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Evaluation of lymphovascular invasion as a prognostic predictor of overall survival after radical prostatectomy

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Abstract

Objective: To assess the prognostic ability of lymphovascular invasion (LVI) as a predictor of overall survival (OS).

Materials and Methods: We included 126,682 prostate cancer (CaP) cM0 patients who underwent radical prostatectomy with lymph node dissection between 2010 and 2015, within the National Cancer Database. Patients who received androgen deprivation therapy were included. Patients were divided into four sub-cohorts based on LVI and lymph node invasion (LNI) status: pL_0N_0, pL_1N_0, pL_0N_1, and pL_1N_1. Kaplan-Meier curves estimated OS and Cox-regression analysis tested the relationship between LVI and OS.

Results: Median (IQR) age and PSA at diagnosis were 62 (57-66) years and 5.7 (4.5-8.9) ng/ml, respectively. Most patients had pT2 stage (68.5%), and pathological Gleason 3+4 (46.7%). 10.0% and 4.0% patients had LVI and LNI, respectively. Median follow-up was 42 months (27-58). At 5-years, OS was 96.5% in pL_0N_0 patients vs 93.1% pL_1N_0 patients vs 93.3% in pL_0N_1 patients vs 86.6% pL_1N_1 patients. LVI was an independent predictor of OS (hazard ratio [HR]:1.28). LVI showed interaction with LNI, as LVI was associated with a higher overall-mortality in patients with LNI (HR:1.66), than in patients without LNI (HR:1.22). (all $P<0.0001$)

Conclusions: Our report highlights the detrimental impact of LVI on OS. Patients with LVI alone fared similarly to patients with LNI alone. Patients with both LVI and LNI had worse OS than those with only LVI or LNI, implying a synergetic detrimental interaction. Our findings demonstrate an important utility that LVI can provide in deciding patients' prognoses. © 2021 Published by Elsevier Inc.

KEYWORDS (MeSH): Prostatic neoplasms; prostatectomy; lymphovascular Invasion; lymph node involvement

1. Introduction

Prostate cancer (CaP) is the second-most common cause of cancer-specific mortality in North American men. Many CaP patients are treated with radical prostatectomy (RP), with or without a pelvic lymph node dissection [1-3]. Lymph node invasion (LNI) on surgical specimen is evidence of regional dissemination and possible metastasis which usually necessitates the use of adjuvant treatments, and is associated with worse prognosis after RP [4,5]. Regional dissemination occurs in 12% of newly diagnosed CaP cases in the United States[6], and is reasonably expected to become more prevalent with US Preventative Task Force recommendations against routine PSA screening [7,8].

The prevalence and significance of LNI underscores the importance of accurate assessment of LNI after RP. However, the only accurate method for defining a patient's LNI status is with histopathological assessment of lymph nodes after lymphadenectomy following RP. This is further complicated by the lack of an unequivocally identified sentinel node for CaP [9], the significant morbidity associated with an all-encompassing lymph node dissection, and the lack of

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standardization in the number of lymph nodes removed by various surgeons [10].

On the other hand, lymphovascular invasion (LVI) at time of RP is recognized as an adverse pathological feature in patients with prostate cancer [11-14]. Theoretically, assessment of LVI status should mirror LNI status, and there have been multiple studies that have identified a strong link between LVI and LNI [13,15]. Further, several studies have observed that the presence of LVI was associated with less favorable biochemical recurrence (BCR) rates [12-14,16]. However, the impact of LVI on overall survival (OS) and how it compares to other pathological features has not been documented in the literature. Our objective was to assess the prognostic ability of LVI and its potential use as a predictor of OS in a large North American Cohort.

2. Methods

2.1. Study population

Our cohort was derived from the National Cancer Database (NCDB), a clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society. The data is sourced from hospital registries leading to data from 1,500 Commission on Cancer-accredited facilities. The data from the NCDB represents approximately 70% of newly diagnosed cancer cases across the United States [17].

Within the NCDB, we identified a total of 126,682 patients with histologically confirmed non-metastatic adenocarcinoma of the prostate, diagnosed between 2010 and 2015, who underwent RP with lymph node dissection. Patients before 2010 were excluded because NCDB did not record LVI status for these individuals. Patients who received androgen deprivation therapy (ADT) were included, in order to mirror the clinical milieu that surrounds these patients.

