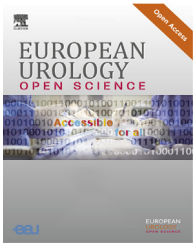
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



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

Giancarlo Marra [a,], Federico Lesma [a], Gabriele Montefusco [a], Claudia Filippini [a], Jonathan Olivier [b], Andres Affentranger [c], Josias Bastian Grogg [c], Thomas Hermanns [c], Luca Afferi [d], Christian D. Fankhauser [d], Agostino Mattei [d], Bartosz Malkiewicz [e], Simone Scuderi [f,g], Francesco Barletta [f,g], Sebastian Gallina [h], Alessandro Antonelli [h], Fabio Zattoni [i], Fabrizio Dal Moro [i], Wever Lieke [j], Timo Soeterik [j], Roderick C.N. van den Bergh [j], Pawel Rajwa [k], Shahrokh F. Shariat [k], Lara Rodriguez-Sanchez [l], Rossella Nicoletti [m,n], Riccardo Campi [m,n], Mohamed Ahmed [o], R. Jeffrey Karnes [o], Michael Ladurner [p], Isabel Heidegger [p], Alberto Briganti [f,g], Paolo Gontero [a], Giorgio Gandaglia [f,g], on behalf of the Young Academic Urologists Prostate Cancer Working Group*

[a] *Division of Urology, Department of Surgical Sciences, University of Turin and Città della Salute e della Scienza, Turin, Italy; ;* [b] *Department of Urology, Lille University Hospital, Lille, France; ;* [c] *Department of Urology, University Hospital Zürich, Zurich, Switzerland; ;* [d] *Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland; ;* [e] *University Center of Excellence in Urology, Department of Minimally Invasive and Robotic Urology, Wroclaw Medical University, Wroclaw, Poland; ;* [f] *Unit of Urology/Division of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; ;* [g] *Vita-Salute San Raffaele University, Milan, Italy; ;* [h] *Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; ;* [i] *Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; ;* [j] *Department of Urology, St. Antonius Hospital, Utrecht, The Netherland; ;* [k] *Department of Urology, Comprehensive Cancer Center, Vienna, Austria; ;* [l] *Department of Urology, Institut Mutualiste Montsouris, Paris, France; ;* [m] *Unit of Urological Robotic Surgery and Renal Transplantation, Careggi Hospital, University of Florence, Florence, Italy; ;* [n] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; ;* [o] *Department of Urology, Mayo Clinic, Rochester, MN, USA; ;* [p] *Department of Urology, Medical University Innsbruck, Innsbruck, Austria*

Article info

Article history:
Accepted June 24, 2024

Associate Editor:
Roderick van den Bergh

Keywords:
Prostate cancer
Negative conventional imaging
Positive lymph nodes
Observation
Salvage therapies

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

* Corresponding author. Department of Urology, San Giovanni Battista Hospital, Città della Salute e della Scienza and University of Turin, C.so Bramante 88/90, 10100 Turin, Italy. Tel. +39 011 633 5574; Fax: +39 011 633 5705.
E-mail address: giancarlo.marra@unito.it (G. Marra).

https://doi.org/10.1016/j.euros.2024.06.016
2666-1683/© 2024 Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.

© 2024 Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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

