

Title: Features and management of men with pN1 cM0 prostate cancer after radical prostatectomy and lymphadenectomy: a systematic review of population-based evidence.

Authors:

Charles Laine¹, Giorgio Gandaglia², Massimo Valerio³, Isabel Heidegger⁴, Igor Tsaour⁵, Jonathan Olivier⁶, Francesco Ceci⁷, Roderick C.N. van den Bergh⁸, Alexander Kretschmer⁹, Constance Thibault¹⁰, Peter K Chiu¹¹, Derya Tilki¹², Veeru Kasivisvanathan¹³, Felix Preisser¹⁴, Fabio Zattoni¹⁵, Christian Fankhauser¹⁶, Claudia Kesch¹⁷, Ignacio Puche-Sanz¹⁸, Marco Moschini², Benjamin Pradere¹⁹, Guillaume Ploussard²⁰, and Giancarlo Marra^{1,21,22} on behalf of the EAU-YAU Prostate Cancer Working Party

Institutions

- 1 Department of Urology, Institut Mutualiste Montsouris, Paris, France
- 2 Department of Urology, San Raffaele Hospital and Scientific Institute, Milan, Italy
- 3 Department of Urology, Lausanne University Hospital, Lausanne, Switzerland
- 4 Department of Urology, Medical University Innsbruck, Innsbruck, Austria
- 5 Department of Urology and Pediatric Urology, Mainz University Medicine, Mainz, Germany
- 6 Department of Urology, University Hospital Lille, Lille, France
- 7 Department of Nuclear Medicine, European Institute of Oncology, Milan, Italy
- 8 Department of Urology, Antonius Hospital, Utrecht, The Netherlands
- 9 Department of Urology, Ludwig-Maximilians-University of Munich, Munich, Germany
- 10 Department of Medical Oncology, Hôpital Européen Georges-Pompidou, Paris, France
- 11 Division of Urology, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China
- 12 Department of Urology, Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
- 13 Department of Urology, University College London, London, UK
- 14 Department of Urology, Goethe University, Frankfurt, Germany
- 15 Urology Unit, Santa Maria della Misericordia University Hospital, Udine, Italy
- 16 Department of Urology, Cantonal Hospital of Lucerne, Lucerne, Switzerland

17 West German Cancer Center; Department of Urology, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany

18 Department of Urology, Bio-Health Research Institute, Hospital Universitario Virgen de las Nieves, University of Granada, Avenida de las Fuerzas Armadas 2, 18014 Granada, Spain

19 Department of Urology, Medical University of Vienna, Vienna, Austria

20 Department of Urology, La Croix du Sud Hospital, Toulouse, France and Institut Universitaire du Cancer Toulouse – Oncopole, Toulouse, France

21 Department of Urology, San Giovanni Battista Hospital, University of Turin, Turin, Italy

22 Department of Urology and Clinical Research Group on Predictive Onco-Urology, APHP, Sorbonne University, Paris, France

Corresponding Author:

Charles Lainé

Email: charleslaine@hotmail.fr

Department of Urology
Institut Mutualiste Montsouris
42 boulevard Jourdan
75014 Paris
France

Abstract:

Introduction: Up to 15% of prostate cancer (PCa) patients harbour lymph node invasion (pN+) at radical prostatectomy (RP) plus lymph node dissection. Nonetheless, the optimal management strategy in this setting is not well characterized so far. We aimed to investigate the features and optimal management of pN+ cM0 PCa according to registry based studies.

Methods: We performed a systematic review in January 2020 following the PRISMA criteria - Web (Embase, Medline and others) and manual search.

Results: Overall, n=13 studies were identified. In population-based studies, the pN+ prevalence was 2.6% (25,114/954,416). Management strategies comprised 13,536 men undergoing observation, 11,149 adjuvant androgen deprivation therapy (aADT), 7,075 adjuvant radiotherapy (aRT) +aADT and 705 aRT. Baseline features showed aggressive PCa in the majority of men (53.1% Gleason \geq 8; 85.1% pT \geq 3; 50.1% PSM). At a median follow-up ranging from 48 to 134 months, Cancer-related death was 5% and overall mortality 16.6%. aADT and aRT alone had no CSS or OS advantages over observation only and over not performing aRT, respectively. aADT plus aRT yielded a survival benefit compared to Observation and aADT, which in one study, were limited to certain intermediate-risk categories. Age, Gleason score, Charlson score, PSM, pathological stage and number of positive nodes, but not PSA, were most relevant prognostic factors.

