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ORIGINAL REPORT

Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
The role of adjuvant radiotherapy (aRT) in treating patients with pN1 prostate cancer is controversial. We tested the hypothesis that the impact of aRT on cancer-specific mortality (CSM) in these individuals is related to tumor characteristics.

Methods
We evaluated 1,107 patients with pN1 prostate cancer treated with radical prostatectomy and anatomically extended pelvic lymph node dissection between 1988 and 2010 at two tertiary care centers. All patients received adjuvant hormonal therapy with or without aRT. Regression tree analysis stratified patients into risk groups on the basis of their tumor characteristics and the corresponding CSM rate. Cox regression analysis tested the relationship between aRT and CSM rate, as well as overall mortality (OM) rate in each risk group separately.

Results
Overall, 35% of patients received aRT. At multivariable analysis, aRT was associated with more favorable CSM rate (hazard ratio [HR], 0.37; $P < .001$). However, when patients were stratified into risk groups, only two groups of men benefited from aRT: (1) patients with positive lymph node (PLN) count ≤ 2, Gleason score 7 to 10, pT3b/pT4 stage, or positive surgical margins (HR, 0.30; $P = .002$); and (2) patients with PLN count of 3 to 4 (HR, 0.21; $P = .02$), regardless of other tumor characteristics. These results were confirmed when OM was examined as an end point.

Conclusion
The beneficial impact of aRT on survival in patients with pN1 prostate cancer is highly influenced by tumor characteristics. Men with low-volume nodal disease (≤ two PLNs) in the presence of intermediate- to high-grade, non–specimen-confined disease and those with intermediate-volume nodal disease (three to four PLNs) represent the ideal candidates for aRT after surgery.

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INTRODUCTION

The presence of lymph node invasion (LNI) in patients with prostate cancer (PCa) treated with radical prostatectomy (RP) represents an adverse pathologic finding associated with a detrimental impact on cancer control outcomes.[1-7] Despite the significant downward PCa stage migration during the last two decades, up to 14% of contemporary patients still harbor LNI at surgery.[8,9] The optimal postoperative management of these patients is still under debate.[10] Indeed, although adjuvant hormonal therapy (aHT) is indicated by all current guidelines based on a Level I evidence trial,[11,12] recent evidence suggests good long-term outcomes for selected patients with LNI without aHT.[13] Moreover, retrospective data have supported a potential benefit of adjuvant radiotherapy (aRT) on patient survival when combined with aHT.[4,14,15] The aim of aRT in these patients would be to maximize local control, given the non-negligible risk of local failure in these patients after surgery.[16] Patients with LNI represent a highly heterogeneous population sharing different survival rates according to their pathologic characteristics.[1,2,5] Therefore, it is possible that the potential beneficial impact of any adjuvant therapy could significantly vary according to the tumor characteristics of each patient. We hypothesized that the effect of aRT on survival of men with LNI treated with RP strongly depends on the primary PCa tumor features. Such a finding could lead to the identification of subgroup(s) of men with nodal metastases who would represent the ideal candidate for aRT, thus sparing unnecessary treatments and related adverse effects in the remaining patients.

METHODS

We evaluated data on 1,107 consecutive patients with pN1 PCa treated with RP and extended pelvic lymph node dissection (ePLND) between 1988 and 2010 at two tertiary care centers (Mayo Clinic [Rochester, MN] and San Raffaele Hospital [Milan, Italy]). Preoperative staging included negative pelvic and/or abdominal computed tomography or ultrasound, bone scan, and chest x-ray. Several surgeons performed RP by using a standardized retropubic technique. ePLND consisted of the removal of obturator, external iliac, and hypogastric nodes at the time of RP, as previously described.[2]

All patients received aHT. In our series, prostate-specific antigen (PSA) level was not routinely tested before administration of aHT, which was thus given in a true adjuvant setting, as indicated by the only Level I evidence available in this setting.[11] Medical hormone-deprivation therapy was generally intended to be lifelong. However, given the retrospective nature of the cohort, it is uncertain whether patients discontinued treatment after a period of androgen-deprivation therapy. Of all patients, 386 (34.9%) received aRT in addition to aHT. The decision to administer aRT was based on the clinical judgment of each treating physician according to patient and cancer characteristics. Details of the aRT technique that was used have been previously published[15,17] and are provided in the Appendix (online only). Adjuvant treatments (both aHT and aRT) were defined as treatments initiated within 90 days from RP. The institutional review board of each center approved the study.

Definition of Variables

The following variables were extracted for all patients: age at surgery, PSA value (ng/mL), pathologic Gleason score, pathologic tumor stage, surgical margin status, number of removed lymph nodes, number of positive lymph nodes (PLNs), aRT status (aRT plus aHT *v* aHT alone), and year of surgery quartiles (1988 to 1993 *v* 1994 to 1999 *v* 2000 to 2005 *v* 2006 to 2010).

Statistical Analyses

χ^2 test and Mann-Whitney *U* tests were used to compare the statistical significance of differences in proportions and medians, respectively.

