducted at this centre allowed the inclusion of a large sample and the calculation of precise estimates for the overall sample with a low margin of error.

In the present study, the exclusion criteria were mainly defined to exclude patients with incomplete follow-up data, as they would not be suitable to estimate 5-year clinical outcomes. A total of 259 patients were excluded from the study due to continuation of treatment outside IPO Porto, which is common in reference oncology centres; namely, when patients looked for a second opinion on the treatment protocol suggested by another hospital, or wished to have access to treatment techniques, such as robotic or laparoscopic surgery, that were not available at IPO at the time of the study. However, these excluded patients are not expected to have more severe disease than the included patients, and therefore their exclusion likely did not limit the internal validity of the results for all patients treated at IPO Porto. Furthermore, a characterisation of the subjects lost to follow-up was not performed, but their exclusion did not introduce any bias in the results considering their low number (n=23), as compared with the total sample size (n=790). Thus, the present sample appears to have been highly representative of all early-stage prostate cancer cases attended at IPO Porto.

It was not expected that the characteristics of the patients treated at IPO Porto differed significantly from those of patients treated at other reference Portuguese oncology centres. Given the small number of patients in palliative care, non-treated or only in HT, the sample of the present study mainly reflected patients being followed up using a multidisciplinary approach and treated with curative intentions including brachytherapy, radical prostatectomy or radiotherapy combined with HT. Missing data was minimal (only missing for ECOG status) due to exclusion criteria and data quality control. The quality of the data retrospectively collected in the present study was ensured by the standard operating procedures for data management and statistical analysis implemented at IPO Porto.

In the present study, 14.3% of all PC diagnoses were high-risk, which is aligned with what has been described in the literature (15%) (8,9). Within the LPC subgroup, there was a higher percentage of patients submitted to prostatectomy in the non-high-risk patients (38.8%) compared with high-risk patients (16.3%). There is likely a judicious use of surgery as a single recommendation for high-risk patients, mainly because most of the time there is a need for multimodal treatments, and this is of the utmost importance to the

Table III. Characterization of the first treatment.

Treatment characteristic	LPC, n=677		LAPC, n=113	Overall, n=790
	Non-high-risk, n=433	High-risk, n=244		
First treatment intention, n (%)				
Curative	361 (83.4)	208 (85.2)	106 (93.8)	675 (85.4)
Palliative	5 (1.2)	25 (10.2)	4 (3.5)	34 (4.3)
No treatment	67 (15.5)	11 (4.5)	3 (2.7)	81 (10.3)
First treatment, n (%)				
ADT[b]	5 (1.4)	25 (10.7)	4 (3.6)	34 (4.8)
Brachytherapy	114 (31.1)	16 (6.9)	1 (0.9)	131 (18.5)
Radical prostatectomy	142 (38.8)	38 (16.3)	5 (4.5)	185 (26.1)
Radiotherapy	59 (16.1)	36 (15.5)	2 (1.8)	97 (13.7)
Radiotherapy + HT	46 (12.6)	118 (50.6)	98 (89.1)	262 (37.0)
First management approach[a], n (%)				
Bicalutamide	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Goserelin	4 (1.1)	18 (7.7)	4 (3.6)	26 (3.7)
Orchidectomy	1 (0.3)	6 (2.6)	0 (0.0)	7 (1.0)
Brachytherapy	114 (31.1)	16 (6.9)	1 (0.9)	131 (18.5)
Radical prostatectomy	87 (23.8)	21 (9.0)	4 (3.6)	112 (15.8)
Radical prostatectomy + radiotherapy	53 (14.5)	17 (7.3)	1 (0.9)	71 (10.0)
Radical prostatectomy + radiotherapy + HT	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.3)
Radiotherapy	59 (15.8)	36 (15.4)	2 (1.8)	97 (13.7)
Radiotherapy + HT	46 (12.6)	107 (45.9)	83 (75.5)	236 (33.3)
Radiotherapy + brachytherapy + HT	0 (0.0)	11 (4.7)	15 (13.6)	26 (3.7)

[a]Percentages calculated within patients treated with curative or palliative intention (non-high-risk LPC n=366, high-risk LPC n=233, LAPC n=110, overall n=709). [b]Includes bicalutamide, goserelin or orchidectomy. LPC, localised prostate cancer; LAPC, locally advanced prostate cancer; ADT, androgen deprivation therapy; HT, hormone therapy.

multidisciplinary board of IPO Porto. There is still a discussion about the use of radical prostatectomy as a first-line treatment for LAPC (28). At IPO Porto, only 4.5% (n=5) of patients with LAPC were submitted to this type of surgery. At IPO Porto, the clinical protocol is to treat patients with LAPC with radiotherapy combined with hormonotherapy, a practice aligned with the European Association of Urology recommendations (22).