Conclusions: pN+ after RP is not frequent. Despite aggressive PCa features, oncological control and survival seem favorable. Different management strategies comprise observation, aRT and/or aADT with more aggressive strategies not always yielding an undiscriminated benefit.

Keywords:

Prostate cancer
Radical prostatectomy
Population based studies
Positive nodes
Lymph node

Key points

1 - The optimal management of pN+ cM0 PCa after radical prostatectomy remains unclear. We performed a systematic review of population based studies including n=13 studies. pN+ after RP is not frequent with a prevalence of 2.6% (25,114/954,416).

2 - Despite presence of aggressive PCa in the majority of men, oncological control and survival seem favorable. At a median follow-up ranging from 48 to 134 months, Cancer-related death was 5% and overall mortality 16.6%.

3 - Different management strategies are available comprising observation, aRT and/or aADT, with more aggressive strategies not always yielding an undiscriminated benefit. Age, Gleason score, Charlson score, PSM, pathological stage and number of positive nodes, but not PSA, were most relevant prognostic factors.

Manuscript

1. Introduction:

Pathologically node positive prostate cancer (PCa) is not an uncommon finding with up to more than one out of ten men being diagnosed with positive nodes (pN+) at radical prostatectomy (RP) (1–3). However, to date, only one randomized controlled trial (RCT) was performed in the context of pN1M0 PCa patients. Results are hardly generalizable to the whole pN1 category. First, as the majority of patients had high-volume disease. Second, as the enrollment took place as far back as in the pre-PSA era (4). This trial showed important survival benefits of immediate androgen deprivation therapy (ADT) versus observation. Hence, current recommendations remain mainly based on these findings. Nonetheless, several retrospective series suggested pN+ men should be considered as a multifaceted and heterogeneous rather than a single and unique group. Namely, survival is influenced by several factors including number of positive nodes, disease extension, margin status after RP, PSA kinetics and other variables (4–6).

As evidence on the optimal pN1 PCa management remains weak and contrasting, we recently performed a systematic review of single- and multi-institutional series to summarize the optimal management of these men (7). In the era of precision and patient-targeted medicine it is thus

advisable to propose a risk-based strategy from the spectrum of treatment options. Those with less aggressive disease may possibly undergo initial expectant management to improve quality of life without jeopardizing oncological results; those at a more advanced stage, on the contrary may require upfront aggressive adjuvant local and/or systemic treatments to improve survival; those in between may undertake intermediate and risk-adapted strategies. Amongst the limitations were the majority of series being retrospective, the relatively low data quality and some cohorts being analyzed multiple times and thus reducing the number of men from approximately 12,000 to 4,067, if excluding multiple entry data (7).

Thus, we thought it was relevant to verify whether large registry-based evidence mirrors or not multi- and single-institutional series. We performed a systematic review of population based studies investigating the baseline features, the optimal management and prognostic factors of M0 PCa yielding pN1 disease at RP and lymphadenectomy (LAD).

2. Methods

2.1 Search Strategy

A web search was systematically performed complying with the PRISMA criteria on January 28th 2020 using the Ovid platform and comprising AMED (Allied and Complementary Medicine), HMIC (Health Management Information Consortium), Embase and Medline. No time restrictions were applied. The following search strategy was used: (“pN1” OR “pN+” OR (“positive” AND “lymph node”)) AND “prostate cancer” AND “radical prostatectomy”. Web Search was implemented with manual search (authors consultation and references of web-search included articles). Two authors (C.L.; G.M.) screened independently all abstracts and full texts. Disagreements were resolved through consultation with a third author (G.G.) or consensus.

2.3 Criteria

We considered full-text publications using Roman alphabet. Only registry-based studies were included. Inclusion criteria were: i) pathologically proved pN1 disease following primary RP and LAD; ii) cM0 status; iii) having oncological outcomes of pN1 patients stratified according to different treatment strategies or the role of prognostic factors assessed at multivariate analysis and adjusted for treatment strategy. Studies with cN+ patients only or not providing at least baseline features of the pN+ group or not excluding cM+ patients were excluded. Analysis using the same registry of previously published works were included.

2.3 Aim

Our aim was to evaluate the registry-based evidence concerning the baseline features and management of pN1 cM0 patients after RP and LAD. Prognostic factors to stratify pN1 disease, possibly guiding PCa management were also assessed.

2.4 Outcome measures and data extraction

The Quality Appraisal tool for case series using a Modified Delphi technique was used for bias evaluation, as previously described (7)(28). The Clavien-Dindo system was used to classify complications and adhering to EAU Guidelines, when available (9).

