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European Association of Urology

Platinum Opinion

Node-positive Nonmetastatic Prostate Cancer: Time to Reconsider Prognostic Staging?

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The current definition of lymph node–positive (LNP) prostate cancer as stage IV disease is driven by the historical paradigm that suggested that the risk of metastasis in patients with LNP cancer was high, minimizing the value of local therapy and leading to the practice of performing pelvic lymph node dissection and abortion of planned prostatectomy if a patient was found to be LNP [1]. However, in contemporary series there has been evidence of acceptable oncologic outcomes and even long-term cures in patients receiving definitive treatment with either surgery or external beam radiation (EBRT) [2–5]. In the radiation cohorts, the survival benefit appears to be approximately 10–20% at both the 5- and 10-yr time points with the addition of EBRT, leading to 5-yr overall survival (OS) of approximately 70% [2,3]. Patients undergoing prostatectomy are generally found to be LNP at the time of their planned surgical resection for presumed localized prostate cancer. The 5-yr OS in this cohort is approximately 80%, and the benefit of adjuvant radiation is of smaller absolute magnitude, adding an absolute benefit of approximately 5–7% to 5-yr OS [4,5]. In comparison, a previous study evaluating patients with M1 disease suggested that even with definitive treatment, 5-yr OS was still only 49% [6].

A previous study evaluating the natural history of LNP prostate cancer after prostatectomy revealed a 65% chance of not having distant metastases at 10 yr after surgery, with predicted 10-yr OS of approximately 60% [7]. In that study, 30% of patients with LNP disease did not experience biochemical failure after prostatectomy, indicating that a proportion of patients with LNP disease can be cured with definitive local therapy. Even though the American Joint Committee on Cancer recently split stage IV into N1M0 as stage IVA and M1 as stage IVB in the 8th edition of the staging manual, such a small change will not sway treatment decisions within the oncologic community. Given the oncologic differences seen, consideration should be given to prognosticating N1M0 as being something less than stage IV, potentially stage III.

To evaluate outcomes in a large cohort of patients, we queried the National Cancer Data Base (NCDB) and identified 75 136 prostate cancer patients who had either LNP nonmetastatic (N1M0) or distant metastatic (M1) disease (Fig. 1). Other variables collected as covariates were Gleason score (53% Gleason $\geq$9), baseline prostate-specific antigen (PSA; median 41.1 ng/ml), and receipt of systemic therapy (73.5% of all patients) with hormones and/or chemotherapy. Receipt of definitive therapy, defined as surgery, EBRT of >60 Gy, or EBRT and brachytherapy (BT), was evaluated. Log-rank tests, Cox proportional hazards models, and χ^2 analyses were used for data analysis.

Rates of definitive therapy receipt were higher in the N1M0 than the M1 group (66.5% vs 5.3%; $p < 0.001$). In the N1M0 group, definitive therapy was with surgery alone (44.2%), EBRT or EBRT + BT (13.2%), or surgery and RT (9.2%). With median follow-up of 28 mo for all patients and 43 mo for survivors, 5-yr OS was higher among N1M0 than M1 patients (71.2% vs 23.1%; $p < 0.001$). On multivariate analysis, M1 patients continued to have worse survival than N1M0 patients (hazard ratio [HR] 1.73; $p < 0.001$; Table 1). Not surprisingly, higher Gleason score and higher baseline PSA were factors associated with worse survival ($p < 0.001$). Receipt of definitive treatment and systemic therapy was associated with better OS (HR 0.39 and 0.87, respectively; $p < 0.001$). Patients with pathologic-only N1M0 disease had better outcomes than those with clinical N1M0 disease (HR 0.64; $p < 0.001$), reflecting the importance of nodal burden and its effect on survival.