First, we used a regression tree approach for censored data to predict cancer-specific mortality (CSM). This approach uses a standard and a recursive algorithm to sequentially divide a group of patients into two subgroups, in which the separation between the two class-specific survival curves in a pair is maximized.[18] The algorithm selects the optimal sequence of classifications, as defined by a hierarchy of prognostic factors and associated cut points. All available predictors, except for aRT treatment status, were included in the regression tree. The results of these analyses were graphically represented. Likewise, we developed a nomogram based on a Cox proportional hazards regression model predicting CSM-free survival. Covariates included pathologic grade, pathologic stage, surgical margin status, and the number of PLNs. The nomogram accuracy (discrimination and calibration) was examined.

Second, we used Kaplan-Meier curves to estimate CSM-free and overall mortality (OM) –free rates in the entire cohort, and in each tree-/nomogram-generated risk group after stratifying patients according to aRT status. Cox regression analyses tested the relationship between aRT status and CSM rate, as well as OM rate in the entire cohort, and in each tree-/nomogram-generated risk group. Multivariable regression models were adjusted for all potential confounders.

Third, given that patients treated with aRT versus those not treated with aRT had significant differences in years of surgery and institution of origin, we reanalyzed survival outcomes in the following two propensity score–matched subcohorts: (1) patients were matched according to aRT status by using the nearest match for all covariates except for years of surgery, which was matched exactly; and (2) patients were matched according to institution of origin by using the nearest match for all covariates except for aRT status, which was matched exactly.

Finally, the validity of the novel tree was examined by using 3,158 patients with pN1 PCa derived from the Surveillance, Epidemiology, and End Results (SEER) database. This cohort consisted of individuals treated with RP with or without aRT between 1999 and 2009. aRT was defined as receiving any radiotherapy after RP. Patients treated with neoadjuvant radiotherapy and patients with missing stage, grade, or number of nodes data were excluded. Given the uncertainty of the cause of death in this cohort, only OM was examined as an end point.

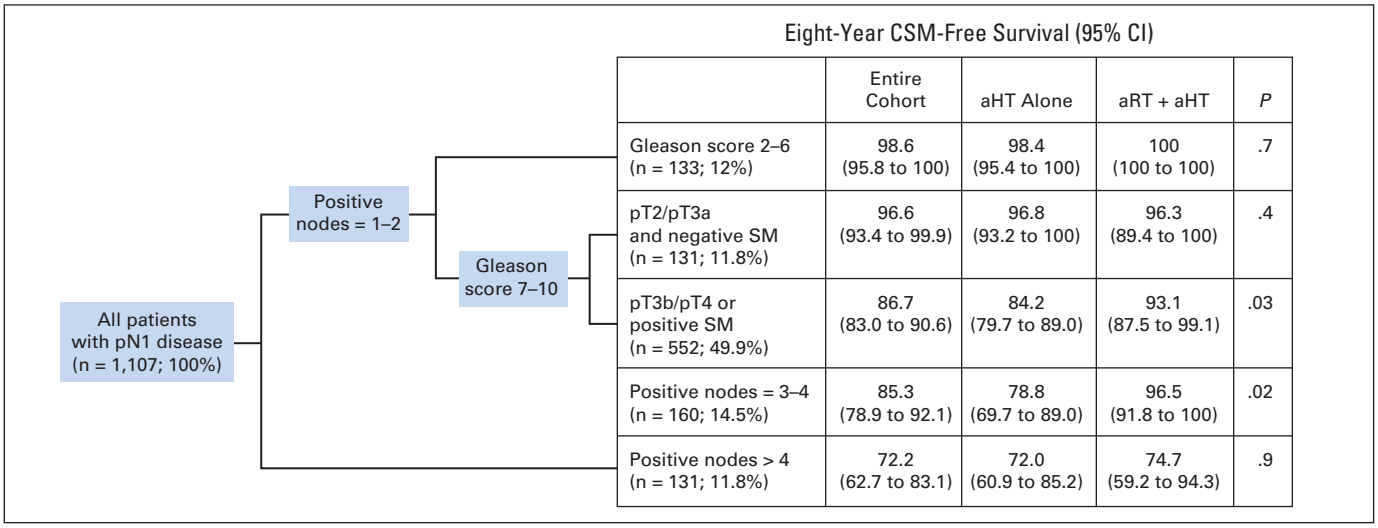
All statistical analyses were performed by using R statistical package (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level set at $P < .05$.

Table 1. Descriptive Statistics for Patients With Nonmetastatic PLN PCa, Treated With RP and ePLND Between 1988 and 2010 at Two Tertiary Care Centers

Variable	All Cohort		aHT		aHT and aRT		*P*
	No.	%	No.	%	No.	%	
No. of patients	1,107	100	721	65.1	386	34.9	
Age (years)							.4
Mean	64.7		64.8		64.5		
Median	65.0		66.0		64.8		
IQR	60.0-70.0		60.0-70.0		60.0-69.7		
PSA (ng/mL)							.2
Mean	25.8		24.6		27.9		
Median	14.0		14.1		14.0		
IQR	7.9-28		7.7-27.1		8.0-31.0		
Pathologic Gleason score							< .001
≤ 6	155	14	123	17.1	32	8.3	
7	518	46.8	358	49.7	160	41.5	
≥ 8	434	39.2	240	33.3	194	50.3	
Pathologic tumor stage							< .001
pT2/pT3a	351	31.7	267	37	84	21.8	
pT3b	681	61.5	427	59.2	254	65.8	
pT4	75	6.8	27	3.7	48	12.4	
Surgical margin status							< .001
Negative	450	40.7	337	46.7	113	29.3	
Positive	657	59.3	384	53.3	273	70.7	
No. of positive nodes							.04
Mean	2.5		2.4		2.8		
Median	1.0		1.0		2.0		
IQR	1.0-3.0		1.0-2.0		1.0-3.0		
No. of removed lymph nodes							< .001
Mean	15.8		14.1		18.9		
Median	14.0		13.0		17.0		
IQR	10.0-20.0		9.0-18.0		12.0-23.0		
Year of surgery (quartiles)							< .001
1988-1993	312	28.2	272	37.7	40	10.4	
1994-1999	251	22.7	193	26.8	58	15	
2000-2005	298	26.9	127	17.6	171	44.3	
2006-2010	246	22.2	129	17.9	117	30.3	
Institution of origin							< .001
San Raffaele Hospital	528	47.7	190	26.4	338	87.6	
Mayo Clinic	579	52.3	531	73.6	48	12.4	