3. Results

3.1 Features of Included Articles

The PRISMA flowchart is detailed in **Figure 1**. We included n=13 articles - patients who received surgery from 1982 up to 2015 (**Table 1**). The majority of the studies were US based (n=11) and used either the SEER (n=7) or NCDB (n=5) registry. All cohorts were retrospective. The analysis provided information on the outcomes of different management strategies and/or prognostic factors for 43,982 pN+ patients. pN+ overall prevalence across the studies was 2.6%, ranging from 1.78 to 6.08%). Primary endpoints included overall survival/mortality in the majority (n=9).

The most frequently stated exclusion criteria comprised cM+ patients (n=11), neo-adjuvant treatments (n=4) and previous radiotherapy (n=4). None of the studies reported the use of PSMA-PET or choline PET for upfront patient staging but all rather used bone scan and/or CT scan. The quality of the studies was overall low (**Supplementary Material 2**).

3.2 Baseline Patients Features

Baseline features of the included studies are displayed in **Table 2**.

The final analysis included 13,536 men undergoing observation, 11,149 aADT alone, 7,075 adjuvant radiotherapy (aRT) plus aADT and 705 aRT alone.

None of the included studies stated the template of lymphadenectomy being performed. Median number of nodes removed, not being reported by n=2 cohorts (10,11), ranged between 7 and 11 but was >9 only in n=2 cohorts. The median number of positive nodes was 1 in all the cohorts reporting it and in all treatment subgroups with the exception of one cohort undergoing aADT+aRT, yielding a median of 2 positive nodes (12). Men with one positive node only were always the majority irrespective of the positive node management, ranging from 76.6% of men undergoing aRT alone to 52.3% of those undergoing aADT alone.

Mean/median age ranged from 60 to 63 years with the exception of one study with a mean age of 70 yrs respectively (11). Comorbidity index was low in the majority of patients, with Charlson score being 0 in 81.3% of men. Median PSA ranged between 9 and 11 ng/mL. Gleason score was rarely of low grade (2.1%) and most frequently showed aggressive PCa with 53.1% having a Gleason score ≥ 8 . Similarly, pT stage at radical prostatectomy revealed a non-organ confined pathology in 85.1%, with the highest percentage (90.1%) in those undergoing aADT plus aRT and lowest (76.4%) in those undergoing observation. Surgical margins were positive in 50.1%, with the highest percentage (64.1%) in those undergoing aADT plus aRT and lowest (39.7%) in those undergoing observation.

3.3 Management Outcomes Patients Features

None of the studies presented details on BCR and local and/or metastatic progression/survival as outcomes with the exception of one study (13) reporting metastases being developed in 18.5% of pN1 men, at a median follow-up of 57 (34–102) months.

Ten studies reported detailed survival and/or effect of different treatment strategies for pN1 (**Table 3**). At a median follow-up ranging from 48 to 134 months cancer-related deaths were 5% (ranging from 2.1 (13) to 9.7% (11,13) and overall mortality 16.6% (ranging from 12.1 (10) to 36.7% (11)). When detailed at ten years, cancer-specific survival (CSS) ranged from 65.1% to 82.1% and overall survival from 72.3 to 73.8%.

Supplementary Material 1 presents a multivariate analysis of the effect of different management strategies on overall and/or cancer-specific survival. aADT was not found to have any benefit in overall survival (10,11,14,15) nor in cancer-specific mortality (11)) compared to observation. Similarly, aRT alone had no survival advantage over observation (14,15). Interestingly one work found advantage of aRT versus no RT (16), but treatment subgroups of those not receiving aRT were not specified. Finally, aADT plus aRT yielded survival benefit compared to observation (10,14,15) and aADT (10,12)) in three and two studies, respectively. In one study aADT plus aRT yielded or not survival advantages depending on patients' risk compared to aADT alone with lower and higher-risk categories not yielding any additional benefit of aRT in addition to aADT and intermediate-risk groups showing survival improvement (17).

3.4 Prognostic Factors

Age (10,14,15), Gleason score (10,12,15) (with the exception of one group (10)), Charlson score (10,12,14,15) (with the exception of one group (12)), and PSM (10,12,14,15) were consistently associated with overall and/or cancer-related survival. Pathological stage and number of positive nodes were generally associated with survival with some studies yielding no significant correlations (10,12,14,15). Finally, PSA and annual income were not associated with survival (10,14) whilst node density was inversely related to cancer-specific survival (16)

Other prognostic factors, including number of retrieved nodes, year of surgery, disease being pathologically extra-nodal, nodal lymph-vascular invasion, PSA persistence, biochemical and or/clinical recurrence were not assessed.

