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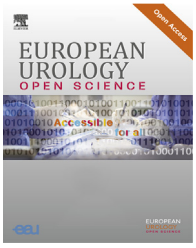

European Association of Urology

Prostate Cancer

Observation With or Without Subsequent Salvage Therapy for Pathologically Node-positive Prostate Cancer With Negative Conventional Imaging: Results From a Large Multicenter Cohort

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Abstract

Background and objective: More than 10% of patients with negative clinical metastatic status (cN0M0) on conventional imaging for prostate cancer (PCa) harbor lymph node involvement (pN+) at final pathology following radical prostatectomy (RP) and lymphadenectomy. Our aim was to assess outcomes of initial observation for cN0M0 pN+ PCa and identify prognostic factors that may help in clinical decision-making.

Methods: We performed a retrospective multicenter study of patients with cN0M0 PCa on conventional imaging (computed tomography and/or magnetic resonance imaging, and a bone scan) who were found to have pN+ disease at RP between 2000 and 2021. Biochemical recurrence (BCR) and systemic progression/recurrence

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were the primary outcomes. Kaplan-Meier curves and Cox proportional hazards model were used for survival and multivariate analysis.

Key findings and limitations: A total of 469 men were included in this retrospective multicenter trial. Median prostate-specific antigen (PSA) was 10.1 ng/ml (interquartile range [IQR] 6.6–18.0). Among these patients, 56% had grade group ≥4, 53.7% had stage ≥pT3b, 42.6% had positive margins, and 19.6% had PSA persistence. The median number of positive nodes and of nodes removed were 1 (IQR 1–3) and 20 (14–28), respectively. At median follow-up of 41 mo, 48.5% experienced BCR. The 5-yr BCR-free survival rate was 31.7% (95% confidence interval [CI] 26.33–37.1%). Salvage treatments were needed in 211 patients and included radiotherapy (RT; *n* = 53), RT + androgen deprivation therapy (ADT; *n* = 88), ADT alone (*n* = 68), and salvage lymphadenectomy (*n* = 2). The 5-yr estimated survival rates were 66.3% (95% CI 60.4–72.1) for metastasis-free survival, 97.7% (95% CI 95.5–99.8%) for cancer-specific survival, and 95.3% (95% CI 92.4–98.1%) for overall survival. On multivariable analysis, PSA persistence was an independent predictor of BCR (odds ratio [OR] 51.8, 95% CI 12.2–219.2), exit from observation (OR 8.5, 95% CI 4.4–16.5), and systemic progression (OR 3.0, 95% CI 1.771–4.971).

Conclusions: Initial observation in the management of pN+ cN0M0 PCa is feasible and has excellent survival rates in the intermediate term. Patients with worse disease features, especially PSA persistence, have a higher likelihood of recurrence and progression and may be candidates for more aggressive upfront management.

Patient summary: We investigated the value of initial observation for men with prostate cancer with negative scan findings for metastasis who were then found to have positive lymph nodes after surgery to remove the prostate. Our results show that initial observation is a good option for patients with less aggressive prostate cancer features.

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1. Introduction

Pathologically positive nodes are found at radical prostatectomy (RP) and lymph node dissection (LND) in approximately 5–10% of cases with clinically localized (cN0M0) disease on conventional preoperative staging for prostate cancer (PCa) [1,2]. However, there is conflicting evidence regarding the optimal management strategy for these patients. The only available randomized controlled trial (RCT) conducted in this context demonstrated survival advantages of adjuvant androgen deprivation therapy (ADT) in comparison to initial expectant management, but the trial was conducted before the prostate-specific antigen (PSA) era [3]. Furthermore, the trial included men with a relatively high pathological burden. Subsequent cohort studies have shown that pN+ disease is not a homogeneous entity, but rather a multifaceted condition that requires a risk-adapted management approach. Proposed strategies include initial observation with potential salvage radiotherapy (RT)/ADT, adjuvant RT with or without ADT, and adjuvant ADT [1,2].

Current guidelines and expert consensus align with these findings, recommending a range of options for management. For patients with less aggressive disease, expectant management with early salvage treatment on relapse may be considered, while upfront adjuvant local and/or systemic treatments are recommended for those at higher risk [4,5]. Real-life practice also reflects the uncertainty surrounding the management of cN0M0 pN+ PCa [6].