NOTE. Data were stratified according to adjuvant treatment status: aHT *v* aHT and aRT.

Abbreviations: aHT, adjuvant hormonal therapy; aRT, adjuvant radiotherapy; IQR, interquartile; PCa, prostate cancer; PLN, positive lymph node; ePLND, extended lymph node dissection; PSA, prostate-specific antigen; RP, radical prostatectomy.



	Eight-Year CSM-Free Survival (95% CI)			
	Entire Cohort	aHT Alone	aRT + aHT	*P*
Gleason score 2–6 (n = 133; 12%)	98.6 (95.8 to 100)	98.4 (95.4 to 100)	100 (100 to 100)	.7
pT2/pT3a and negative SM (n = 131; 11.8%)	96.6 (93.4 to 99.9)	96.8 (93.2 to 100)	96.3 (89.4 to 100)	.4
pT3b/pT4 or positive SM (n = 552; 49.9%)	86.7 (83.0 to 90.6)	84.2 (79.7 to 89.0)	93.1 (87.5 to 99.1)	.03
Positive nodes = 3–4 (n = 160; 14.5%)	85.3 (78.9 to 92.1)	78.8 (69.7 to 89.0)	96.5 (91.8 to 100)	.02
Positive nodes > 4 (n = 131; 11.8%)	72.2 (62.7 to 83.1)	72.0 (60.9 to 85.2)	74.7 (59.2 to 94.3)	.9

Fig 1. A novel cancer-specific mortality (CSM) risk stratification tree based on data for 1,107 patients with pN1 prostate cancer treated with radical prostatectomy, anatomically extended pelvic lymph node dissection, and adjuvant hormonal therapy (aHT) with or without adjuvant radiotherapy (aRT). SM, surgical margins.

RESULTS

Baseline Patient Characteristics

Clinicopathologic demographics of the cohort, stratified by adjuvant treatment status, are reported in Table 1.

Regression Tree/Nomogram Development

All available potential predictors of CSM, except for aRT status, were included in the regression tree analysis. The regression tree analysis identified four variables to stratify patients according to their CSM risk and indicated the cutoffs that maximized the separation in class-specific survival. These variables consisted of the number of PLNs, pathologic Gleason score, tumor stage, and surgical margin status. On the basis of these variables, the cohort was stratified into five risk groups: very low risk (two or fewer PLNs and Gleason score 2 to 6), low risk (two or fewer PLNs, Gleason score 7 to 10, pT2/pT3a stage, and negative surgical margins), intermediate risk (two or fewer PLNs, Gleason score 7 to 10, and pT3b/pT4 stage or positive surgical

