Differences in the rate of lymph node invasion in men with clinically localized prostate cancer might be related to the continent of origin

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OBJECTIVE

To test whether the rate of lymph node invasion (LNI) differs between patients treated with radical prostatectomy (RP) at a European or a North American centre.

PATIENTS AND METHODS

In all, 1385 men had RP with bilateral lymphadenectomy for clinically localized prostate cancer (587 from Dallas, Texas and 798 from Milan, Italy). Univariate and multivariate analyses focused on the association between the continent of origin and the rate of LNI, after controlling for prostate-specific antigen (PSA) level, clinical stage, biopsy Gleason sum and the number of examined and removed lymph nodes.

RESULTS

European men had higher PSA levels (9.1 vs 7.8 ng/mL), a higher proportion of palpable cancers (44.5 vs 32.8%), more nodes removed (mean 14.9 vs 7.8) and a higher rate of LNI (9.0% vs 1.2%; all differences $P < 0.001$). In multivariate analyses that controlled for PSA level and clinical variables, European men had an 8.9-fold higher risk of LNI ($P < 0.001$) than their counterparts from the USA. Among preoperative variables, the continent of origin was the third most informative predictor of LNI (67.5%), after biopsy Gleason sum (74.3%) and the number of examined lymph nodes (71.0%), and improved the ability to predict LNI by 4.7%.

CONCLUSION

Men treated at a European centre had a 7.3–8.9-fold higher rate of LNI, despite adjusting for all clinical and pathological variables. It remains to be shown what predisposes European men to a higher rate of LNI.

KEYWORDS

prostate cancer, radical prostatectomy, lymph node invasion, pelvic lymphadenectomy

INTRODUCTION

Pelvic lymphadenectomy (PLND) has been considered an essential staging procedure for patients undergoing radical prostatectomy (RP) for localized prostate cancer [1]. The extent of PLND is associated with the rate of LN invasion (LNI). Higher LNI rates are reported with more extensive PLNDs [2–5]. The presence and extent of LNI predicts disease progression and long-term survival [6,7]. Therefore, LNI drastically changes the prognosis and the management of most men with prostate cancer.

Several variables are known to affect the rate of LNI. Besides PSA level, clinical stage and biopsy Gleason sum, the treatment institution represented a statistically significant predictor of LNI, in 5511 patients treated on three different continents [8]. Although the institution appears to represent an important predictor of LNI, no study directly tested for the presence and the magnitude of the difference in LNI rate between European and North American patients, after accounting for clinical and pathological variables, as well as the extent of PLND.

We hypothesized that the continent of origin is related to the rate of LNI in patients undergoing RP. To address this hypothesis we analysed the univariate and multivariate effect of the continent of origin on the rate of LNI in a large cohort of European and North American men treated with bilateral PLND before RP.

PATIENTS AND METHODS

Between July 1994 and August 2005, 1644 patients were treated with RP and bilateral PLND for localized prostate cancer at the University Vita-Salute San Raffaele, Milan, Italy (944) and at the University of Texas Southwestern Medical Center, Dallas, Texas, USA (700). Incomplete clinical data led to the exclusion of 259 patients (40 for missing PSA data, 21 for clinical stage, 44 for biopsy Gleason sum and 140 for the number of nodes removed and examined). Moreover, 14 patients were excluded as they had PSA level of >50 ng/mL, as these are highly indicative of metastatic disease [9]. These selection criteria yielded 1385 evaluable patients; of these, 798 (57.6%) were treated at a European and 587 (42.4%) at an American centre (Table 1). The extent of PLND was determined according to the preference of the operating surgeon. Pelvic LN specimens were submitted for pathology in multiple packages, which improves the quality of specimen assessment [10]. A central pathological review was not