Although initial observation has shown better functional outcomes and similar oncological outcomes in comparison to adjuvant RT for localized or locally advanced PCa, including high-risk disease, inclusion of pN+ disease in these randomized trials was lacking [7]. Retrospective cohort analyses in the pN+ context have demonstrated 10-yr biochemical recurrence (BCR)-free survival rates of 28–59% with acceptable oncological outcomes [8–12]. However, these series primarily consisted of single-center cohorts and patients who underwent surgery before 2013, raising concerns about the generalizability of the findings to contemporary clinical practice.

To address these gaps in knowledge, we conducted a large multicenter study with the objective of assessing outcomes for patients managed with initial observation in a relatively contemporary cohort of men with cN0M0 pN+ PCa. The aim of our study was to provide valuable insights into management for this specific patient population and offer evidence that reflects the current clinical practice landscape.

2. Patients and methods

2.1. Study population

Data were retrospectively collected at 18 tertiary referral centers between 2000 and 2021 for men with pN+ PCa at RP with LND and managed with initial observation (no adjuvant treatments). Observation consisted of PSA measurement every 3 mo for the first 2 yr in cases with

undetectable levels. Subsequent PSA measurements after 2 yr of undetectable PSA or in cases with detectable and/or rising PSA were in accordance with institutional and/or physician preference, as was the choice of when to schedule follow-up imaging and/or salvage treatment. Negative preoperative staging (cN0M0) via conventional imaging (multiparametric magnetic resonance imaging and/or computed tomography [CT] and a bone scan) was a mandatory inclusion criterion. Men with preoperative nodal uptake on prostate-specific membrane antigen (PSMA) and/or choline positron emission tomography (PET)/CT but negative conventional imaging were not excluded (n = 40). We excluded patients undergoing salvage RP, those who received RT or other treatment before surgery, RP cases performed before 2000, and patients with missing data for postoperative follow-up, preoperative PSA, or preoperative staging.

2.2. Variable definitions

The following definitions were used for oncological outcomes: (1) PSA persistence: PSA ≥0.1 ng/ml at 6 wk after RP; (2) BCR: PSA ≥0.2 ng/ml and two consecutive rises; (3) systemic progression/recurrence: lymph-node/bone/visceral progression of disease on imaging; (4) exit from observation: receipt of any salvage treatment (RT and/or ADT and/or salvage LND); and (5) castration-resistant PCa: three consecutive rises in PSA 1 wk apart resulting in two 50% increases over the nadir, and PSA >2 ng/ml despite castrate serum testosterone. LND template definitions were as follows: (1) limited, if only the obturator nodes were removed; (2) extended limited, if the external iliac and obturator nodes were removed; (3) extended, if at least the external iliac, internal iliac, obturator, and presacral nodes were removed; and (4) retroperitoneal, if the retroperitoneal nodes were removed.

2.3. Study outcomes

The primary outcome was assessment of initial observation as a management strategy for men with pN+ PCa in terms of systemic progression and BCR-free survival. Secondary outcomes included evaluation of overall survival (OS), cancer-specific survival (CSS), the preferred management strategy on exit from surveillance, and possible factors predicting exit from surveillance and oncological outcomes.

2.4. Statistical analysis

Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). For univariable analyses, a Wilcoxon-Mann-Whitney or Kruskal-Wallis test was used for continuous variables, and a χ^2 or Fisher's test for categorical variables, as appropriate. Survival curves were constructed using the Kaplan-Meier method. Multivariable models were constructed using significant variables from a priori covariates known to be associated with the study outcomes. To overcome possible problems of overfitting in the estimation model for mortality risk, stepwise iterative techniques were used to select the combination of covariates that best explained the probability of the event.