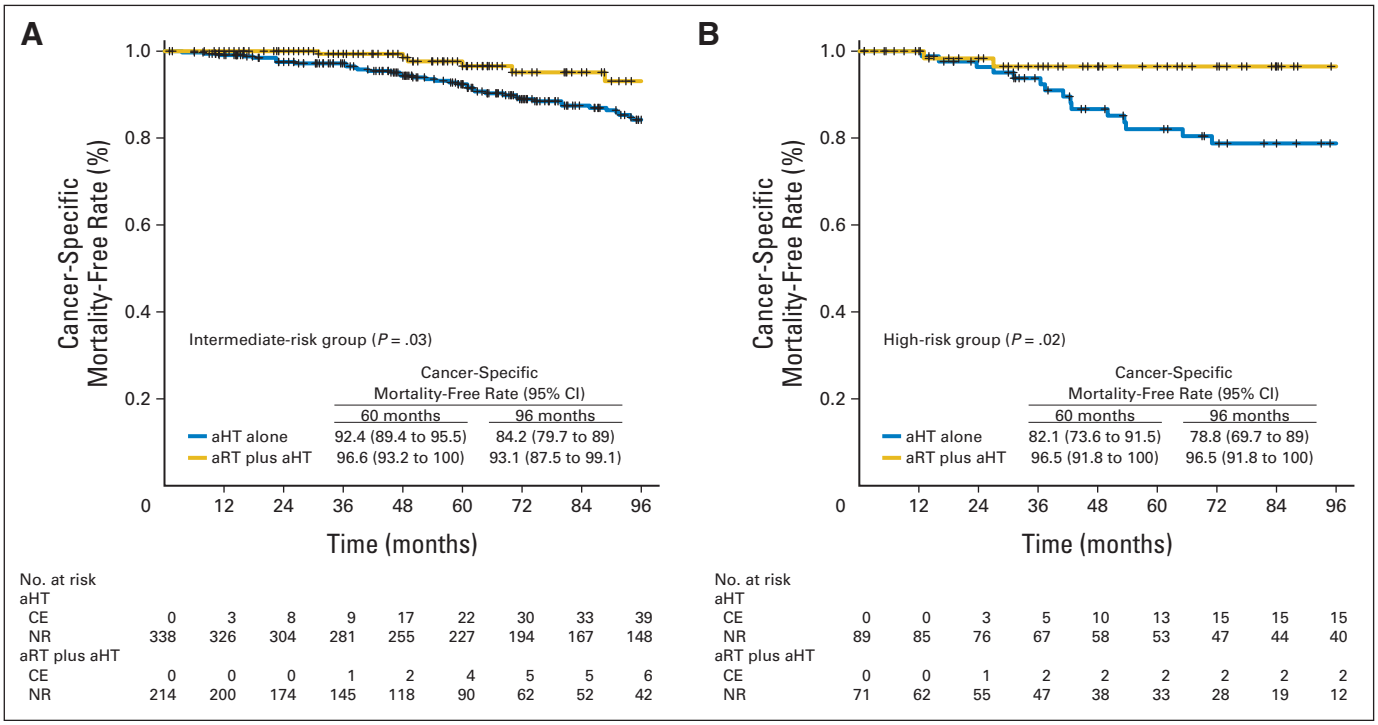


Fig 2. Kaplan-Meier curves depicting cancer-specific mortality-free rate in 1,107 patients with pN1 prostate cancer treated with surgery and adjuvant radiotherapy (aRT) plus adjuvant hormonal therapy (aHT) versus aHT alone. Patients were stratified according to the regression tree risk categories. Results are shown for (A) the intermediate-risk group and (B) the high-risk group. CE, cumulative events; NR, No. at risk.

margins), high risk (3 to 4 PLNs), and very high risk (> four PLNs). The characteristics of each risk group, as well as the corresponding 8-year CSM-free rates, are summarized in Figure 1. A nomogram based on independent predictors of CSM was also developed and internally validated (Data Supplement).

Survival Estimates and Cox Regression Analyses

Mean and median follow-up times were 8.4 and 7.1 years, respectively. At 8 years, the CSM-free survival rate was 87.8%; it was 92.4% in patients treated with aRT plus aHT versus 86.2% in patients treated with aHT alone ($P = .08$). At 8 years, the OM-free survival rate was 78.1%; it was 87.6% in patients treated with aRT plus aHT versus 75.1% in patients treated with aHT alone ($P < .001$).

When patients were stratified according to aRT status (Fig 2 and Data Supplement), the 8-year CSM-free survival rate was statistically significantly higher in patients treated with aRT plus aHT versus patients treated with aHT alone in the intermediate-risk (93.1% *v* 84.2%; $P = .03$) and high-risk (96.5% *v* 78.8%; $P = .02$) groups only. These findings were confirmed when OM-free survival was examined as an end point (Fig 3 and Data Supplement).

When patients were stratified by using the nomogram-predicted survival quintiles and aRT status (Data Supplement), the 8-year CSM-free survival rate was statistically significantly higher in patients treated with aRT plus aHT versus patients treated with aHT alone in patients with a nomogram-predicted CSM-free rate ≤ 87.7% only (all $P \leq .02$).

In multivariable analyses predicting CSM, patients treated with aRT plus aHT had a more favorable CSM rate than their counterparts treated with aHT alone (hazard ratio [HR], 0.37; $P < .001$). When patients were stratified according to risk groups, men treated with aRT plus aHT had more favorable CSM rates compared with those treated with aHT alone in the intermediate-risk (HR, 0.30; $P = .002$), and high-risk (HR, 0.21; $P = .02$) groups only. In all other risk groups, aRT status was not an independent predictor of CSM rate (Table 2). Similar findings were observed when OM-free survival was examined as an end point (Table 3).

In propensity score–matched analyses (Data Supplement) and in multivariable analyses, the beneficial impact of aRT on CSM was limited to the intermediate- and high-risk groups (Data Supplement). Similar results were observed in the external validation cohort (Data Supplement).

DISCUSSION

Previous retrospective data showed a potential benefit of aRT on cancer outcomes in men with LNI.[4,14,15] The reason for considering aRT in these individuals was to maximize local cancer control. Although one might argue that such an approach may not have a rationale in men with nodal metastatic disease, several studies have shown that patients with LNI are not invariably affected by disseminated PCa.[4,13-15] Indeed, in a non-negligible proportion of patients with LNI, the pattern of recurrence has been shown to be pelvic rather than systemic.[16] Nevertheless, patients with LNI represent an extremely heterogeneous population that shares different outcomes according to their pathologic characteristics.[1,2,5] Among these patients, combined local treatment may be considered only in those with adverse features but without systemic disease. For these reasons, a substratification of individuals with LNI should be advocated to optimize their outcome prediction and their postoperative management. Despite these considerations, no previous report examined the effect of aRT in