2.2. Covariates

The following variables were extracted for all patients: age at diagnosis, serum prostate specific antigen (PSA) value at diagnosis, baseline Charlson Comorbidity Index (CCI) category (0, 1, ≥2), pathological tumor stage (≤pT2, pT3a, pT3b, and pT4), pathological Gleason score (≤6, 3+4, 4+3, 8, and 9 − 10), surgical margin status (negative or positive), number of nodes removed, number of positive nodes, pathological LNI status (pN_0, pN_1), and pathological LVI status (pL_0, pL_1). Specifically, LVI was defined as the presence of tumor cells in lymphatic channels or blood vessels within the primary tumor, but not the lymph nodes. Lastly, adjuvant radiotherapy (aRT) status and adjuvant ADT status were also abstracted and accounted for.

2.3. Endpoints

The main endpoint of this study was OS, defined as the period in months from diagnosis until death due to any cause, or last available follow-up. For this cohort, follow-up data was available through December 31, 2016**.**

2.4. Statistical analyses

Medians and interquartile ranges (IQRs) were reported for continuous variables, while proportions and frequencies were reported for categorical variables. The Mann-Whitney-U test and chi-square tests were used to compare continuous, and categorical variables, respectively. Kaplan-Meier curves were used to estimate OS. Given the strong relationship between LNI and LVI reported in literature [13,15], we divided our patients into four groups: patients without LVI or LNI (pL_0N_0), patients with LVI but no LNI (pL_1N_0), patients with LNI but no LVI (pL_0N_1), and patients with LVI and LNI (pL_1N_1). The log-rank test was used to compare OS between these groups. Cox-regression analysis tested the relationship between LVI status and OS, after adjusting to all available covariates. We also examined the interaction between LVI and LNI in the multivariable analysis predicting overall mortality.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Two-sided statistical significance was defined as a p-value<0.05. An institutional review board waiver was obtained before the study was conducted, in accordance with institutional regulation when dealing with de-identified previously collected data.

3. Results

3.1. Descriptive characteristics

Descriptive data are represented in Table 1. Median (IQR) age and PSA value at time of diagnosis were 62 (57-66) years and 5.9 (4.5-8.9) ng/ml, respectively. Most patients had pT2 stage disease (68.5%), pathological Gleason 3+4 (46.8%), and negative surgical margins (76.0%). The median (IQR) of number of nodes removed was 5 (3-9) nodes. Overall, 10.0% (12,632), 4.0% (5,010), and 2.3% (2,919) of patients had LVI, LNI, and LVI and LNI, respectively. The median (IQR) of positive nodes in men with LNI was 1 (1-2) nodes. 4,014 patients received adjuvant ADT.

Patients with LVI were older (median: 63 vs. 62 years), had a higher PSA at time of diagnosis (median: 7.5 vs. 5.7), had a higher rate of ≥ pT3a disease (74.4% vs. 26.5%), pathological Gleason ≥ 8 disease (46.5% vs. 10.8%), higher rates of positive surgical margins (43.7% vs. 21.3%), and LNI (23.3% vs. 1.8%), than their counterparts without LVI (all P <0.0001).

Table 1
Descriptive statistics of 126,682 non-metastatic prostate cancer patients treated with radical prostatectomy and lymph node dissection, between 2010 and 2015, within the National Cancer Database