Table 1 – Patient characteristics

Parameter	Result
Median age, yr (IQR)	65.8 (60.3–70.0)
ASA score, *n* (%)	
1	58 (14.4)
2	302 (74.7)
3	43 (10.6)
4	1 (0.3)
Median PSA, ng/ml (IQR)	10.1 (6.6–18.0)
Imaging results, *n* (%)	
Negative	183 (42.1)
Positive prostate	212 (48.7)
Nodes (PET)	3 (0.7)
Prostate and nodes (PET)	37 (8.5)
RP approach, *n* (%)	
Open	106 (22.7)
Laparoscopic	24 (5.1)
Robotic	338 (72.2)
Degree of nerve-sparing, *n* (%)	
None	254 (56.2)
Unilateral	96 (21.2)
Bilateral	102 (22.6)
ISUP grade group, *n* (%)	
1	4 (0.9)
2	55 (11.8)
3	146 (31.3)
4	94 (20.2)
5	167 (35.8)
pT stage, *n* (%)	
pT2	75 (16.0)
pT3a	142 (30.3)
pT3b	246 (52.6)
pT4	5 (1.1)
Positive surgical margin, *n* (%)	200 (42.6)
Lymphadenectomy template, *n* (%)	
Limited	26 (5.6)
Extended limited	145 (31.1)
Extended	278 (59.7)
Retroperitoneal	17 (3.6)
Median number of nodes removed, *n* (IQR)	20.0 (14.0–28.0)
Median number of positive nodes, *n* (IQR)	1.0 (1.0–3.0)
Number of positive nodes, *n* (%)	
1	253 (55.1)
2	91 (20.1)
≥3	115 (25.4)
Laterality of positive nodes, *n* (%)	
Unilateral	252 (67.2)
Bilateral	123 (32.8)
Positive node sites, *n* (%)	
Obturator	113 (42.0)
External iliac	72 (26.8)
Internal iliac	62 (23.0)
Preprostatic	15 (5.6)
Presacral	5 (1.9)
Pelvic and retroperitoneal	2 (0.7)

ASA = American Society of Anesthesiologists; PSA = prostate-specific antigen; IQR = interquartile range; ISUP = International Society of Urological Pathology; PET = men with negative preoperative conventional imaging but positive preoperative prostate-specific membrane antigen and/or choline positron emission tomography/computed tomography; RP = radical prostatectomy.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 469 patients are listed in Table 1. The median age at RP was 66 yr (interquartile range [IQR] 60–70) and 89.1% of the patients (n = 360) had an American Society of Anesthesiologists score ≤2. Median PSA was 10.1 ng/ml (IQR 6.6–18.0). More than half of the patients had International Society of Urological Pathology (ISUP) grade group ≥4 (56%) and/or pT stage ≥pT3b

(53.7%), and 42.6% had positive surgical margins. LND with at least an extended template was performed in 63.3%. The median number of positive nodes and of nodes removed were 1 (IQR 1–3) and 20 (14–28), respectively. The most frequent positive site was the obturator nodes (42%). No patients received preoperative ADT.

3.2. Oncological outcomes

Overall, 91 patients (19.6%) had PSA persistence after RP. At median follow up of 41 mo (IQR 18–67), 48.5% had developed BCR (median time to BCR 12 mo, IQR 5–33) and 26.5% had experienced systemic progression (median time 28.0 mo, IQR 13–52; Table 2). Salvage treatments were received by 49% (n = 209), including RT (n = 53), RT + ADT (n = 88), ADT (n = 68), and salvage LND (n = 2). Overall, 26 men (5.6%) died, with 15 deaths attributed to PCa.

3.3. Survival analysis

Survival results are presented in Figure 1. The 5-yr rates were 31.7% (95% CI 26.33–37.1%) for BCR-free survival, 66.3% (95% CI 60.4–72.1%) for metastasis-free survival (MFS), 97.7% (95% CI 95.5–99.8%) for CSS, and 95.3% (95% CI 92.4–98.1) for OS.

MFS was lower for cases with PSA persistence ($p < 0.01$) and higher ISUP grade group at RP ($p = 0.01$), but not for a greater number of positive nodes ($p = 0.08$) or higher pT stage ($p = 0.26$; Fig. 2).

Supplementary Figures 1–3 show stratification for BCR-free survival, exit from observation, and OS; the number of pathologically positive nodes was not associated with significantly lower survival rates (all $p > 0.05$).

