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Brief Correspondence

Impact of Adjuvant Radiotherapy in Node-positive Prostate Cancer Patients: The Importance of Patient Selection

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Abstract

Using institutional data, we have previously developed an algorithm to identify the optimal candidates for adjuvant radiotherapy (aRT) among men with pN1 prostate cancer (PCa) at radical prostatectomy (RP). This study aimed to test the external validity of our previous findings using a nationwide database while focusing on overall mortality as an endpoint. To this end, we identified 5498 pN1 PCa patients who were treated with RP, pelvic lymph node dissection, and androgen deprivation therapy with or without aRT, within the National Cancer Database, between 2004 and 2015. Patients were divided into five groups based on our previously published algorithm. Similar to our previous report, multivariable Cox regression analysis showed that only two of these groups benefit from aRT: (1) those with one to two positive nodes, pathological Gleason score 7–10, and pT3b/4 disease or positive surgical margins (hazard ratio [HR] = 0.75); and (2) those with three to four positive nodes, regardless of local tumor characteristics (HR = 0.57, both $p = 0.01$). In the remaining patients (25% of the cohort), aRT had no significant survival benefit. Results were confirmed on sensitivity analyses using 1:1 propensity score-matched cohorts, excluding men who died within 3 yr of surgery and using cut-off of 6 mo post-surgery to identify receipt of aRT. Our findings corroborate the validity of our previously published criteria and highlight the importance of patient selection in pN1 PCa patients who are considered for aRT.

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The treatment of prostate cancer (PCa) patients with pathological lymph node invasion (LNI) is rapidly evolving. For a long time, these patients were considered to harbor a systemic disease, and thus, early androgen deprivation therapy (ADT) was considered as the treatment of choice [1]. However, there is a scarcity of level-one evidence on this subject, and the only available randomized clinical trials originate from the pre-prostate-specific antigen (PSA) era and might not be applicable to contemporary patients [2,3]. Several recent reports have challenged the notion that LNI is always a systemic disease by demonstrating that it can benefit from maximizing local control with radical surgery and adjuvant radiotherapy (aRT) [4–6]. In this context, we have previously reported that only certain subsets of patients with LNI can benefit from aRT using institutional data [5]. In this study, our objective was to test the external validity of our previous findings in a nationwide database using overall mortality (OM) as an endpoint.

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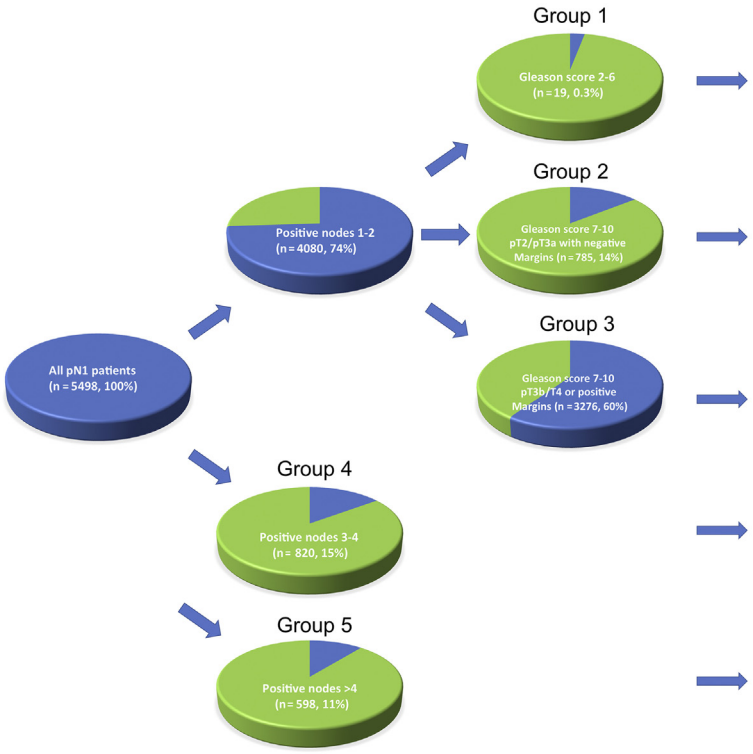
We utilized the National Cancer Database (NCDB) which captures around 70% of new incident tumors in the United States [7]. We focused on a total of 13 678 pN1M0 PCa patients who were treated with radical prostatectomy (RP) and pelvic lymph node dissection between 2004 and 2015. Given that our previous report focused exclusively on patients treated with ADT ± aRT [5], we excluded 7738 patients who did not receive ADT within 1 yr from their surgery. These patients were excluded from the previous and current report because they did not receive the current standard of care [1]. Furthermore, we excluded 442 patients with missing staging, grading, or treatment data. These selection criteria yielded a final cohort of 5498 patients.

aRT was identified as receiving radiation therapy within 1 yr from surgery. As a sensitivity analysis, we restricted cut-off for identifying aRT to 6 mo following surgery to minimize the inclusion of patients undergoing salvage treatment.

Survival time was calculated from the time of diagnosis to OM or the last available follow-up. Using a previously developed algorithm, we divided our patients into five groups as follows: group 1, patients with one to two positive nodes and pathological Gleason score 2–6; group 2, patients with one to two positive nodes, pathological Gleason score 7–10, pT2/pT3a disease, and negative surgical margins; group 3, patients with one to two positive nodes, pathological Gleason score 7–10, pT3b/pT4 disease, or positive surgical margins; group 4, patients with three to four positive nodes; and group 5, patients with more than four positive nodes. The relationship between aRT treatment status and OM was tested using Kaplan-Meier curve estimates, log-rank test, and multivariable Cox regression model using interaction term between treatment status (aRT + ADT vs ADT only) and group assignment (groups 2 through 5; group 1 was excluded because of the limited number of patients). Covariates consisted of age, and Charlson comorbidity index. We performed two additional sensitivity analyses, given the likely inherent differences in patient population selected to receive aRT: (1) 1:1 propensity score-matched analyses (based on the aforementioned covariates) and (2) survival analysis excluding all men who died within 3 yr of surgery.



8-year Overall survival in entire cohort; % (95% CI)	8-year overall survival in ADT only; % (95% CI)	8-year overall survival in aRT plus ADT; % (95% CI)	P – value
77 % (42-92)	76 % (33-94)	80 % (20-97)	0.7
80 % (75-85)	83 % (76-87)	75 % (63-84)	0.2
67 % (64-70)	64 % (60-68)	71 % (66-76)	<0.001
55 % (48-62)	49 % (40-58)	70 % (56-80)	0.003
55 % (46-64)	55 % (44-75)	56% (38-70)	0.5

Fig. 1 – – Eight-yr overall mortality-free survival in 5498 patients with pN1 prostate cancer treated with radical prostatectomy, pelvic lymph node dissection, and adjuvant hormonal therapy without or without adjuvant radiotherapy in the National Cancer Database between 2004 and 2015. Patients were stratified into sub-groups (1–5) [a] based on previously published criteria [5].
ADT = androgen deprivation therapy; aRT = adjuvant radiotherapy; CI = confidence interval; HR = hazard ratio.
[a] Details of risk groups are as follows:
Group 1: patients with one to two positive nodes and pathological Gleason score 2–6
Group 2: patients with one to two positive nodes, pathological Gleason score 7–10, pT2/pT3a disease, and negative surgical margins
Group 3: patients with one to two positive nodes, pathological Gleason score 7–10, pT3b/pT4 disease, or positive surgical margins
Group 4: patients with three to four positive nodes
Group 5: patient with more than four positive nodes.

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