Characteristics	Entire Cohort	No LVI	LVI	*P*-value
Age (IQR)	62 (57 - 66)	62 (56 - 66)	63 (57 - 67)	<0.0001
Median PSA (IQR)	5.9 (4.5 - 8.9)	5.7 (4.4 - 8.5)	7.5 (5.1 - 12.8)	<0.0001
Regional Lymph Nodes Examined	5 (3 - 9)	5 (3 - 9)	6 (3 - 10)	<0.0001
Regional Lymph Nodes Positive	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	<0.0001
Age Group				<0.0001
≤50	8,784 (6.9%)	8,097 (7.1)	697 (5.6%)	
51 - 59	40,370 (31.9%)	36,772 (32.2%)	3,598 (28.7%)	
60 - 69	62,500 (49.3%)	56,082 (49.1%)	6.418 (51.2%)	
≥70	15,018 (11.9%)	13,199 (11.6%)	1,819 (14.5%)	
Pathologic tumor stage				<0.0001
pT1	238 (0.2%)	229 (0.2%)	9 (0.1%)	
pT2	86,783 (68.5%)	83,589 (73.2%)	3,194 (25.5%)	
pT3a	26,868 (21.2%)	22,833 (20%)	4,035 (32.2%)	
pT3b	12,348 (9.8%)	7,239 (6.3%)	5,109 (40.8%)	
pT4	372 (0.3%)	196 (0.2%)	176 (1.4%)	
Gleason grade				<0.0001
≤6	23,863 (18.9%)	23,500 (20.6%)	363 (2.9%)	
3+4	59,219 (46.8%)	56,521 (49.5%)	2,698 (21.5%)	
4+3	25,480 (20.1%)	21,842 (19.1%)	3,638 (29%)	
8	7,897 (6.2%)	6,121 (5.4%)	1,776 (14.2%)	
9 - 10	10,188 (8%)	6,137 (5.4%)	4,051 (32.3%)	
Lymph Node Invasion				<0.0001
pNo	121,672 (96.1%)	112,059 (98.2%)	9,613 (76.7%)	
pN1	5,010 (3.9%)	2,091 (1.8%)	2,919 (23.3%)	
Surgical Margin				<0.0001
Negative Surgical Margin	96,266 (76.3%)	89,287 (78.6%)	6,979 (56.0%)	
Positive Surgical Margin	29,828 (23.7%)	24,355 (21.4%)	5,473 (44.0%)	
PSA Group				<0.0001
≤4	29,142 (23%)	26,826 (23.5%)	2,316 (18.5%)	
4 - 10	74,254 (58.6%)	68,041 (59.6%)	6,213 (49.6%)	
10 - 20	15,296 (12.1%)	12,936 (11.3%)	2,360 (18.8%)	
> 20	7,990 (6.3%)	6,347 (5.6%)	1,643 (13.1%)	

3.2. Overall survival analysis

Overall, the median (IQR) follow-up of the cohort was 42.0 months (27.0-58.0). At 5-years, the estimated OS rate was 96.5% in patients with pL_0N_0 disease vs. 93.1% in patients with pL_1N_0 disease vs. 93.3% in patients with pL_0N_1 disease, vs. 86.6% in patients with pL_1N_1 disease (Fig. 1, log-rank test P <0.0001).

3.3. Cox regression analysis

On Cox regression analysis, LVI was an independent predictor of higher overall mortality (hazard ratio [HR]: 1.283, 95% CI: 1.151 − 1.430, P<.0001). The presence of LVI was also shown to interact significantly with LNI status. Specifically, LVI was associated with a higher risk of overall mortality in patients with concomitant LNI (HR: 1.657, 95% CI: 1.276 − 2.151, P<.0001), than in patients without LNI (HR: 1.216, 95% CI: 1.078 − 1.372, P<.0001). Other covariates that had a detrimental prognostic impact on overall mortality are detailed in Table 2.

4. Discussion

Lymph node dissection remains a necessary tool in the accurate staging of CaP. However, there is an ongoing debate about the therapeutic utility of extended pelvic lymph node dissection [18] as well as multiple difficulties with regards to its standardization [10], and potential complications [19]. This identifies an important role and benefit for a prognostic factor that may supplement and complement the prognostic impact of LNI. LVI is an established adverse pathological finding [11-14] and has a strong relationship/correlation with LNI status [13,15]. Further, it has also been shown to be an adverse prognostic factor for BCR [20,21]. However, its impact on OS, which is the most important oncological endpoint, has not been evaluated. We set to address this void and evaluate the prognostic role of LVI in CaP patients.