Table 2 – Oncological results

Parameter	Result
PSA persistence, *n* (%) [a]	91 (19.6)
Biochemical recurrence, *n* (%) [b]	227 (48.5)
Median time to biochemical recurrence, mo (IQR)	12.6 (5.0–32.0)
Continued observation	228 (51.9)
Salvage treatment, *n* (%)	211 (48.1)
Radiotherapy alone	53 (12.1)
Radiotherapy + ADT	88 (20.0)
ADT alone	68 (15.5)
Salvage node dissection	2 (0.5)
Systemic progression, *n* (%)	121 (26.5)
Bone	34 (7.5)
Lung	3 (0.7)
Liver	8 (1.7)
Other visceral site	4 (0.9)
Multiple (bone and visceral)	54 (11.8)
Multiple bone lesions	18 (3.9)
Median time to systemic progression, mo (IQR)	28.0 (13.0–52.0)
Status at follow up, *n* (%)	
Cancer-free	184 (39.3)
Hormone-sensitive prostate cancer	225 (48.1)
CRPC	7 (1.5)
CRPC (second-line therapies)	26 (5.6)
Death, *n* (%)	
Prostate cancer death	15 (3.2)
Non–prostate cancer death	11 (2.3)
Median time to death, mo (IQR)	79.0 (52.0–128.0)

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; IQR = interquartile range; PSA = prostate-specific antigen.
[a] PSA persistence defined first postoperative PSA ≥0.1 ng/ml at least 1 mo after radical prostatectomy.
[b] Biochemical recurrence defined as PSA ≥0.2 ng/ml and two consecutive rises.

3.4. Univariable and multivariable analysis results

Univariable analysis results are listed in Supplementary Table 1. Multivariable analysis results are presented in Table 3.

Multivariable analysis revealed that PSA persistence was an independent predictor of exit from observation (OR 8.5, 95% CI 4.4–16.5) and systemic progression (OR 3.1, 95% CI 1.875–5.172). No other significant variables were found with the exception for age, which was a predictor of exit from observation (OR 0.94, 95% CI 0.91–0.98) and systemic progression (OR 0.96, 95% CI 0.93–0.99).

4. Discussion

In this retrospective observational multicenter study, we assessed oncological outcomes for patients who had positive nodes at RP after initial negative staging via conventional imaging and managed with initial observation. To the best of our knowledge, this is the largest multicenter study detailing previously unpublished and contemporary data on initial expectant management in this setting [2]. Several findings are of interest.

First, node-positive PCa has excellent medium-term outcomes when managed with initial observation. We found that at 5 yr, approximately one in three men on initial observation did not have BCR, and cancer-related death was a rare event. While our BCR and metastasis rates are in line with previous findings from older series, the high CSS probably reflects therapeutic improvements in recent years [2,10,13]. Survival and overall outcomes are likely to further improve given the recent advantages observed for combination therapies in comparison to ADT alone in the high-risk BCR setting [14].

Second, the number of positive nodes was not predictive of survival. This contrasts with previous studies in which the number of positive nodes was a good predictor of oncological control [2]. The number of patients, limited follow-up, and therapeutic improvements in PCa management may partly explain these differences. Similarly, other relevant variables, including ISUP grade at RP and pT stage, were not always independent predictors of oncological outcomes.

Third, PSA persistence was the most important factor predicting BCR, observation failure, and systemic progression. While PSA persistence is a well-known negative prognostic factor in PCa after surgery [4,5], assessment in the context of pN+ disease has been evaluated in very few studies [2,15]. Nonetheless, models for prognostic prediction do not consider PSA persistence in clinical decision-making [10,16]. Similarly, studies investigating the role of observation for pN+ PCa usually lack patients with PSA persistence [10,13]. The proportion of men with postoperative PSA >0.1 ng/ml was high in our series at approximately one in five. Despite the paucity of PSA persistence data for pN+ disease, this rate is in line with a recent series detailing outcomes of initial observation and early salvage versus adjuvant RT for