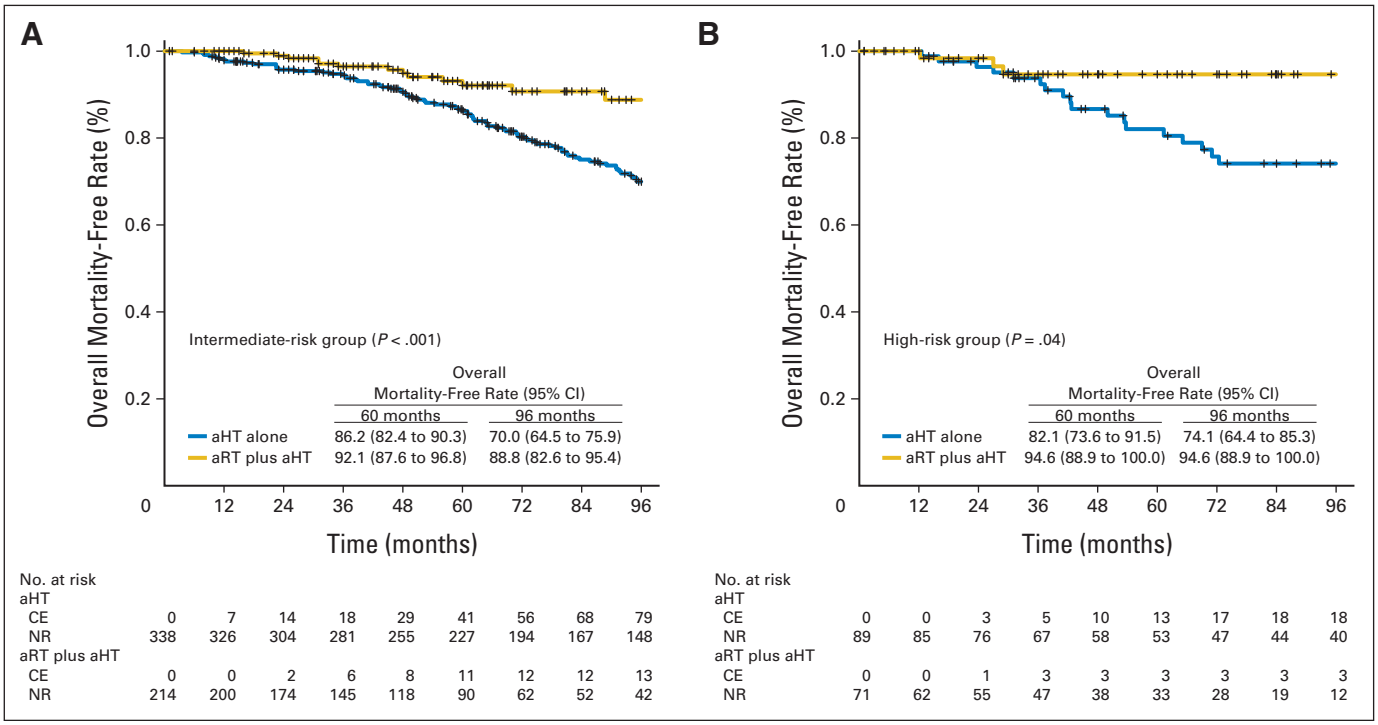


Fig 3. Kaplan-Meier curves depicting overall mortality-free rate in 1,107 patients with pN1 prostate cancer treated with surgery and adjuvant radiotherapy (aRT) plus adjuvant hormonal therapy (aHT) versus aHT alone. Patients were stratified according to the regression tree risk categories. Results are shown for (A) the intermediate-risk group and (B) the high-risk group. CE, cumulative events; NR, No. at risk.

Table 2. Univariable and Multivariable Cox Regression Analyses Predicting CSM in 1,107 Patients With pN1 PCa Treated With RP, ePLND, and Adjuvant Therapy

Predictors	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Entire Cohort						
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	0.66	0.42 to 1.06	.08	0.37	0.22 to 0.62	< .001
Age (years)	0.99	0.97 to 1.02	.5	1.00	0.97 to 1.03	.9
PSA (ng/mL)	1.00	1.01 to 1.01	.001	1.00	0.99 to 1.11	.5
Pathologic Gleason score						
≤ 6	1.00 (ref.)		—	1.00 (ref.)		—
7	2.25	1.14 to 4.46	.02	1.73	0.87 to 3.44	.1
≥ 8	5.03	2.57 to 9.86	< .001	3.84	1.94 to 7.60	< .001
Pathologic tumor stage						
pT2/pT3a	1.00 (ref.)		—	1.00 (ref.)		—
pT3b	2.5	1.49 to 4.22	.001	1.91	1.12 to 3.25	.01
pT4	6.13	3.21 to 11.71	< .001	3.48	1.65 to 7.32	.001
Surgical margin status						
Negative	1.00 (ref.)		—	1.00 (ref.)		—
Positive	2.61	1.68 to 4.06	< .001	2.1	1.32 to 3.35	.002
No. of positive nodes	1.15	1.11 to 1.19	< .001	1.1	1.05 to 1.16	< .001
Very Low Risk*						
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	0.01	0.01 to 12.93	.7	0.01	< 0.01 to 15.8	.9
Age (years)	1.1	0.95 to 1.27	.1	1.12	0.95 to 1.32	.1
PSA (ng/mL)	1.02	0.99 to 1.04	.1	1.02	0.99 to 1.05	.1
Pathologic Gleason score						
≤ 6	—		—	—		—
7						
≥ 8						
Pathologic tumor stage						
pT2/pT3a	1.00 (ref.)		—	1.00 (ref.)		—
pT3b	1.92	0.35 to 10.48	.4	1.31	0.17 to 9.95	.7
pT4	NA		NA	NA		NA
Surgical margin status						
Negative	1.00 (ref.)		—	1.00 (ref.)		—
Positive	2.19	0.4 to 11.99	.365	0.95	0.14 to 6.61	.9
No. of positive nodes	6.95	1.27 to 38	.02	5.35	0.88 to 32.66	.06
Low Risk†						
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	2.05	0.38 to 11.25	.4	2.27	0.35 to 14.88	.4
Age (years)	0.92	0.74 to 1.14	.4	0.73	0.46 to 1.15	.1
PSA (ng/mL)	0.80	0.53 to 1.23	.3	0.67	0.36 to 1.26	.2
Pathologic Gleason score						
7	1.00 (ref.)		—	1.00 (ref.)		—
≥ 8	2.81	0.17 to 46.48	.4	2.49	0.17 to 45.9	.1
Pathologic tumor stage						
pT2/pT3a	—		—	—		—
pT3b						
pT4						
Surgical margin status						
Negative	—		—	—		—
Positive						
No. of positive nodes	0.01	0.01 to 21.09	.9	0.01	0.01 to 12.5	.8
Intermediate Risk‡						
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	0.48	0.23 to 0.97	.03	0.30	0.14 to 0.64	.002