Our analyses yielded several findings worth highlighting. For example, we observed a detrimental impact of LVI on OS. At 5-years, the OS-rate was 96.5% in patients with pL_0N_0 disease, while it was 93.1% in patients with pL_1N_0

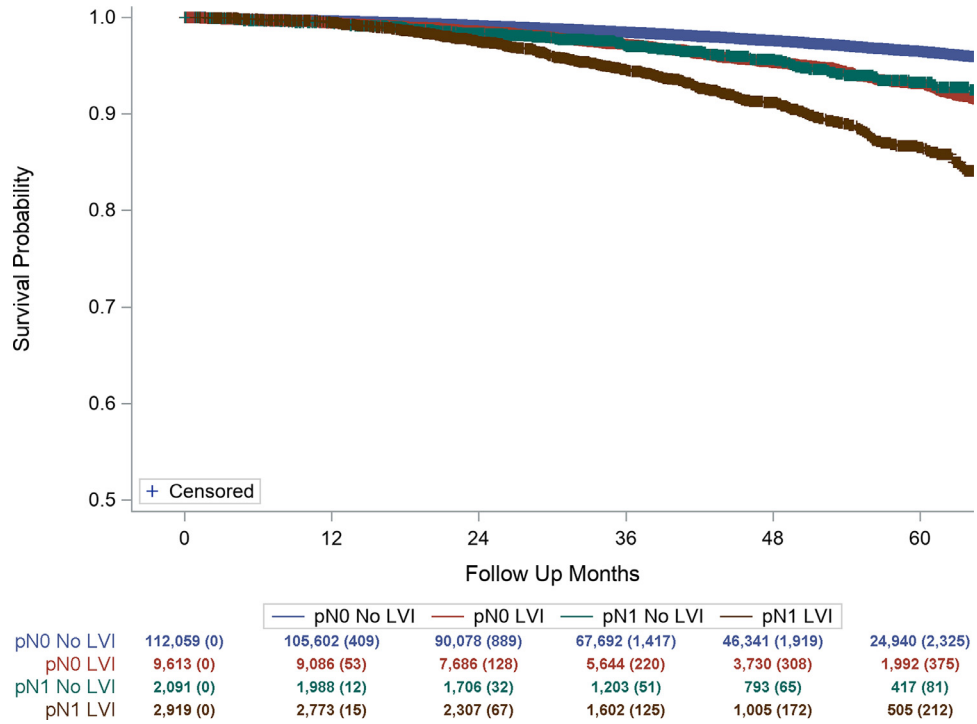

Figure 1. Kaplan-Meier figure depicting survival estimates in all patients vs. patients with lymphovascular invasion vs. lymph node involvement vs. lymphovascular invasion and lymph node involvement at time of radical prostatectomy, diagnosed between 2010 and 2015, within the National Cancer Database.

Table 2
Cox regression analysis predicting overall mortality in 126,682 non-metastatic prostate cancer patients treated with radical prostatectomy and pelvic lymph node dissection, between 2010 and 2015, within the National Cancer Database

Variable		Univariable Analysis			Multivariable Analysis		
		Hazards Ratio	95% CI	p value	Hazards Ratio	95% CI	*P* value
PSA		1.011	1.009–1.014	<.0001	1.004	1.002–1.007	0.0012
Age		1.06	1.054–1.065	<.0001	1.046	1.04–1.052	<.0001
CDCC Comorbidity							
	0	Ref			Ref		
	1	1.762	1.627–1.908	<.0001	1.646	1.511–1.793	<.0001
	2+	3.073	2.636–3.583	<.0001	2.676	2.267–3.158	<.0001
Gleason Grade							
	≤6	Ref			Ref		
	3+4	1.327	1.19–1.479	<.0001	1.211	1.072–1.368	0.0023
	4+3	1.687	1.496–1.903	<.0001	1.255	1.092–1.443	0.0019
	8	2.235	1.924–2.597	<.0001	1.471	1.237–1.749	<.0001
	9-10	4.548	4.039–5.121	<.0001	2.431	2.085–2.833	<.0001
Positive Surgical Margin		1.617	1.506–1.738	<.0001	1.154	1.061–1.255	0.0008
Pathologic Stage							
	pT1/2	Ref			Ref		
	pT3a	1.516	1.396–1.646	<.0001	1.116	1.013–1.229	0.0368
	pT3b+	2.973	2.731–3.236	<.0001	1.519	1.347–1.714	<.0001
Pathologic Positive Lymph Node Involvement (LNI)		2.795	2.496–3.131	<.0001	1.247	1.079–1.441	0.0027
Pathologic Positive Lymphovascular Invasion (LVI)		2.374	2.183–2.583	<.0001	1.283	1.151–1.43	<.0001
Adjuvant Radiotherapy within 1 year of RP		2.06	1.844–2.301	<.0001	1.042	0.908–1.196	0.582
Adjuvant Androgen Deprivation therapy within 1 year of RP		3.07	2.731–3.452	<.0001	1.231	1.051–1.441	0.0094
	Legend PSA: Prostate Specific Antigen						