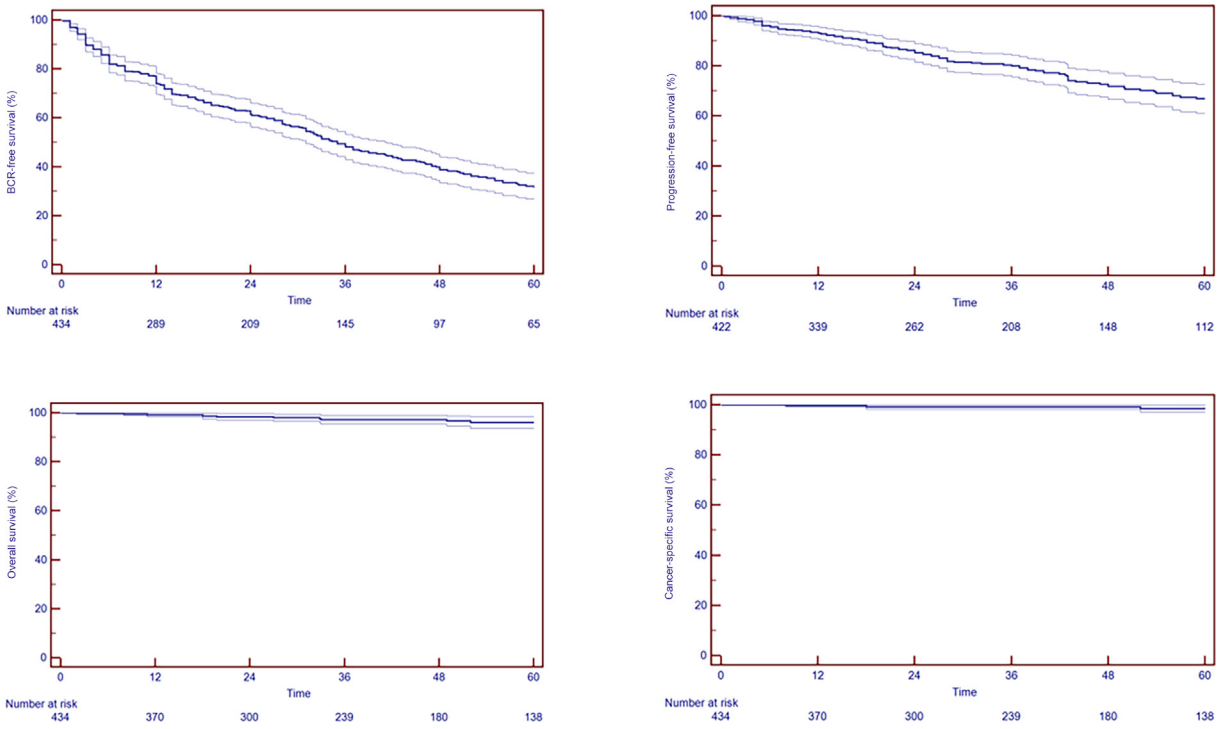

Fig. 1 – Survival results. (A) BCR-free survival, (B) systemic progression–free survival, (C) overall survival, and (D) cancer-specific survival. BCR = biochemical recurrence.

