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Impact of Lymphovascular Invasion on Overall Survival in Patients With Prostate Cancer Following Radical Prostatectomy: Stage-per-Stage Analysis

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Impact of Lymphovascular Invasion on Overall Survival in Patients With Prostate Cancer Following Radical Prostatectomy: Stage-per-Stage Analysis

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ABSTRACT

The detrimental impact of lymphovascular invasion (LVI) in prostate cancer on biochemical recurrence has been described; the impact of LVI on overall survival remains unclear. In this study, we determined that patients with LVI identified on final pathology after radical prostatectomy fared worse than those without.

Background: The detrimental impact of lymphovascular invasion (LVI) in prostate cancer (PCa) on biochemical recurrence has been described; the impact of LVI on overall survival (OS) remains unclear. This investigation sought to evaluate the impact of LVI on OS in patients with PCa. **Methods:** We examined men with nonmetastatic PCa treated with radical prostatectomy between 2010 and 2015. Only men with documented LVI status were included ($n = 232,704$). Patients were stratified according to final pathologic T stage (pT2, pT3a, and pT3b). **Results:** Of the 232,704 patients who met inclusion criteria, 17,758 (8%) were found to have LVI on final pathology. Overall, 174,838 (75%), 40,281 (17%), and 17,585 (8%) patients had pT2, pT3a, and pT3b disease, respectively. Median follow-up was 42.7 months (27.1-58.7). At 5 years, the OS in LVI versus non-LVI patients was 94% versus 95% in pT2 ($P = .0004$), 92% versus 95% in pT3a ($P < .0001$), and 86% versus 92% in pT3b ($P < .0001$). On multivariable analysis, LVI status was not an independent predictor of OS in pT2 disease (hazard ratio, 1.12; 95% confidence interval [CI], 0.93-1.36; $P = .2$). In pT3a and pT3b disease, presence of LVI had 1.2-fold (95% CI, 1.03-1.44; $P = .02$) and 1.4-fold (95% CI, 1.20-1.59; $P < .001$) higher overall mortality than their counterparts without LVI. **Conclusions:** Our report demonstrates the detrimental impact of LVI on OS in locally advanced PCa (pT3a and higher). This information may prove valuable when risk stratifying based on final pathology.

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed solid organ malignancy and the second leading cause of cancer-specific mortality in men within the United States, with an estimated 191,930 new diagnosis and 33,330 deaths in 2020.[1] Clinical and pathologic staging are integral in assigning risk-stratification and determining appropriate treatment.[2,3] Of the available treatments, radical prostatectomy remains one of the most commonly performed interventions for patients with clinically localized PCa.[4] Despite the many advances in the treatment of PCa; the rates of biochemical recurrence (BCR) remain high, with estimations of 20% to 30%,[5,6] Therefore, it remains of paramount importance to identify those pathologic features that increase a patient's risk of recurrence, because it is expected that more high-risk and more locally advanced disease is to be identified in the coming years with the 2012 US Preventative Task Force's recommendations against routine prostate-specific antigen (PSA) screening owing to concerns of overtreatment.[7]

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Lymphovascular invasion (LVI) has been recognized as an adverse pathologic feature, estimations on the incidence differ widely, between 5.1% and 46.3% of patients with prostate cancer who undergo radical prostatectomy are found to have LVI on final pathology.[8] Various investigations have demonstrated the association between LVI and higher PSA, higher Gleason score, more advanced stage, higher rate of lymph node involvement and a higher risk of BCR.[6,9-14] However, the impact of LVI on overall survival (OS) has been scarcely addressed in the literature and remains unclear, with a majority of the focus primarily on the effect of LVI on BCR-free survival, which may not necessarily be a good surrogate for OS.[15-17] Finally, although few studies have assessed the role of LVI as an adverse prognostic factor in pT3 patients, no studies have assessed its prognostic impact in PCa of other stages.[12,13] Our objective was, therefore, to evaluate the prognostic capacity of LVI as a predictor of OS stratified by pathologic tumor stage.

Materials and Methods

Study Population

Data were obtained from the National Cancer Database, a national registry that is jointly sponsored by American Cancer Society and the Commission on Cancer of the American College of Surgeons, which captures approximately 70% of newly diagnosed malignancies within the United States annually. The National Cancer Database extracts data from more than 1500 commission-accredited cancer programs in the United States.[18]

Within the National Cancer Database, we identified a total of 232,704 patients with histologically confirmed nonmetastatic adenocarcinoma of the prostate who were treated with radical prostatectomy between 2010 and 2015. Patients before 2010 were excluded, owing to a lack of recorded LVI status within the National Cancer Database. Complete inclusion and exclusion criteria are detailed in Fig. 1.