(continued on following page)

Table 2. Univariable and Multivariable Cox Regression Analyses Predicting CSM in 1,107 Patients With pN1 PCa Treated With RP, ePLND, and Adjuvant Therapy (continued)

	Univariable Analysis			Multivariable Analysis		
Predictors	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.00	0.96 to 1.04	.9	1.00	0.97 to 1.04	.8
PSA (ng/mL)	1.00	0.99 to 1.01	.6	1.00	0.99 to 1.01	.7
Pathologic Gleason score						
7	1.00 (ref.)		—	1.00 (ref.)		—
≥ 8	2.08	1.26 to 3.45	.004	2.39	1.43 to 4	.001
Pathologic tumor stage						
pT2/pT3a	1.00 (ref.)		—	1.00 (ref.)		—
pT3b	1.6	0.72 to 3.54	.2	1.95	0.85 to 4.46	.1
pT4	2.5	0.88 to 7.14	.08	3.61	1.18 to 11.1	.02
Surgical margin status						
Negative	1.00 (ref.)		—	1.00 (ref.)		—
Positive	1.97	1.00 to 3.89	.05	2.47	1.23 to 4.99	.01
No. of positive nodes	1.12	0.66 to 1.89	.6	1.07	0.63 to 1.83	.8
			High Risk§			
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	0.27	0.08 to 0.93	.02	0.21	0.06 to 0.79	.02
Age (years)	1.02	0.96 to 1.08	.5	1	0.94 to 1.06	.9
PSA (ng/mL)	1.01	1 to 1.03	.02	1.02	1 to 1.03	.01
Pathologic Gleason score						
≤ 6	1.00 (ref.)		—	1.00 (ref.)		—
7	1.02	0.27 to 3.9	.9	1.36	0.34 to 5.46	.6
≥ 8	1.46	0.41 to 5.24	.5	2.29	0.58 to 9.12	.2
Pathologic tumor stage						
pT2/pT3a	1.00 (ref.)		—	1.00 (ref.)		—
pT3b	0.86	0.31 to 2.35	.7	0.98	0.33 to 2.88	.9
pT4	2.09	0.4 to 10.84	.3	2.34	0.38 to 14.37	.3
Surgical margin status						
Negative	1.00 (ref.)		—	1.00 (ref.)		—
Positive	1.72	0.68 to 4.36	.2	1.69	0.61 to 4.65	.3
No. of positive nodes	0.95	0.37 to 2.4	.9	0.71	0.27 to 1.92	.5
			Very High Risk‖			
aRT						
No	1.00 (ref.)		—	1.00 (ref.)		—
Yes	1.03	0.45 to 2.34	.9	0.53	0.19 to 1.48	.2
Age (years)	0.98	0.93 to 1.02	.3	0.98	0.93 to 1.04	.5
PSA (ng/mL)	1	1 to 1.01	.6	1	0.99 to 1	.1
Pathologic Gleason score						
≤ 6	1.00 (ref.)		—	1.00 (ref.)		—
7	2.29	0.29 to 17.91	.4	2.67	0.32 to 22.08	.3
≥ 8	6.41	0.83 to 49.33	.07	6.55	0.78 to 55.17	.08
Pathologic tumor stage						
pT2/pT3a	1.00 (ref.)		—	1.00 (ref.)		—
pT3b	3.97	0.53 to 29.97	.1	3.81	0.5 to 29	.1
pT4	13.85	1.77 to 108.35	.01	8.03	0.9 to 71.75	.06
Surgical margin status						
Negative	1.00 (ref.)		—	1.00 (ref.)		—
Positive	1.37	0.52 to 3.61	.5	0.64	0.21 to 1.91	.4
No. of positive nodes	1.13	1.07 to 1.19	< .001	1.11	1 to 1.24	.06

NOTE. Patients were stratified into risk groups based on regression tree analysis predicting CSM.