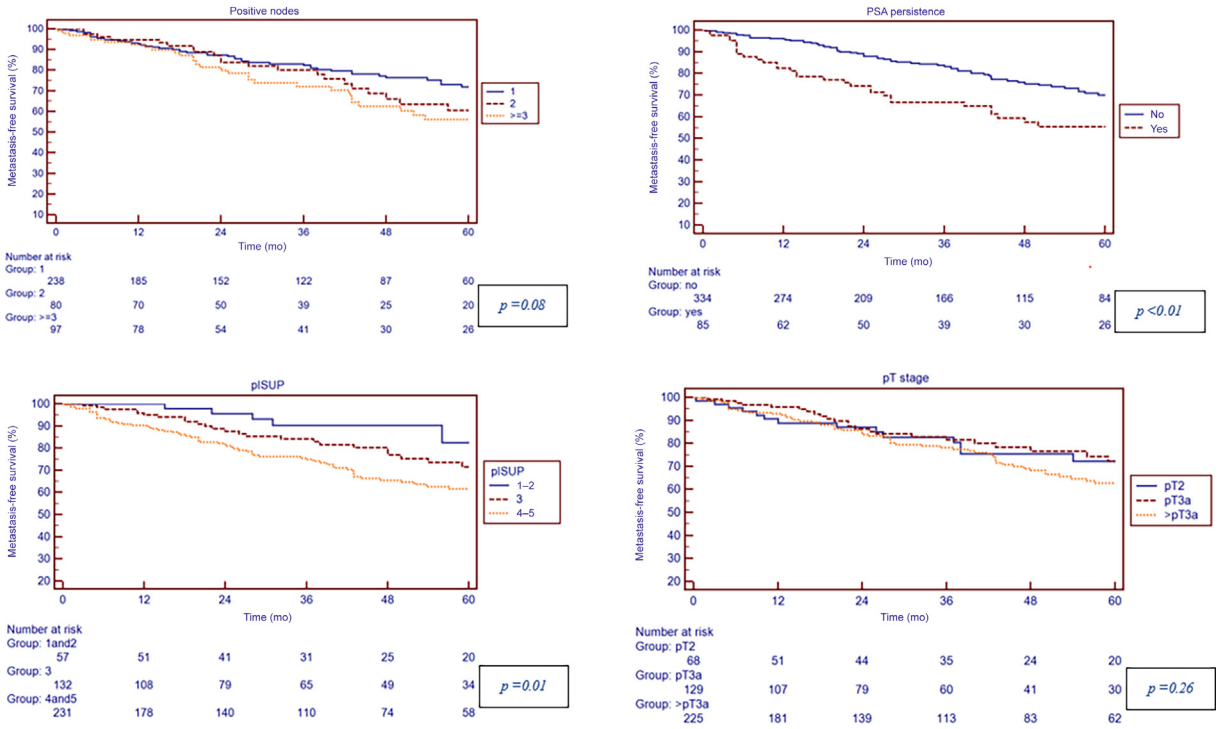

Fig. 2 – Kaplan-Meier curves for the probability of 5-yr metastasis-free survival stratified by (A) the number of positive nodes, (B) PSA persistence, (C) pathological ISUP grade, and (D) pT stage. Estimated survival rates by stratification factor are presented in the Supplementary material. ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.

pN+ disease [17]. Immune surveillance may cause nodal micrometastasis to enter a quiescent state of "tumor dormancy" [18]. A better understanding of the impact of initial observation on disease natural history in this specific subgroup of patients is needed. However, PSA persistence was associated with an eightfold higher probability of exiting

Table 3 – Multivariable analysis results

Parameter	Odds ratio (95% confidence interval) [a]			
	EOB	SP/R	BCR	Death
Age	**0.944 (0.914–0.975)**	**0.956 (0.925–0.989)**		
Pre-RP PSA			1.007 (0.997–1.017)	1.027 (1.013–1.041)
pISUP				
1–2	Reference	Reference	Reference	
3	1.342 (0.650–2.772)	1.146 (0.514–2.553)	0.800 (0.431–1.486)	
4–5	**2.015 (1.006–4.036)**	1.893 (0.896–3.998)	1.116 (0.617–2.019)	
pT stage				
pT2	Reference		Reference	
pT3a	0.669 (0.350–1.278)		0.725 (0.411–1.278)	
≥pT3b	1.577 (0.861–2.887)		1.501 (0.871–2.589)	
Positive nodes				
1 node	Reference	Reference		
2 nodes	0.915 (0.523–1.599)	1.231 (0.695–2.179)		
≥3 nodes	**0.571 (0.334–0.976)**	1.025 (0.599–1.755)		
PSA persistence	**8.529 (4.429–16.425)**	**3.114 (1.875–5.172)**		1.128 (0.335–3.799)

BCR = biochemical recurrence after surgery; EOB = exit from observation; pISUP = pathological International Society of Urological Pathology grade; PSA = prostate-specific antigen; RP = radical prostatectomy; SP/R = systemic progression or recurrence.
[a] Results in bold font are statistically significant.

from observation and a threefold higher probability of systemic progression. Hence, initial observation for men with pN+ PCa and postoperative PSA persistence may not be the optimal management strategy for the majority of these cases.