Covariates

The following variables were extracted for all patients: age at diagnosis, race (Caucasian, African American, and other), serum PSA value at diagnosis, Charlson Comorbidity Index category (0, 1, or ≥2), pathologic tumor stage (pT2, pT3a, or pT3b), pathologic Gleason score (≤6, 3 + 4, 4 + 3, or 8-10), surgical margin status (negative or positive), number of nodes examined, number of positive nodes, pathologic nodal status (pN_0 or pN_1), and pathologic LVI status (pL_0 or pL_1). LVI was defined as the presence of tumor cells in lymphatic channels or blood vessels within the primary tumor.[18]

End Points

The primary end point investigated in this study was OS, which was defined as the months between diagnosis and death owing to any cause, or last available follow-up. Follow-up data were available through December 21, 2016.

Statistical Analyses

Frequencies and proportions were reported for categorical variables, while medians with interquartile ranges were reported for continuous variables. The χ^2 and Mann-Whitney *U* tests were used to compare categorical and continuous variables, respectively.

After stratification of patients based on LVI status, Kaplan-Meier curves were used to estimate OS. Next, Cox regression analyses were used to test the relationship between LVI status and OS using all available covariates. These analyses were repeated in all subcohorts after stratifying for pathologic stage. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Two-sided statistical significance was defined as a *P* value of less than .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.

Results

Descriptive characteristics of our cohort are reported in Table 1. The median age (interquartile range) and PSA for all patients was 62 years (56-67 years) and 5.6 ng/mL (4.3-8.2 ng/mL), respectively. The median (interquartile range) follow-up was 42.7 months (27.1-58.7 months). Most patients had pT2 disease (75%). Gleason score (3 + 4) was the most frequently identified Gleason score (44%). A total of 17,758 patients (8%) had LVI identified on final pathology. Patients with LVI had higher rates of Gleason score of 8 to 10 (43% vs 8%; $P < .0001$), higher pathologic tumor stage (pT3b, 31% vs 4%; $P < .0001$) and higher rates of lymph node involvement (20% vs 1%; $P < .0001$) than their counterparts without LVI.