Only four studies with Portuguese patients with LPC/LAPC published in indexed journals were identified for the purpose of the present study. A previous study (29), including 300 Portuguese patients with LPC and a first prostate biopsy at another Portuguese oncology reference centre (Portuguese Oncology Institute of Coimbra, Coimbra, Portugal) between January 2014 and December 2018, reported 17.3% (vs. 30.1% at IPO Porto) patients who underwent radical prostatectomy, 39.3% (vs. 43.2%) who underwent external radiotherapy, 29.3% (vs. 21.7%) who underwent brachytherapy and 14.1% (vs. 5.0%) who were treated with other options (active surveillance, cryotherapy and hormonal therapy). Since there is no information on the risk of these patients, the differences in treatment practices between IPO Coimbra and IPO Porto could not be justified.

A registry-based study (30) carried out in 43 Portuguese centres and published in 2010 included 1,767 patients with early-stage prostate cancer, of whom 69.8% had LPC (vs. 85.7% at IPO Porto) and 30.2% had LAPC. In patients with LPC, the most common treatments were radical prostatectomy (43.9%), radical radiotherapy (25.3%) and pelvic adjuvant radiotherapy (9.3%). In LAPC, 67.8% were first treated with HT. However, the study was published >10 years ago, and the authors recognized limitations on the sampling methods and external validity.

In addition, a Portuguese single-centre retrospective study (31) was identified that reported 6-year real-world outcomes in non-high-risk LPC [defined according to European Organisation for Research and Treatment of Cancer (32)] between 2003 and 2013; however, in this previous study, the patients were only treated with brachytherapy, and therefore it cannot be used for comparing outcomes or treatment patterns with the present study.

Botelho *et al* (26) performed a nationwide study which described treatment patterns over time in localized prostate cancer in the Portuguese National Health System hospitals between 2000 and 2020. Still, the results were mainly presented at treatment-level rather than patient-level, focused mostly on hospital case volume (cumulative number of treatments per year) and data for radiotherapy were not available after 2012. Therefore, the lack of recent real-world Portuguese studies in patients with LPC and/or LAPC limited our understanding and

Table IV. Kaplan-Meier estimates of time-to-event outcomes.

	LPC			
Time-to-event outcome	Non-high-risk	High-risk	LAPC	Overall
PSA progression-free survival[a]				
n	361	208	106	675
Median (95% CI), months	n.a.	n.a.	n.a.	n.a.
1-year rate (95% CI), %	98.9	97.1	100.0	98.5 (97.6-99.4)
5-year rate (95% CI), %	87.4	78.7	79.9	82.9 (77.3-100.0)
Metastasis-free survival[b]				
n	366	233	110	709
Median (95% CI), months	n.a.	n.a.	n.a.	n.a.
1-year rate (95% CI), %	98.9	98.3	100.0	98.9 (98.1-99.7)
5-year rate (95% CI), %	91.8	78.5	91.7	87.5 (82.6-92.7)
Disease-free survival[a]				
n	361	208	106	675
Median (95% CI), months	n.a.	n.a.	n.a.	n.a.
1-year rate (95% CI), %	99.2	98.1	100.0	98.9% (98.2-99.7)
5-year rate (95% CI), %	88.4	79.9	79.1	83.7 (78.0-89.8)
Progression-free survival[c]				
n	22	39	10	71
Median (95% CI), months	32.9 (27.1-46.0)	29.5 (24.4-44.5)	29.1 (26.3-41.8)	29.9 (26.5-41.0)
1-year rate (95% CI), %	90.5	86.5	100.0	89.7 (92.7-97.2)
5-year rate (95% CI), %	0.0	0.0	0.0	0.0
Overall survival[d]				
n	433	244	113	790
Median (95% CI), months	n.a.	n.a.	n.a.	n.a.
1-year rate (95% CI), %	100.0	99.2	100.0	99.8 (99.4-100)
5-year rate (95% CI), %	96.8	88.8	87.9	92.9 (90.2-95.7)