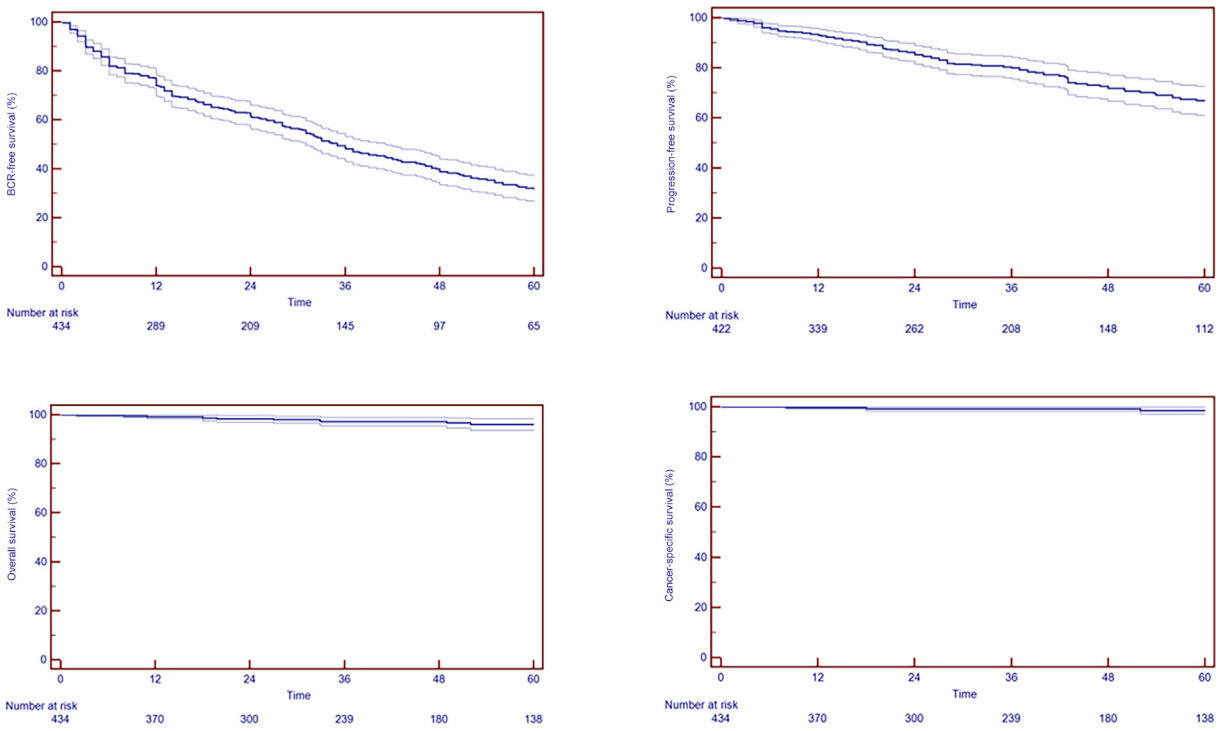


Fig. 1 – Survival results. (A) BCR-free survival, (B) systemic progression–free survival, (C) overall survival, and (D) cancer-specific survival. BCR = biochemical recurrence.

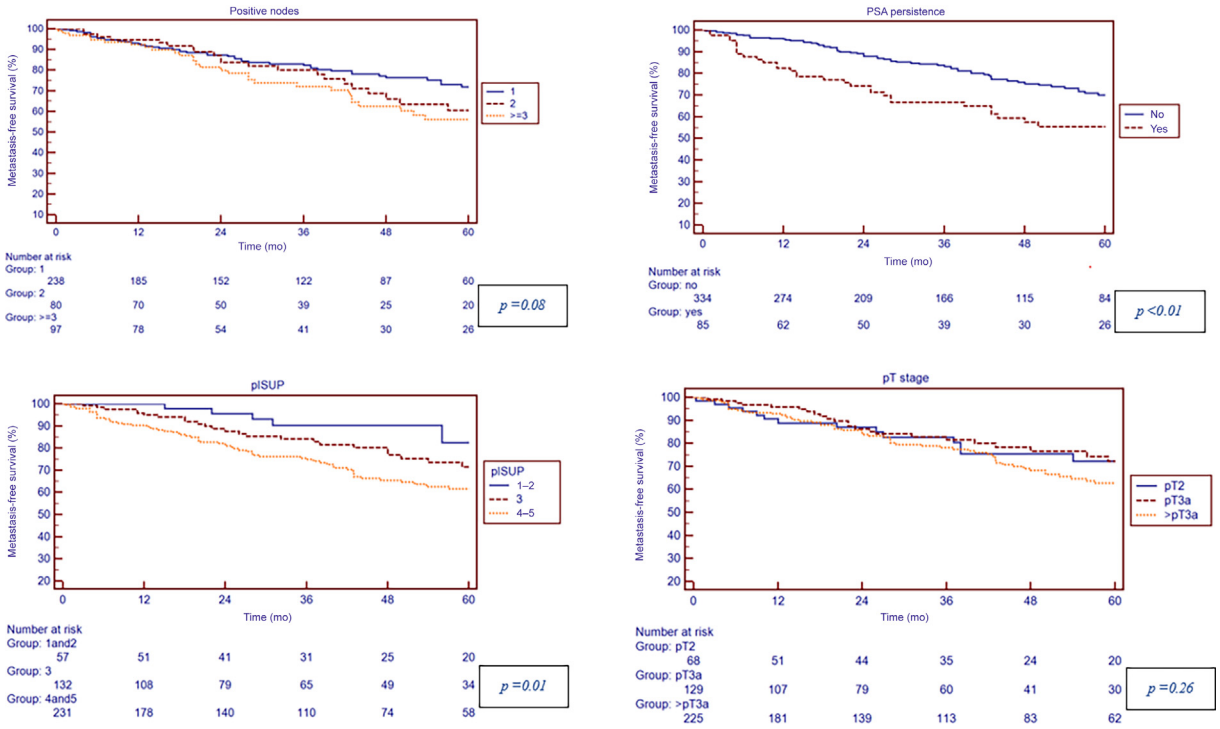


Fig. 2 – Kaplan-Meier curves for the probability of 5-yr metastasis-free survival stratified by (A) the number of positive nodes, (B) PSA persistence, (C) pathological ISUP grade, and (D) pT stage. Estimated survival rates by stratification factor are presented in the Supplementary material. ISUP = International 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.
Statistical analysis: Filippini.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: All authors.
Other: None.