Abbreviations: aRT, adjuvant radiotherapy; CSM; cancer-specific mortality; ePLND, extended pelvic lymph node dissection; HR, hazard ratio; NA, not applicable; PCa, prostate cancer; PLN, positive lymph node; PSA, prostate-specific antigen; ref., reference; RP, radical prostatectomy.

*Very low risk: No. of positive lymph nodes (PLNs) ≤ 2, and Gleason score 2 to 6.

†Low risk: two or fewer PLNs, Gleason score 7 to 10, pT2/pT3a stage, and negative surgical margins.

‡Intermediate risk: two or fewer PLNs, Gleason score 7 to 10, pT3b/pT4 stage, or positive surgical margins.

§High risk: 3 to 4 PLNs.

‖Very high risk: > 4 PLNs.

Table 3. Multivariable Cox Regression Analyses Testing the Relationship Between aRT Treatment and Overall Mortality in 1,107 Patients With pN1 PCa Treated With RP, ePLND, and Adjuvant Therapy

	Multivariable Analysis		
Group	HR	95% CI	*P*
Very low risk*	0.01	< 0.01 to > 99.9	.9
Low risk†	0.63	0.22 to 1.82	.4
Intermediate risk‡	0.42	0.25 to 0.70	.001
High risk§	0.32	0.12 to 0.83	.02
Very high risk‖	0.59	0.28 to 1.28	.2

NOTE. Patients were stratified into risk groups based on regression tree analysis predicting cancer-specific mortality. All multivariable analyses were adjusted for age, prostate-specific antigen, pathologic Gleason score, pathologic stage, surgical margin, and positive lymph node count.

Abbreviations: aRT, adjuvant radiotherapy; ePLND, extended pelvic lymph node dissection; HR, hazard ratio; PCa, prostate cancer; PLN, positive lymph node; RP, radical prostatectomy.

*Very low risk: two or fewer PLNs, and Gleason score 2 to 6.

†Low risk: two or fewer PLNs, Gleason score 7 to 10, pT2/pT3a stage, and negative surgical margins.

‡Intermediate risk: two or fewer PLNs, Gleason score 7 to 10, pT3b/pT4 stage, or positive surgical margins.

§High risk: 3 to 4 PLNs.

‖Very high risk: > 4 PLNs.

node-positive disease according to characteristics of single patients. We therefore evaluated the impact of aRT in this population after stratifying men into different risk groups on the basis of their tumor characteristics and CSM risk. This approach aimed to identify the optimal candidates for aRT among patients with LNI.

In our cohort of 1,107 patients with LNI, all men were treated with RP, ePLND, and aHT. Moreover, 35% of patients received aRT. It is of note that the latter group of patients had more aggressive tumor characteristics than their counterparts who did not receive aRT. For the entire cohort, the 8-year CSM-free rate was roughly 88%. When patients were stratified according to aRT status, those who received aRT plus aHT had more favorable, although not statistically significant, CSM-free rates than their counterparts treated with aHT at univariable analysis (8-year CSM-free rate, 92% *v* 86%; $P = .08$). However, when tumor features were accounted for in multivariable analyses, aRT was associated with a significant improvement in survival (HR, 0.37; $P < .001$). These results confirm our previous findings imparting a favorable impact of aRT in node-positive patients in a larger population.[1,2,5] However, to further examine the validity of the aforementioned inference, we performed further analyses that consisted of two main steps. First, we stratified our patients according to their CSM risk by using a regression tree analysis. Second, we examined the relationship between aRT and CSM rate in each risk group separately.

In the first step, all available patient characteristics were included as potential predictors of CSM. The regression tree analysis selected the independent predictors of CSM as well as their most appropriate cutoffs to maximize survival difference between the newly created risk groups. We found that patients with more than four PLNs, regardless of the other tumor characteristics, had the least favorable 8-year CSM-free rate (72%). Conversely, patients with two or fewer PLNs and a pathologic Gleason score ≤ 6 had the most favorable 8-year CSM-free rates (99%). The CSM-free rates of all the other risk groups were in between (Fig 1). In the second step, we tested the role of aRT in each risk group. We found that patients with LNI benefited from maximizing local control with aRT in two cases: first, if they had a low volume of nodal invasion (≤ two PLNs) but high-grade (pathologic Gleason score ≥ 7) and locally advanced disease (pT3b/pT4 and/or positive surgical margins); second, if they harbored intermediate-volume LNI (3 to 4 PLNs) regardless of other tumor characteristics. In these two groups of patients, aRT showed a relative risk reduction in CSM rates of 70% to 79%. Conversely, maximizing local control with aRT in patients with LNI did not improve survival in patients with extremely favorable (two or fewer PLNs, specimen-confined, and/or low-grade tumor) or extremely unfavorable (> four PLNs) PCa features. In the first case, the CSM-free rate was excellent even without aRT. Conversely, in the second case, patients had unfavorable survival rates regardless of the aRT status, suggesting the possible presence of a disease outside the pelvis at the time of treatment. Therefore, in both clinical scenarios, use of aRT would represent an unnecessary therapeutic approach. These findings were confirmed in sensitivity analyses as well as when OM was examined as an end point.