[a]In patients treated with curative intent (n=675), [b]in patients treated with curative or palliative intent (n=709), [c]in patients treated with palliative intent (n=71), [d]in all patients (n=790). LPC, localised prostate cancer; LAPC, locally advanced prostate cancer; CI, confidence interval; n.a., median not achieved.

the comparison of the current clinical practice and outcomes in other hospitals vs. IPO Porto.

Furthermore, the comparison with published studies from other countries is not straightforward due to differences in the included patient population (namely the stage of the disease), treatments, outcome definitions and study period. Goy *et al* (33) compared clinical outcomes of radical prostatectomy vs. EBRT vs. brachytherapy for patients with intermediate-risk prostate cancer only (a subgroup included in the non-high-risk LPC of PEarlC study) treated between 2004 and 2007 and followed-up for 10 years. The 5-year survival rate seen in the PEarlC study for the non-high-risk group (96.8%) is within the range estimates by treatment in the former study (90.6-98.1%) as well as the PSA progression-free survival rate (87.4% in PEarlC study vs. 73-90.7% in Goy *et al*).

In the PEarlC study, the majority of patients with early-stage prostate cancer appear to have a favourable 5-year prognosis, with positive real-world outcomes, namely metastasis-free survival, disease-free survival, progression-free survival and OS. No statistical difference was observed between the results of patients with LPC vs. LAPC patients. Notably, patients with high-risk LPC exhibited worse outcomes compared with non-high-risk but only the difference in OS was statistically significant. Indeed, the short follow-up to measure clinical outcomes of patients at an early stage of the disease may have been a study limitation, due to the availability and quality of electronic data and urgency to accelerate evidence generation, which is at present scarce. In addition, when analysing some outcomes (progression-free survival, PSA response rate, no evidence of residual tumour), the number of available patients was small, particularly in the LAPC subgroup. This may have also contributed to the lack of statistical significance. In fact, the study was not powered to compare results between subgroups of patients. The comparison of clinical outcomes between different treatments were not aimed in the present study, since the choice of the treatment depends on patient and disease characteristics, including severity which is itself a prognostic variable. Finally, the healthcare resource use and corresponding costs estimated for these patients were previously presented (34) and beyond the scope of the current analysis.