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https://doi.org/10.1016/j.eururo.2018.09.017

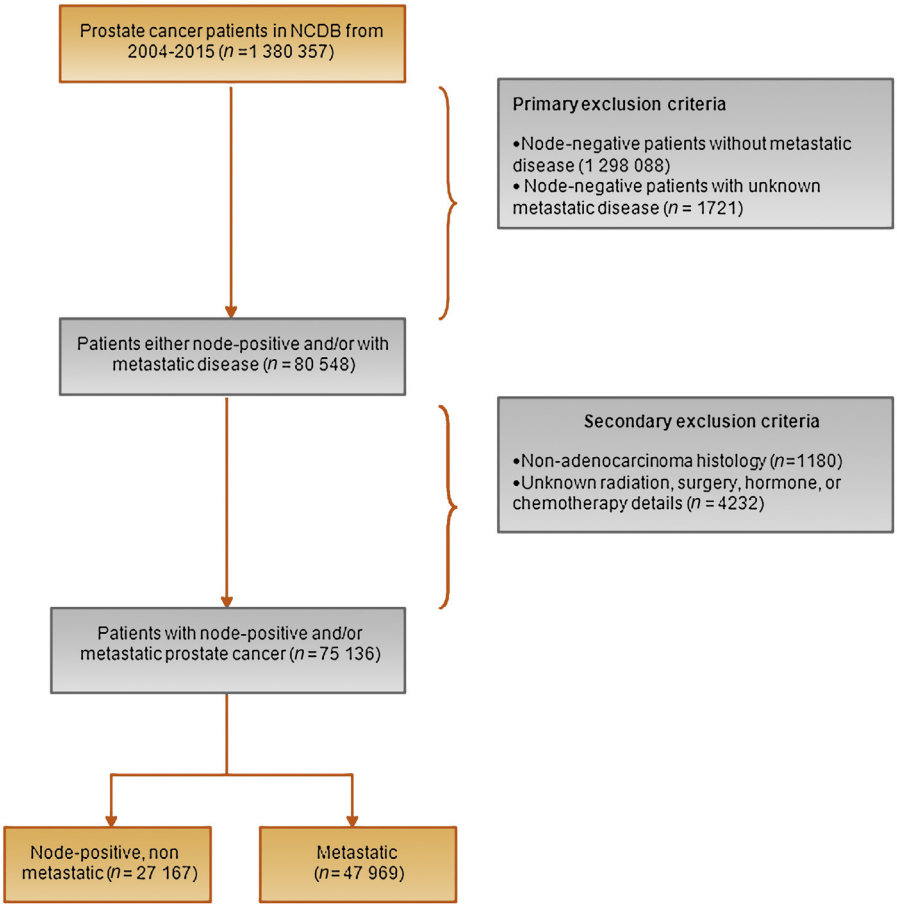

Fig. 1 – Diagram illustrating the exclusion criteria and case selection for the patient cohort from the National Cancer Data Base (NCDB).

Table 1 – Multivariable Cox proportional hazards models for overall survival among 75 136 patients

Significant factors	Patients, *n* (%)	HR (95% CI)	*p* value
Gleason score			
≤ 7	11 663 (15.5)	Reference	
8	10 911 (14.5)	1.20 (1.14–1.25)	<0.001
9	21 256 (28.3)	1.68 (1.61–1.75)	<0.001
10	4073 (5.4)	2.37 (2.24–2.50)	<0.001
Unknown	27 233 (36.2)		
Baseline prostate-specific antigen[a]		1.003 (1.003–1.004)	<0.001
Clinical stage			
cN1M0	12 674 (16.9)	Reference	
pN1M0	14 493 (19.3)	0.64 (0.60–0.69)	<0.001
M1	47 969 (63.8)	1.73 (1.65–1.81)	<0.001
Received definitive treatment			
No	54 673 (72.8)	Reference	
Yes	20 463 (27.2)	0.39 (0.37–0.41)	<0.001
Received systemic therapy			
No	19 887 (26.5)	Reference	
Yes	55 249 (73.5)	0.87 (0.84–0.91)	<0.001

[a] Median 41.1 ng/ml (interquartile range 11.8–98).

From this national data set, approximately one-third of patients with N1M0 prostate cancer are not receiving definitive therapy for their disease, which is probably partly driven by the stage IV designation for this patient population. Classification as stage IV also adds unnecessary anxiety for patients and their caregivers given the association of stage IV with incurable disease. Improved survival among N1M0 compared to M1 patients was maintained on multivariate analysis controlling for confounders such as differences in the rates of definitive local treatment. Given the survival outcomes and cure rates observed in this patient population, we feel that the stage IV designation for N1M0 prostate cancer should be re-evaluated.

Conflicts of interest: The authors have nothing to disclose.

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