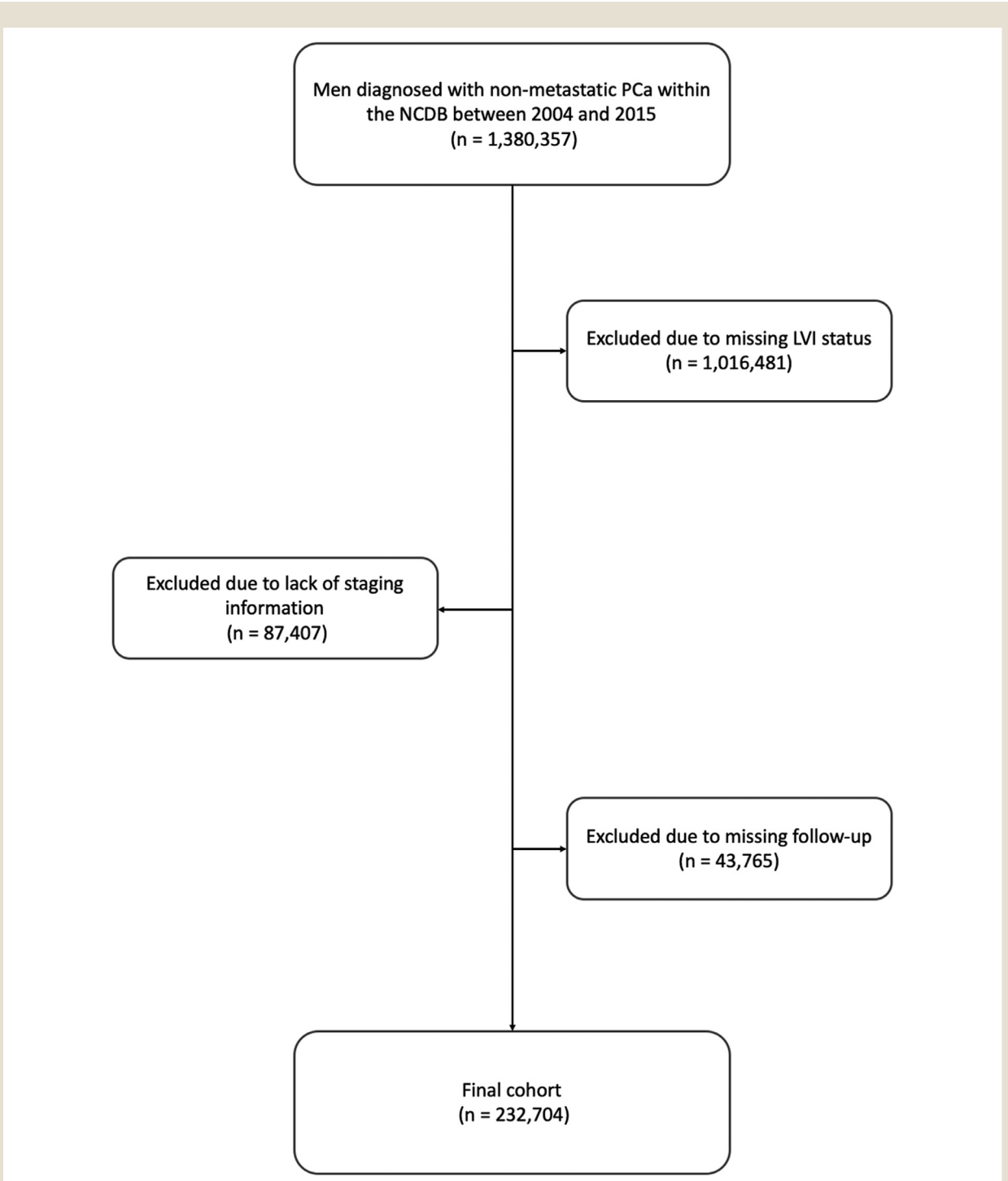
At 5 years, the OS in LVI versus non-LVI were 94% versus 95% in pT2 ($P = .0004$), 93% versus 95% in pT3a ($P < .0001$), and 86% versus 92% in pT3b ($P < .0001$), respectively (Fig. 2). A time to event analysis is available in Supplementary Table 1. On multivariable analysis, in all patients LVI status was an independent predictor of OS (hazard ratio, 1.41; 95% confidence interval [CI], 1.22-1.61; $P < .001$). When assessing specific stages of disease, LVI status was not an independent predictor of OS in pT2 disease (hazard ratio, 1.12; 95% CI, 0.93-1.36; $P = .2$). However, in pT3a and pT3b disease, the presence of LVI had a 1.2-fold (95% CI, 1.03-1.44; $P = .02$) and 1.4-fold (95% CI, 1.20-1.59; $P < .001$) higher overall mortality than their counterparts without LVI (Table 2).

Discussion

The objective of our study was to assess the impact of LVI on OS in patients who underwent radical prostatectomy for clinically localized PCa using a large contemporary cohort of North American patients. Historically, some investigations have attempted to evaluate the impact of LVI on oncological outcomes, these findings have frequently been inconsistent. This phenomenon may have been due to the recent standardization of LVI reporting by the International Society of Urological Pathology in 2009.[19] More contemporary reports assessing the outcomes of patients with LVI on final pathology have focused primarily on BCR, a parameter that has not been shown to be an ideal surrogate for OS in patients with prostate cancer.[15-17] Thus, our study aimed to address an important void in the literature by focusing on OS as an end point.

The results of our analysis were able to provide insight into the effects of LVI on patients with PCa according to pathologic tumor stage. The rate of LVI within the present study was 8%, which lies within the lower end of the variable range of the reported rates

Fig. 1 Patient selection flow diagram. LVI = lymphovascular invasion; PCa = prostate cancer; NCDB = National Cancer Database.



within the literature.[6,8,10,20,21] At 5 years, the OS in LVI versus non-LVI patients was 94% versus 95% in pT2 ($P = .0004$), 93% versus 95% in pT3a ($P < .0001$), and 86% versus 92% in pT3b ($P < .0001$). This deleterious impact of LVI on OS was most pronounced for patients with pT3b disease who demonstrated a 1.4-fold (95% CI, 1.20-1.59; $P < .001$) higher overall mortality than patients with pT3b without LVI. In an investigation conducted by Park et al,[12] the authors assessed patients with both LVI and seminal vesical invasion (SVI), patients with +LVI/+SVI were shown to have a far worse 5-year BCR-free survival rate compared with patients with

Table 1 Descriptive Characteristics of All 232,704 Patients Identified Within the National Cancer Database Stratified by the Presence or Absence of LVI on Final Pathologic Specimen.