Our findings were confirmed when externally validated in a cohort of 3,158 patients with pN1 status. This implies the generalizability of our results. However, given the limitations of the SEER data, Gleason score was stratified into 2 to 7 versus 8 to 10 instead of 2 to 6 versus 7 to 10 for the first three risk groups. Likewise, stage subclass and surgical margin data were ignored because these were inaccurate and/or missing for many patients. It is also noteworthy that some of these patients could have received RT in the salvage and not the adjuvant setting. These limitations must be considered when interpreting the results of the external validation.

We used all independent predictors of CSM except for aRT to develop a novel nomogram. Patients were stratified according to the quintiles probability predicted by the nomogram. When examined, the beneficial impact of aRT was evident only in patients with a nomogram-predicted 8-year CSM-free rate ≤ 87.7%. However, it is noteworthy that Cox regression analysis used to develop the nomogram might not be able to identify small subgroups, as in the case of regression tree analysis. This might explain why the nomogram analysis failed to identify the lack of aRT benefit in patients with more than four PLNs (very-high-risk group).

There are several clinical implications of our findings. First, our observations confirmed that cancer control outcomes of patients with LNI are extremely heterogeneous. The CSM-free rate ranged between 72% to 99% at 8 years (Fig 1). For this reason, it can be highly misleading to consider all these patients in a single risk category, namely pN1. From a clinical perspective, this may lead to miscounseling patients regarding their prognosis, which may in turn result in biased clinical decision making. From a scientific perspective, grouping all patients with LNI into one risk category, such as in the case of the current TNM staging system, would affect the accuracy of any model predicting CSM in these individuals. Second, our risk-stratification model defined the exact characteristics of patients with LNI who may benefit from aRT (ie, intermediate- and high-risk groups). The direct application of this model in clinical practice could optimize the use of aRT by improving CSM rate in selected individuals and avoiding the unnecessary adverse effects of aRT in others. Third, we evaluated the prognostic importance of local disease status in patients with LNI. In our analyses, the effect of local tumor stage and grade on survival was evident only in men with a low volume of LNI (≤ two PLNs) as expected. Conversely, the prognosis of patients with a higher volume of nodal invasion (> two PLNs) was not affected by

local disease status (Fig 1). In this context, it is noteworthy that the proposed cutoff of two PLNs, which had been previously suggested in men with LNI,[1,2,5] has been further confirmed in our analysis. However, in addition to this, a further substratification has been introduced for those with more than two PLNs. This included men with three or four PLNs (intermediate-volume LNI) and more than four PLNs (high-volume LNI). These two groups of patients did have different CSM-free rates and different response to aRT (Fig 1), regardless of local disease stage and grade.

Our study has some limitations. First, our results derive from retrospective, observational data. Although our data confirm, in a larger two-institution series, previous findings regarding the benefit of aRT on survival of patients with LNI, no prospective randomized studies support the association between aRT and cancer outcomes in these patients. Therefore, our data should be considered in this context, which may also be affected by selection biases over the study period. For example, as previously mentioned, use of aRT was left to the clinical judgment of each treating physician on the basis of patient and cancer profile. Therefore, a patient selection bias might have been introduced. However, we tried to circumvent this limitation by using multivariable analyses that accounted for these characteristics. Second, a pathology review has not been performed. In our study, pT stage was coded according to the 2002 TNM classification system. Thus, patients with pT3b harbored a seminal vesicle invasion with or without extracapsular extension, and patients with pT3a had extracapsular extension only. Third, data regarding quality of life related to the delivery of aRT could not be obtained in this retrospective series. Fourth, all patients included in the analyses were submitted to aHT after surgery. Consequently, our novel models may not be applicable in patients with PLNs who received no aHT. However, the use of aHT reflects a practice that is not uncommon among urologists, based on Level I evidence of improved survival in patients with pN1 PCa who received aHT.[11] Nevertheless, it is possible that a certain proportion of these patients might have been overtreated with the use of aHT.[13] Finally, our results still need further validation.

In conclusion, the beneficial impact of aRT on survival in patients with PCa with LNI can depend on individualized tumor characteristics. Specifically, patients who benefited from aRT were those with low-volume LNI ($\leq$ two PLNs) in the presence of intermediate- to high-grade non–specimen-confined disease and those with intermediate-volume LNI (3 to 4 PLNs), regardless of other tumor characteristics. Conversely, all other patients with LNI did not seem to benefit significantly from aRT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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GLOSSARY TERMS

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

Gleason score: a pathologic description of prostate cancer grade on the basis of the degree of abnormality in the glandular architecture. Gleason patterns 3, 4, and 5 denote low, intermediate, and high levels of histologic abnormality and tumor aggressiveness, respectively. The score assigns primary and secondary numbers on the basis of the most common and second most common patterns identified.

prostate-specific antigen (PSA): a protein produced by cells of the prostate gland. The blood level of prostate-specific antigen (PSA) is used as a tumor marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL to be the normal range. Levels of 4 to 10 and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.

Appendix

Overall, 70% and 85% of patients treated with adjuvant radiotherapy received whole pelvis radiotherapy between 1988 and 2000 and between 2000 and 2010, respectively. Median dose to the prostatic bed slightly increased from 66.6 to 70.2 Gy in patients treated between 1988 and 2000 and in those treated between 2000 and 2010, respectively. Similarly, median dose to pelvic lymph nodes slightly increased from 45 to 50.4 Gy in patients treated between 1988 and 2000 and in those treated between 2000 and 2010, respectively.