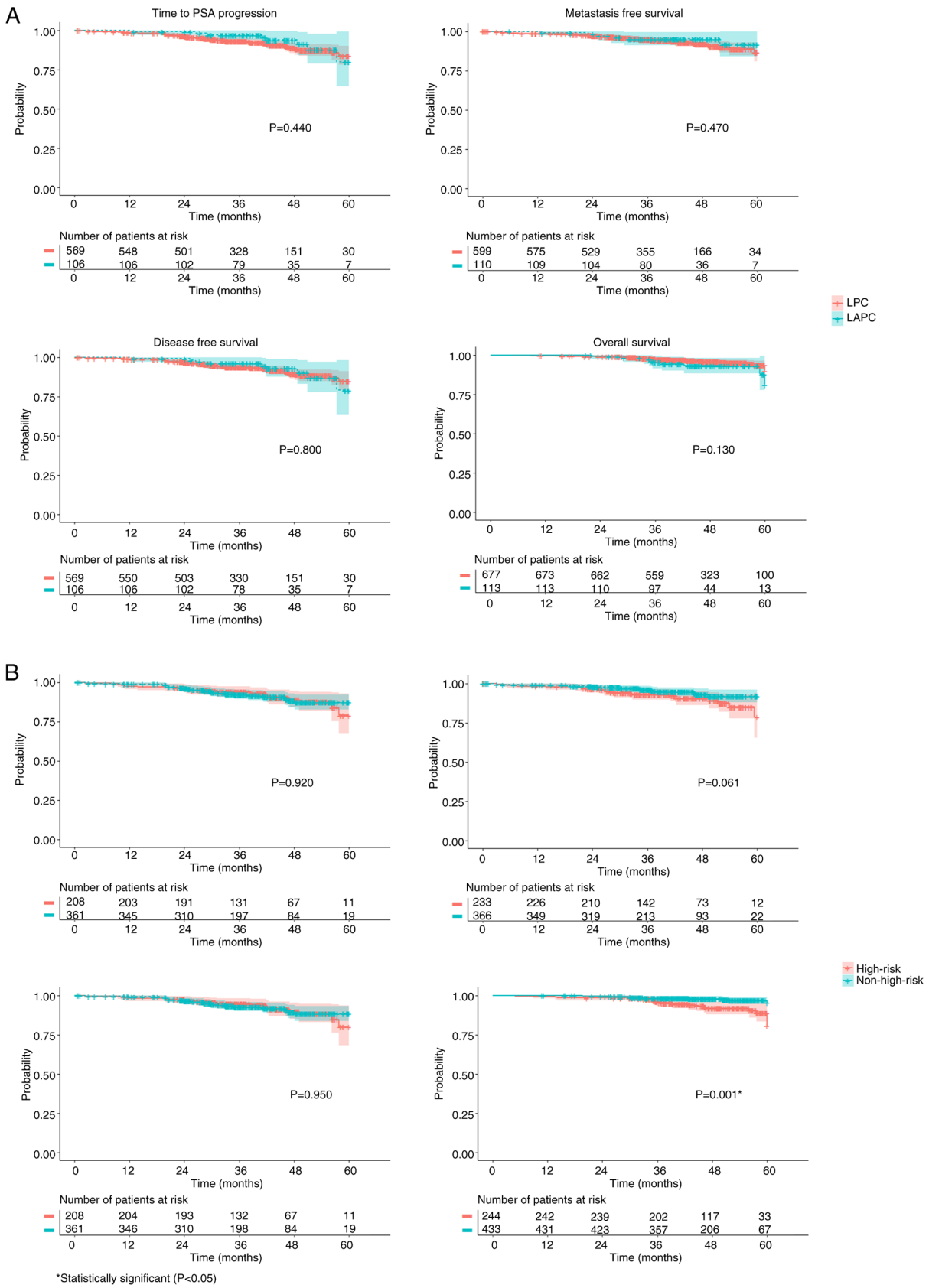

Figure 2. Kaplan-Meier estimates and corresponding 95% confidence intervals of clinical outcomes for (A) patients with LPC vs. LAPC and (B) patients with high-risk vs. non-high-risk LPC. LPC, localised prostate cancer; LAPC, locally advanced prostate cancer; PSA, prostate-specific antigen.

To conclude, the clinical management of patients with early-stage prostate cancer is multifactorial, considering patient-related factors, such as age, comorbidities, previous treatments or conditions, and cancer-related factors, such as tumour grading, staging or risk group, with some patients showing an indolent course of the disease and being more suited