Characteristics	Entire Cohort	No LVI	LVI	*P* Value*
Age	62 (56-67)	62 (56-67)	63 (57-67)	<.0001
Median PSA† (IQR)	5.6 (4.3-8.2)	5.5 (4.3-7.9)	7.3 (5-12.6)	.01
Race				
Caucasian	193,842 (83%)	178,898 (83%)	14,944 (84%)	ref
AA	29,328 (13%)	27,196 (13%)	2,132 (12%)	<.0001
Other	6556 (3%)	6053 (3%)	503 (3%)	.002
Missing	2978 (1%)	2799 (1%)	179 (1%)	
CCI				
0	190,569 (82%)	176,372 (82.1%)	14,197 (80%)	ref
1	36,781 (16%)	33,657 (15.7%)	3124 (17.6%)	<.0001
2	5354 (2%)	4917 (2.3%)	437 (2.5%)	<.0001
Gleason Score				
≤6	63,631 (27%)	62,799 (29%)	832 (5%)	ref
3 + 4	103,030 (44%)	98,872 (46%)	4,158 (23%)	.0002
4 + 3	37,052 (16%)	32,250 (15%)	4,802 (27%)	.009
8-10	24,859 (11%)	17,187 (8%)	7,672 (43%)	<.0001
Missing	4132 (2%)	3838 (2%)	294 (2%)	
LVI status		214,946 (92%)	17,758 (8%)	.5
pTstage				
pT2	174,838 (75%)	169,615 (79%)	5223 (29%)	ref
pT3a	40,281 (17%)	34,730 (16%)	5551 (31%)	.007
pT3b	17,585 (8%)	10,601 (5%)	6984 (39%)	<.0001
pNstage				
pN0	138,045 (59%)	127,236 (59%)	10,809 (61%)	ref
pN1	6129 (3%)	2617 (1%)	3512 (20%)	<.0001
pNX	50,535 (22%)	48,764 (23%)	1771 (10%)	0.2
Missing	37,995 (16%)	36,329 (17%)	1666 (9%)	
Nodes examined	3 (0-7)	3 (0-7)	5 (2-10)	<.0001
Surgical margins				
Positive	50,468 (22%)	42,904 (20%)	7564 (43%)	
Negative	179,388 (77%)	169,425 (79%)	9963 (56%)	
Unknown	2848 (1%)	2617 (1%)	231 (1%)	

AA = African American; CCI = Charlson Comorbidity Index; IQR = interquartile range; LVI = lymphovascular invasion; PSA = prostate-specific antigen (*ng/mL); ref = reference.
* The χ^2 *P* values refer to the comparison between patients with and without LVI in each respective clinical and pathologic parameter.

+LVI/–SVI, –LVI/+SVI or –LVI/–SVI (22.4%, 42.8%, 54.1%, and 61.5%, respectively). Although the primary outcomes between the referenced study and the present study are different, namely BCR versus OS, these findings reinforce the premise that patients with LVI in higher stage disease fare worse. The same authors also observed, through random survival Forest analysis modeling, that LVI was one of the most important predictors of BCR in patients with pT3 disease, second only to Gleason grade, further highlighting the importance of LVI.[12]

The implications of our findings are 2-fold. First, it aids providers with the necessary information to council patients on overall outcomes after radical prostatectomy, for one could only extrapolate rates of BCR and lymph node involvement in patients with LVI given the available literature.[6,9,12-14] LVI is a readily available pathologic finding that could be added to the armamentarium of providers, alongside other new prognostic tools, biomarkers, and genomic tests. Second, these findings may be used as a point of reinforcement when deciding which patients may require adjuvant treatment for marginal cases. Similar to our investigation, Fajkovic et al[6] investigated a cohort of 7427 patients treated by radical prostatectomy between 2000 and 2011 and identified that LVI was associated with BCR in patients with adverse pathologic features such as extracapsular extension, SVI, and a higher Gleason grade versus patients with a lower Gleason grade (Gleason grade 6) and organ-confined disease. Ultimately, the authors suggest possibly using LVI as a marker to decide which of these higher risk patients warrant adjuvant treatment. Given the multitude of investigations which have demonstrated worse BCR-free survival in patients with LVI and higher risk disease, and the present investigation demonstrating worse OS in patients with positive LVI status, this notion is consistent with the present authors opinions[6,9,11-14,20,21]