4. Discussion

This article systematically reviewed patients being found with pN+ status after RP and LAD and their management based on cohort studies. Several findings of our work are of potential interest.

First, prevalence of pN+ at RP is relatively low compared to what described previously (3) as only 2% of men were detected with positive nodes at final pathology. This number is also inferior to the 12% rate of PCa presenting with nodal invasion described in the most recent global cancer updates (18). Such a discrepancy between what has been observed in series from tertiary referral centers and what has been reported in population-based studies might be explained by different reasons. The adherence to guidelines recommending to perform a nodal dissection in selected patients who are candidate for surgery is generally low at a population-base level; also, the number of nodes removed, which could be considered as a proxy of the extension of a nodal dissection, is generally lower in population-based studies. As such, the nodal staging in this setting is at least sub-optimal (19); finally, men in the included studies were selected on the basis of their eligibility for RP, which usually excludes cN+ disease and may select a priori lower risk patients (20)

Second, the vast majority of pN+ patients share aggressive PCa features per se, namely, high Gleason scores in more than one in two and extracapsular disease in more than three in four men; margins were positive in approximately one in two patients. Conversely, median PSA was relatively low, never being higher than eleven and only one positive node was detected in the majority of pN+ men, possibly showing non-clinical apparent positive nodes are usually diagnosed at a relatively early stage in PCa natural history.

Third, the long-term survival rates remain high with almost nine out of ten men with pN+ disease being alive at ten years. On the one hand, considering that no men from the last six years were included, outcomes are likely even better in the present era, where several new PCa drugs are available to improve survival (21). The high survival rates mirror evidence of single and multi-institutional studies on pN+ disease. This favors the hypothesis that at least part of node-positive disease does not automatically expose to an evolution to systemic disease which, on the contrary, is associated with poor prognosis (22). Positive PCa lymph nodes should not be indiscriminately considered as the first step in hematogenous spread. Some may represent true solitary lymphatic spread rather than an automatic transition to distant metastatic progression, whilst in others, PCa may be blocked by reduced angiogenesis and immune-control, favoring apoptosis over PCa proliferation, a phenomenon also known as “tumor dormancy” (23,24).

Fourth, the effect of different management strategies was overall contrasting. aADT plus aRT always yielded survival advantages over aADT or observation alone (10,12,14,15). This may suggest stronger upfront treatment improves survival. Nonetheless, when patients were divided in subgroups according to different prognostic categories, lower- and higher-risk groups had no benefit compared to aADT alone. Furthermore, although baseline features of those undergoing observation were likely less aggressive, no advantages were found for aADT or aRT alone compared to observation (10,11,14,15). Hence, some selected patients may undergo initial expectant management. Finally, the strength of registry-based studies was evaluation of overall survival; however, no treatment-related side effects and patients quality of life details were available. This is consistent with what reported in single- and multi-institutional retrospective series (7). As in the context of cancer treatment these are increasingly relevant, it seems reasonable for pN+ men to undergo a risk-adapted strategy with those at a lower risk possibly avoiding immediate radiation and ADT together with their related side effects.

Fifth, we confirmed main prognostic factors in the pN+ context are PCa histology, stage, number of positive nodes and surgical margins, as they likely have a relevant impact on overall survival and on cancer-related survival. On the contrary, PSA is less relevant, perhaps because in the context of early and clinically undetectable extra-prostatic spread, PSA levels are closer to those of localized disease than to a metastatic context. Of note, several prognostic factors, which were investigated by retrospective series, were not investigated in population-based cohorts.

From a clinical perspective our findings confirm the evidence of single and multi-center series suggesting pN+ nodes have an overall relatively favorable high survival, but are a multi-faceted group rather than a single category (7) with the same prognosis. Consequently, treatment choice should be tailored according to a risk- and patient-adapted strategy to maximize the balance between oncological control and side effects. Observation and early adjuvant or salvage treatment seem a reasonable upfront option in many patients with a lower risk whilst upfront adjuvant treatments may yield advantages in those with multiple negative prognostic factors or adverse risk

scores. Modern imaging tools such as PSMA-PET/CT may be used in an expectant management situation, to identify the location of metastasis in an early stage of BCR, and guide salvage therapies.

From a research perspective we implemented previous work from our group claiming for new high-quality evidence in this context. In particular, the sole RCT in pN+ disease included men with a high number of positive nodes (4). This finding does not apply to the current era as the majority of pN+ men have only one cancerous node. Also, we highlighted pN+ disease is a relatively rare finding. Hence, multi-institutional efforts will be key to reach adequate inclusion numbers when envisaging future trials. Our group is currently planning large multi-center collaborations in the field.