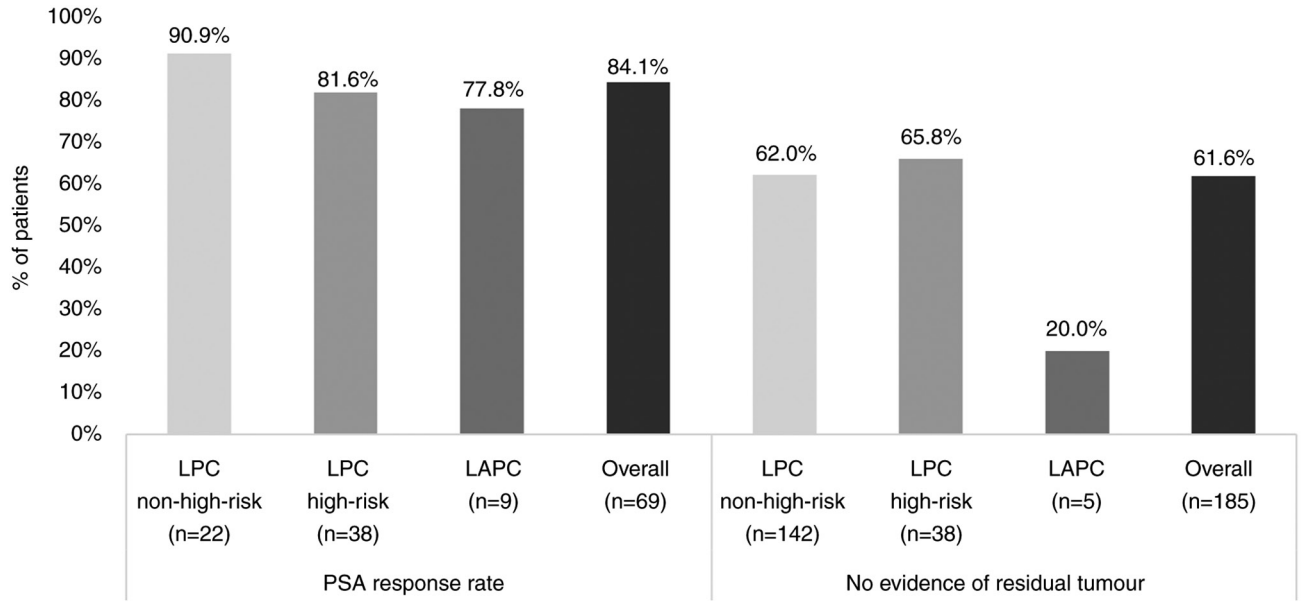

Figure 3. PSA response rate evaluated in patients who received palliative treatment after PSA progression and no evidence of residual tumour rate evaluated in patients who underwent radical prostatectomy.

to surveillance, and others with indications to start active local treatment with curative intent, such as surgery or radiotherapy. The best approach should be decided in a multidisciplinary team setting. At IPO Porto and following recommendations from several medical societies (especially from the European Urology Oncology), the treatment modality is always decided in a multidisciplinary meeting, and patients included in this study were treated with a wide range of therapies. In LPC or LAPC, systemic therapies have a potentiating role in curative treatment in selected patient subgroups, or as subsequent treatment lines following the failure of local treatment. The range of prognostic factors and therapeutic options, often with overlapping efficacy rates but different toxicity profiles, highlights the importance of taking the therapeutic decision in a truly multidisciplinary setting, of which IPO Porto was a pioneer. The PEarlC study highlighted that the current strategy has high success rates in disease control and survival, and there is a need for long follow-ups, due to the often indolent course of this disease. Overall, the prognosis for most patients is rather positive, as there is a possibility to adjust the type of therapy to the clinical characteristics of the patient. There is a confined subgroup of patients (high-risk), who in most cases are not eligible for curative therapy, and for whom future pharmacological innovation may bring improvements, namely in OS or metastasis-free survival.

In the future, treatments closely tailored to disease risk, the advancement of the technical development of local therapies, such as surgery and radiotherapy, with improved results in clinical outcomes and less side effects, together with the development of new medicines and an improved disease control with a first-line treatment or following treatment failure are expected. Furthermore, it will be relevant to periodically update the results of the present study for a close monitoring of the ongoing practice, its clinical benefits and expand evidence on respective outcomes. The present large real-world study is an important contribution to reducing the evidence gap for early stages of prostate cancer, ultimately improving public health impact of this disease in the future.

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Availability of data and materials

The data generated in the present study are not publicly available due to data access and ownership compliance regulations but may be requested from the corresponding author.

Authors' contributions

IB, SGM, RC, MR, EM, JLC, AR, AO, ACF, SS, PR and MJB provided substantial contributions to the conception and design of the study. SGM, RC and PR were involved in the acquisition, analysis and interpretation of the study data. All authors substantially contributed to critically reviewing the manuscript for important intellectual content. IB and PR confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript. All authors agreed to be accountable for the work in ensuring that questions related to the integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of IPO Porto (approval no. CES126/021; Porto, Portugal) and by the Data Protector Officer at IPO Porto. Patient's informed consent was exempt from the Ethics Committee of IPO Porto.

Patient consent for publication

Not applicable.

Competing interests

IB, SGM, RC, MR, EM, JLC, AR, AO, PR and MJB are employees of IPO Porto, which established a financial contract with Johnson & Johnson Innovative Medicine for the data extraction, statistical analysis and data interpretation. ACF and SS are employees of Johnson & Johnson Innovative Medicine.

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