Fig. 2 Five-year overall Kaplan-Meir survival analysis for all 232,704 patients after radical prostatectomy with and without lymphovascular invasion on final pathology stratified by pathologic tumor stage. pTstage = pathologic tumor stage; LVI = lymphovascular invasion; OS = overall survival.

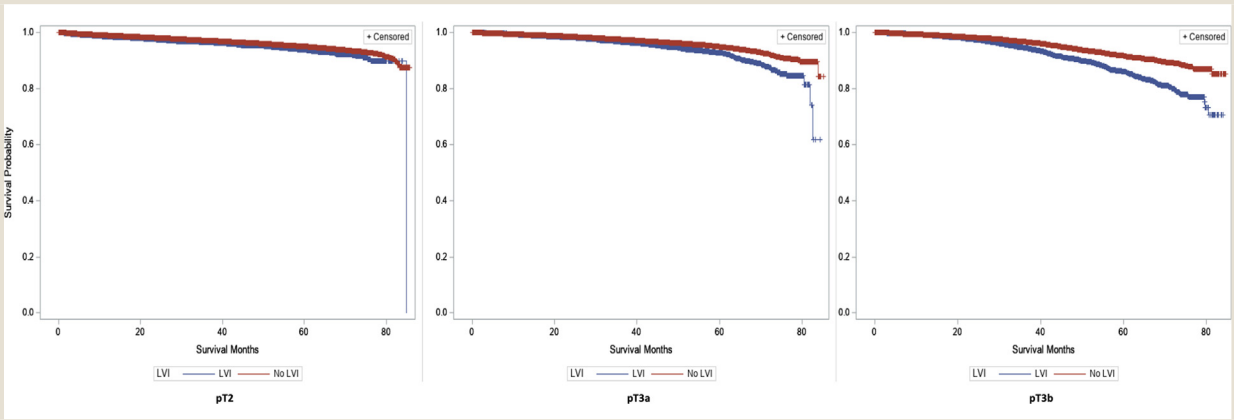


Table 2 Cox Multivariable Regression Predicting Overall Survival in All 232,704 Patients Identified Within the National Cancer Database Diagnosed With Prostate Cancer With Documented Presence or Absence of LVI on Final Pathologic Specimen Stratified by Pathologic Tumor Stage.

	pT2		pT3a		pT3b/pT4	
	HR (95% Confidence Interval)	*P* Value	HR (95% Confidence Interval)	*P* Value	HR (95% Confidence Interval)	*P* Value
Age	1.08 (1.08-1.09)	<.0001	1.05 (1.04-1.06)	<.0001	1.03 (1.02-1.04)	<.0001
Race						
AA	1.37 (1.23-1.53)	<.0001	1.23 (1.0-1.5)	.04	1.08 (0.87-1.34)	.5
Other	0.68 (0.51-0.90)	.009	0.77 (0.51-1.15)	.2	0.82 (0.54-1.23)	.4
Caucasian	ref		ref		ref	
CCI						
≥2	2.73 (2.3-3.2)	<.0001	3.18 (2.50-4.06)	<.001	2.05 (1.50-2.84)	<.001
1	1.64 (1.5-1.8)	<.001	1.80 (1.50-2.05)	<.001	1.51 (1.30-1.76)	<.001
0						
PSA	1.0 (0.99-1.00)	.1	1.05 (1.04-1.06)	.0007	1.00 (1.00-1.01)	.01
Gleason Grade						
3 + 4	0.85 (0.77-0.92)	<.0001	1.17 (0.86 -1.59)	.3	0.55 (0.30-1.11)	.07
4 + 3	0.87 (0.77-0.98)	.02	1.26 (0.92-1.73)	.2	0.67 (0.38-1.37)	.2
8-10	1.02 (0.88-1.19)	.8	1.80 (1.31-2.50)	.0003	1.48 (0.86-3.04)	.2
3 + 3	ref		ref		ref	
Pathologic N stage						
pN1	1.58 (1.14-2.20)	.006	1.19 (0.93-1.52)	.2	1.50 (1.20-1.71)	<.0001
pNX	1.04 (0.95-1.14)	.4	0.91 (0.75-1.11)	.4	0.84 (0.63-1.10)	.2
pN0	ref		ref		ref	
Nodes examined	1.03 (1.02-1.04)	<.0001	0.99 (0.99-1.01)	.8	0.99 (0.97-1.00)	.009
LVI						
Positive	1.12 (0.93-1.36)	.2	1.22 (1.03- 1.44)	.02	1.41 (1.22-1.61)	<.0001
Negative	ref		ref		ref	
Surgical margins						
Positive	0.99 (0.89-1.09)	.8	1.18 (1.04-1.34)	.009	1.31 (1.14-1.50)	<.0001
Negative	ref		ref		ref	