Financial disclosures: Giancarlo Marra certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

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

Colloboration authors

William Berchiche [q], Guillaume Ploussard [r,s], Peter Chiu [t], Charles Dariane [u], Ignacio Puche-Sanz [v], Kamil Kowalczyk [w], Alberto Bianchi [x], Alessandro Magli [y], Fabrizio Tonetto [y], Matteo Facco [z]

[q] *Department of Urology, Marseille North Hospital, Marseille, France;* [r] *Department of Urology, La Croix du Sud Hospital, Toulouse, France;* [s] *Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse, France;* [t] *SH Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China;* [u] *Department of Urology, Hôpital Européen Georges-Pompidou, AP-HP, Paris University, Paris, France;* [v] *Department of Urology, Bio-Health Research Institute, Hospital Universitario Virgen de las Nieves, University of Granada, Granada, Spain;* [w] *University Center of Excellence in Urology, Department of Minimally Invasive and Robotic Urology, Wroclaw Medical University, Wroclaw, Poland;* [x] *Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy;* [y] *Radiation Oncology, Azienda Sanitaria-Universitaria Friuli Centrale, Udine, Italy;* [z] *Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy*

References

[1] Laine C, Gandaglia G, Valerio M, et al. Features and management of men with pN1 cM0 prostate cancer after radical prostatectomy and lymphadenectomy: a systematic review of population-based evidence. Curr Opin Urol 2022;32:69–84. https://doi.org/10.1097/MOU.0000000000000946.

[2] Marra G, Valerio M, Heidegger I, et al. Management of patients with node-positive prostate cancer at radical prostatectomy and pelvic lymph node dissection: a systematic review. Eur Urol Oncol 2020;3:565–81. https://doi.org/10.1016/j.euo.2020.08.005.

[3] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9. https://doi.org/10.1016/s1470-2045(06)70700-8.

[4] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62. https://doi.org/10.1016/j.eururo.2020.09.042.

[5] Gillessen S, Bossi A, Davis ID, et al. Management of patients with advanced prostate cancer. Part I: intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: report of the Advanced Prostate Cancer Consensus Conference 2022. Eur Urol 2023;83:267–93. https://doi.org/10.1016/j.eururo.2022.11.002.

[6] Sacco M, Gandaglia G, Aas K, et al. The changing face of cN0M0 prostate cancer being found with pN+ after surgery in the contemporary era: results of an international European survey on disease management. Clin Genitourin Cancer 2023;21:416.e1–e10. https://doi.org/10.1016/j.clgc.2022.11.012.

[7] Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020;396:1422–31. https://doi.org/10.1016/S0140-6736(20)31952-8.

[8] Mandel P, Rosenbaum C, Pompe RS, et al. Long-term oncological outcomes in patients with limited nodal disease undergoing radical prostatectomy and pelvic lymph node dissection without adjuvant treatment. World J Urol 2017;35:1833–9. https://doi.org/10.1007/s00345-017-2079-4.

[9] Fleischmann A, Schobinger S, Schumacher M, Thalmann GM, Studer UE. Survival in surgically treated, nodal positive prostate cancer patients is predicted by histopathological characteristics of the primary tumor and its lymph node metastases. Prostate 2009;69:352–62. https://doi.org/10.1002/pros.20889.

[10] Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. Eur Urol 2014;65:20–5. https://doi.org/10.1016/j.eururo.2013.03.053.

[11] Dorin RP, Lieskovsky G, Fairey AS, Cai J, Daneshmand S. Outcomes after radical prostatectomy for patients with clinical stages T1–T2 prostate cancer with pathologically positive lymph nodes in the prostate-specific antigen era. Urol Oncol 2013;31:1441–7. https://doi.org/10.1016/j.urolonc.2012.03.006.

[12] Palapattu GS, Allaf ME, Trock BJ, Epstein JI, Walsh PC. Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term followup. J Urol 2004;172:1860–4. https://doi.org/10.1097/01.ju.0000139886.25848.4a.

[13] Tilki D, Preisser F, Tennstedt P, et al. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. BJU Int 2017;119:717–23. https://doi.org/10.1111/bju.13679.

[14] Freedland SJ, De Giorgi U, Gleave M, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with

rising PSA after local therapy: EMBARK study design. BMJ Open 2021;11:e046588. https://doi.org/10.1136/bmjopen-2020-046588.
[15] Bianchi L, Nini A, Bianchi M, et al. The role of prostate-specific antigen persistence after radical prostatectomy for the prediction of clinical progression and cancer-specific mortality in node-positive prostate cancer patients. Eur Urol 2016;69:1142–8. https://doi.org/10.1016/j.eururo.2015.12.010.
[16] Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014;32:3939–47. https://doi.org/10.1200/JCO.2013.54.7893.
[17] Tilki D, Chen MH, Wu J, Huland H, Graefen M, D'Amico AV. Adjuvant versus early salvage radiation therapy after radical prostatectomy for pN1 prostate cancer and the risk of death. J Clin Oncol 2022;40:2186–92. https://doi.org/10.1200/JCO.21.
[18] Briganti A, Passoni NM, Abdollah F, Nini A, Montorsi F, Karnes RL. Treatment of lymph node–positive prostate cancer: teaching old dogmas new tricks. Eur Urol 2014;65:26–8. https://doi.org/10.1016/j.eururo.2013.07.003.