Finally, early salvage RT in pN+ patients was never assessed. With the recent evidence from RCTs and meta-analysis detailing no benefit of adjuvant versus early salvage RT for localized high-risk PCa in terms of oncological control, but worse functional results (25,26), population-based and also institutional cohorts should indeed investigate the role of salvage RT in the context of pN+ disease.

Limitations of our work should be kept in mind. The present evidence is low per definition as it derives from retrospective population-based studies. Also, only three registries, all from the US, were used, with several patients being re-analyzed multiple times depending on the years of overlap. Inclusion of men from the eighties and the nineties likely does not reflect contemporary results of pN+ disease; furthermore, none of the studies included men after 2015. Hence, the effect of new imaging modalities, especially of PSMA-PET, which recently proved its superiority in terms of staging compared to conventional imaging, are not accounted for in our work (27).

Nonetheless, data in the present study come from large registries with a generally long follow-up and, compared to institutional series, are not restricted to high-volume centers only, providing additional and complementary information on pN+ disease.

5. Conclusions

Pathologically positive nodes after RP are not frequent and are generally associated with baseline aggressive PCa features. Nonetheless, oncological control and survival seem favorable at an intermediate term. Different management strategies comprise observation, aRT and/or aADT with more aggressive strategies not always yielding an undiscriminated benefit in terms of survival. Different management may thus be tailored accounting for patients and disease prognostic features and/or using available risk stratification tools. Importantly, registry-based evidence is of low level and, for pN+, derives from three registries re-using the same patients cohorts multiple times.

Ethics: Not applicable. The present work is a systematic review of the literature and did not directly involve patients' data.

Conflict of Interest: none to declare.

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

Study concept and design: Lainé, Marra, Gandaglia

Analysis and interpretation of data: Lainé, Marra, Gandaglia

Statistical analysis: Lainé, Marra

Manuscript Draft: Lainé, Marra, Gandaglia

Critical revision of the manuscript: All authors

Tables and Figures Legend

Table 1. Main Features of the included studies. [^]= n=1 paper from US and Italy; SEARCH=Shared Equal Access Regional Cancer Hospital (SEARCH) database - A national registry type; NCDB=National Cancer Database; SEER=Surveillance, Epidemiology and End Results; *=pT3 subtype not specified for n=292; **=pT3 subtype not specified for n=256; ***= pT stage not provided; authors provided data on the cT stage which were not reported in our table; RT= radiotherapy; RP=radical prostatectomy; GS=Gleason Score; E=Excluded; NS=Not Stated.

Table 2. Baseline features of the included studies. Johnstone et al was not included in the table as no baseline info of pN+ patients are provided; ^{^^}= patients not receiving and/or refusing adjuvant radiotherapy (not specified alternative management not specified); ^{'''}= p values not provided; final percentages overall and per treatment group were calculated based on the total number of patients of only the studies reporting the corresponding value;

Table 3. Survival of pN1 patents in the included studies . *=also aADT+aRT vs aADT was calculated: 0.76 (0.63–0.93);

Table 4. Prognostic factors analyzed in the included studies.

Supplementary Material 1. Multivariate analysis detailing the effect of different management strategies on survival. OS=Overall Survival; CSM=Cancer Specific Mortality; CSS=Cancer Specific Survival; *Group 1: 1 to 2 positive nodes and p Gleason score 2–6 (excluded because of the limited number of patients) ; Group 2: 1 to 2 positive nodes, p Gleason score 7–10, pT2/pT3a disease, R0; Group 3: 1 to 2 positive nodes, p Gleason score 7–10, pT3b/pT4 disease, R+
Group 4: 3 to 4 positive nodes
Group 5: > 4 positive nodes.

Supplementary Material 2. Quality Appraisal tool for case series using a modified Delphi technique CI=Competing interests

Figure 1. PRISMA (Preferred Reporting Items of Systematic Review and Meta-Analysis) flowchart. N<100 = less than 100 patients with positive nodes included in final analysis; sRT or sLAD= salvage radiotherapy or salvage lymphadenectomy papers not suitable for inclusion; No outcomes info= not providing informations on oncological outcomes of pN+ patients or not providing oncological outcomes according to pN+ treatment type; No prognostic info= not providing informations on prognostic factors using multivariate analysis including treatment type; Cohort duplicate= studies providing data of cohorts updated in the following years and adding no treatment and/or prognostic information compared to studies with a longer follow up; Registry=studies providing analysis from national or international registries rather than institutional series.

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