AA = African American; CCI = Charlson Comorbidity Index; HR = hazard ratio; LVI = lymphovascular invasion; PSA = prostate-specific antigen; ref = Reference.

Our investigation is not without limitations; we acknowledge the limitations of using a large database such as the National Cancer Database, which could potentially result in a potential overpowering given the large sample size. Second, our analysis was preformed retrospectively and lacked centralized pathologic review. This limitation may contribute to either an overestimation or underestimation of the rates of LVI in radical prostatectomy specimens. It has been reported previously that processing artifacts may mimic LVI, and only unequivocal cases of LVI should be reported as so.[6,22,23] Therefore, it may be difficult to ascertain the impact of a lack of centralized pathologic review and hence the use of a large cohort may represent more of a realistic representation of the general population. Third, the median follow-up in our cohort was 42.7 months and, given the natural disease progression of PCa, this relatively short follow-up period may not truly capture the long-term negative implications of LVI on OS. Furthermore, when assessing characteristics that may also contribute to worsening OS in such a short follow-up period, factors such as pathologic lymph node status was not seen to be significant in patients with pT3a disease, as it was in patients with pT3b disease, which may be contrary to the available literature. This result may have been in fact the result of the shortened follow-up. Last, our investigation is unable to provide information regarding any potential treatment's patients received postoperatively.

That said, our investigation, to our knowledge, is one of the first to provide insight into the negative effects of LVI on OS, and the first to stratify the impact of LVI on OS by pathologic stage. This information may prove essential in counseling patients regarding the potential outcomes after radical prostatectomy and may augment the discussion between physicians and patients in regard to adjuvant treatment in high risk PCa.

Conclusion

Our report demonstrates the detrimental impact of LVI on OS in locally advanced prostate cancer (pT3a and higher). This information may prove valuable when risk stratifying patients based on final pathology and counseling patients regarding outcomes and determining the necessity of further treatment.

Clinical Practice Points

- Lymphovascular invasion (LVI) has been recognized as an adverse pathologic feature. Various investigations have demonstrated the association between LVI and higher prostate-specific antigen, a higher Gleason score, more advanced stage, higher rate of lymph node involvement and higher risk of biochemical recurrence.
- The impact of LVI on overall survival has been scarcely addressed in the literature and remains unclear, with a majority of the focus primarily on the effect of LVI on biochemical recurrence-free survival, which may not necessarily be a good surrogate for overall survival.
- Our report demonstrates the detrimental impact of LVI on overall survival in locally advanced prostate cancer (pT3a and higher).
- This information may prove valuable when risk stratifying based on final pathology and counseling patients regarding outcomes and determining the necessity of further treatment.

CRediT author statement

Marcus Jamil MD: Conceptualization, methodology, validation, investigation, writing, original draft/review & editing, visualization, project administration **Nikola Rakic BS:** Conceptualization, methodology, validation, investigation, writing, original draft/review & editing, visualization, project administration, **Akshay Sood:** Conceptualization**,** methodology, **Jacob Keeley:** software, formal analysis, resources, **Daniele Modonutti**: Conceptualization, **Giacomo Novara**: Conceptualization**,** methodology, review **Wooju Jeong:** Conceptualization**,** methodology, review **Mani Menon:** Conceptualization**,** methodology, **Craig G Rogers:** Conceptualization**,** methodology, **Firas Abdollah MD**: Conceptualization, methodology, validation, investigation, writing, original draft/review & editing, visualization, project administration

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Disclosure

Firas Abdollah is a consultant for GenomeDx Biosciences.

All other authors state that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.04.009.

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