disease, indicating less favorable survival in patients with LVI alone. Patients with LNI, but no LVI, had a similar OS (93.3%) to those who had LVI, but no LNI. Conversely, patients that had both LVI and LNI fared worse than patients who had only one of those two features, as their OS rate was 86.6%. Such observations ascertain a synergetic detrimental interaction between LVI and LNI, which was also confirmed on Cox-Regression Analysis. Our findings elucidated the prognostic importance of LVI by confirming that the presence of LVI increased overall mortality risk by 28% within the entire cohort (HR:1.28, $P<0.0001$). The increased overall mortality risk was considerably higher in patients that had concomitant LNI (HR: 1.66, $P<0.0001$), compared to patients that did not (HR:1.22, $P<0.0001$). Due to the synergetic detrimental interaction shown by our analyses, LVI should not be considered for use as a surrogate for LNI, but actually provides important complementary prognostic information of its own accord. To our best knowledge, our report is the first to document such findings.

Our results also show that LVI has a similar prognostic impact to Gleason 4+3 disease and indicates a worse prognosis than the presence of positive surgical margins, or pT3a disease, all of which carry significant prognostic weight and indicate adverse pathology. In addition to its impact on OS, this further establishes the importance of assessing LVI when determining patient's prognosis after RP.

Our study corroborates and adds to several previous reports on this topic. For example, several prior studies have established the association between LVI and increased BCR [12-14,22]. However, our assessment of OS is an important next step as BCR has recently been shown to not be an ideal surrogate for OS [23-26]. Our findings are also the first to show the detrimental prognostic impact of LVI on OS in a contemporary, large, North American cohort, adding to prior single [27,28] and multi-institutional studies [14], as well as a smaller, nationwide Asian cohort [20]. Lastly, while previous reports showed a possible relationship between LVI and LNI, our report is the first to explain in depth the nature of this relationship. Interestingly, we found the relationship to be synergistic and not simply additive, which implies a possibly different mechanism of disease spreading in patients with LVI, a point which definitely warrants further investigation.

Our studies also somewhat contradict the findings of a previous report by Wilczak et al [16], which assessed the prognostic value of LVI and whether it may complement or replace lymph node assessment in clinical practice. While our findings mirrored theirs in identifying that patients with LVI alone had similarly unfavorable survival as patients with LNI alone, in their cohort they identified no significant difference between patients that had both LNI and LVI and patients that had only LVI or only LNI. This incongruent finding may be due to the difference in the examined cohorts, specifically a nationwide US cohort vs. a single institutional European cohort, exclusion criteria, and/or the examined endpoints, as we assessed OS, while Wilczak et al assessed BCR-free survival.

Our study has several limitations. For example, our study lacks a centralized pathological review. While this is a limitation, contrarily, in some ways it may function as a strength as it lends reproducibility and applicability of our results to the clinical practice within the United States. Further, our study might be limited by imprecise nodal status assessment, as most patients received a limited lymph node dissection, which is the current practice in the US. Last but not least, due to the retrospective and observational nature of our cohort, our results should only be considered as hypothesis generating. Further due to the retrospective nature, there is possibility of increased confounding as compared to prospective or randomized controlled studies. Thus, a univariable analysis alone would be insufficient for a study of this nature. Our multivariable analysis isolated and evaluated the prognostic impact of each variable while adjusting for all other abstracted covariates. Thus, confirming the prognostic impact of various variables, including the negative impact of LVI (HR:1.283, 95% CI: 1.15 -1.43, $P<.0001$).

5. Conclusion

Within a large, contemporary nationwide cohort, men with LVI had worse OS outcomes when compared to those without LVI. Moreover, LVI also showed a synergistic interaction with LNI, leading to considerably increased mortality risk in patients that have both adverse pathological features. Our findings highlight an important utility that LVI can provide in deciding a patient's prognosis following RP, and further exploration is necessary to determine the true role of LVI as a prognostic indicator.

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Declaration of Competing Interest

No conflicts of interest to disclose

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