Fourth, this study offers a snapshot of contemporary use of observation at several referral centers. In the present series, one in four men initially managed with observation had three or more positive nodes, more than half had ISUP ≥4 and/or pT stage ≥3b, and 43% had positive surgical margins. An older cohort from the USA had slightly lower rates of adverse pathological findings: 22% had three or more positive nodes, 50% had ISUP ≥4, and 37% had positive surgical margins [10]. Similarly, less recent data from Europe also show slightly less aggressive features, with rates of 21.6%, 32.3%, 64%, and 42% reported for three or more positive nodes, ISUP ≥4, pT stage ≥3b, and positive margins, respectively [13]. On the one hand, these findings and the relatively high rates of PSA persistence in our cohort may reflect a trend towards expanding initial observation indications for cN0M0 pN+ disease in comparison to previous series. On the other hand, these differences, together with the use of novel and more sensitive imaging modalities (PET PSMA), may partly explain the lower MFS despite similar rates of BCR and, notably, high OS and CSS.

Fifth, RT was the preferred salvage strategy and was delivered in almost three-quarters of patients with recurrence needing treatment. Conversely, ADT was used in a minority. This reflects results from a recent survey among mainly European urologists, the majority of whom stated that ADT is not their standard of care for patients with pN + disease [6].

Sixth, with the availability of more sensitive imaging in the BCR setting (PET PSMA), clinicians may favor expectant management until the location of the recurrence has been visualized instead of risk-based suspicions and decisions on salvage therapy [6].

From a clinical perspective, we confirmed previous findings suggesting that initial observation is a feasible and safe option in pN+ cN0M0 PCa. Certainly, as advocated by our group and others, personalized management remains key in pN+ PCa, as no approach fits all patients [2,4,5,10,17]. Among those experiencing systemic recurrence, the median time to metastasis was slightly longer than 2 yr. Whether this subgroup of patients may have benefitted from upfront adjuvant treatment to prevent systemic spread or micrometastatic disease already present at the time of surgery remains to be understood [17]. In this context, men with PSA persistence after RP are at higher risk of surveillance failure, have worse outcomes, and may be good candidates for more aggressive upfront management. Efforts must be made to better define risk categories for men with pN+ disease. The majority of men with a low disease burden may be managed with curative-intent treatment as for high-risk nonmetastaic PCa, and a significant proportion will not need any additional treatment [7]. Conversely, men with worse disease characteristics may have a prognosis closer to that for oligometastatic PCa and could possibly benefit from adjuvant active treatment and/or systemic therapies [5].

From a research perspective, the high and improved CSS and OS rates should be kept in mind when planning future studies for pN+ disease, as the low number of events is likely to hamper survival as a primary outcome, even over medium-term follow-up. Hence, other surrogate endpoints such as systemic progression should be preferred. In addition, despite the lack of level 1 evidence, ADT was not the salvage treatment most frequently used; salvage RT with or without ADT was the preferred approach [2]. Again, future studies are urgently needed to support and clarify the role of adjuvant RT and the usefulness of adding ADT.

Our study has some limitations. First, it is a retrospective analysis. The multicenter nature probably introduced heterogeneity, as no predefined management protocols were shared among the institutions. Nonetheless, no standardized recommendations for pN+ management exist and the high number of centers involved is in our view a strength that allows a snapshot of clinical practice in some European and US referral centers. The number of PCa deaths was relatively low, which is probably related to the medium-term rather than long-term follow-up. Nonetheless, median follow-up remains sufficient to hypothesize

an improvement in oncological outcomes in comparison to older series.

5. Conclusions

Our study shows that initial observation in the management of pN+ cN0M0 PCa appears to be feasible and has excellent survival in the intermediate term. Patients with worse disease features including PSA persistence have a higher likelihood of recurrence and progression and may be candidates for more aggressive upfront management. Future studies, possibly RCTs, should be carried out for this patient subgroup to confirm the appropriateness of initial observation and early salvage treatments versus adjuvant options.

Author contributions: Giancarlo Marra 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.

Study concept and design: Marra, Gandaglia.
Acquisition of data: All authors.
Analysis and interpretation of data: Marra, Gandaglia.
Drafting of the manuscript: Marra, Gandaglia.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.06.016.

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