TABLE 1 Patient characteristics and descriptive statistics

Variable	All	European	USA	P
n (%) or mean (median, range)				
Total patients	1385	798 (57.6)	587 (42.4)	NA
Age, years	63.4 (63.7, 39–85)	65.8 (66.6, 45–85)	60.0 (60.6, 39–75)	<0.001
Clinical stage				<0.001
T1c	838 (60.5)	433 (55.5)	395 (67.3)	
T2	522 (37.7)	335 (42.0)	187 (31.9)	
T3	25 (1.8)	20 (2.5)	5 (0.9)	
PSA level, ng/mL	8.6 (6.6, 0.1–49.9)	9.1 (7.0, 0.2–49.9)	7.8 (6.1, 0.1–44.5)	0.001
0–4.0	186 (13.4)	105 (13.2)	81 (13.8)	
4.01–10.0	858 (61.9)	461 (57.8)	397 (67.6)	
10.01–20.0	266 (19.2)	185 (23.2)	81 (13.8)	
>20	75 (5.4)	47 (5.9)	28 (4.8)	
Biopsy Gleason sum				0.281
≤6	914 (66)	529 (66.3)	385 (65.6)	
7	371 (26.8)	205 (25.7)	166 (28.3)	
8–10	100 (7.2)	64 (8.0)	36 (6.1)	
Stage pT2	956 (69.0)	554 (69.4)	402 (68.5)	0.341
Missing	17 (1.2)	17 (2.1)	–	
ECE	260 (18.8)	126 (15.8)	134 (22.8)	0.002
Missing	17 (1.2)	17 (2.1)	–	
SVI	144 (10.4)	93 (11.7)	51 (8.7)	0.055
Missing	17 (1.2)	17 (2.1)	–	
LNI	79 (5.7)	72 (9.0)	7 (1.2)	<0.001
Number of LNs removed and examined	11.9 (11, 1–42)	14.9 (14, 2–40)	7.8 (7.0, 1–42)	<0.001
Number of +ve LNs	2.3 (1.0, 1–13)	2.4 (1.5, 1–13)	1.8 (1.0, 1–5)	0.541
Positive LN density	0.162 (0.1, 0.03–0.87)	0.153 (0.09, 0.03–0.87)	0.257 (0.166, 0.10–0.60)	0.103

used, but all specimens were analysed by dedicated genitourinary pathologists.

LNI represented the outcome variable; the main predictors included preoperative PSA level, clinical stage, biopsy Gleason sum, number of removed and examined LNs and the institution of origin (Europe vs USA). Additional adjustment was made for pathological stage, i.e. the presence of extracapsular extension (ECE) and seminal vesicle invasion (SVI), and RP Gleason sum.

Two-sided tests with significance set at 0.05 were used. The association between the predictors and LNI was tested in univariate and multivariate logistic regression models. The aim of these analyses was to determine whether the variable defining the institution of origin represents a statistically significant predictor of LNI. Also, multivariate analyses tested whether the institution of origin represents an independent predictor of LNI. Finally, the univariate accuracy of predictor variables, and the multivariate accuracy of regression models, was quantified with the area under the receiver operating characteristics curve and 200 bootstrap re-samples were used to reduce overfit bias. Predictive accuracy (PA) tests were aimed at quantifying the ability of the variable defining the institution of origin to predict LNI, as well as the ability of that variable to increase the accuracy of the established clinical predictors to predict the rate of LNI.

RESULTS

The age of the 1385 patients was 39–85 years; most had clinical stage T1c disease, serum PSA values of 4–10 ng/mL and biopsy Gleason sums of ≤6. LNI was detected in 79 of 1385 patients. The number of nodes removed was 1–42, while the number of positive nodes was 1–13; detailed results are shown in Table 1.

European men were significantly older, had a higher preoperative PSA level, a higher proportion of palpable cancers, more nodes removed (mean 14.9 vs 7.8) and had a higher rate of LNI (9.0% vs 1.2%; both differences $P < 0.001$). Conversely, biopsy Gleason sums and the number of positive LNs were similar between the continents. ECE was more prevalent in North American men, while SVI was slightly more prevalent in Europeans.

Univariate and multivariate logistic regression models predicting LNI with PSA level, clinical stage, biopsy Gleason sum and total number of removed and examined LNs are shown in Table 2. In univariate analyses, there was a significant association between the continent of origin and the rate of LNI (odds ratio, OR, 8.2; $P < 0.001$). All other predictors (PSA level, clinical stage, biopsy Gleason sum and the number of removed and examined LNs) were also significantly associated with LNI (all $P \leq 0.001$). In univariate analyses, among preoperative variables, the continent of origin (67.5%) was the second most informative predictor of LNI, after biopsy Gleason sum (74.3%).

In multivariate analyses, after accounting for PSA level, clinical stage and biopsy Gleason sum, European patients had an 8.9-fold greater risk of having LNI than their American counterparts ($P < 0.001$). The association between European origin (OR 7.3; $P < 0.001$)

TABLE 2 Univariate and multivariate analyses predicting LNI based on pretreatment PSA level, clinical stage, biopsy Gleason sum, number of removed and examined LNs and the continent of origin (Europe vs North America)

	Univariable		Multivariable			
Predictors	OR; P	PA, %	OR; P	OR; P	OR; P	OR; P
Age	1.06; <0.001	62.8	1.1; 0.002	1.02; 0.4	1.04; 0.01	1.0; 0.6
Preoperative PSA level	1.06; <0.001	67.0	1.03; 0.1	1.03; 0.08	1.0; 0.9	1.0; 0.8
Clinical stage	–; <0.001	64.1	–; <0.001	–; <0.001	–; –	–; –
T2 vs T1c	2.05; 0.004		1.5; 0.1	1.5; 0.2	–; –	–; –
T3 vs T1c	24.8; <0.001		12.5; <0.001	10.1; <0.001	–; –	–; –
Biopsy Gleason sum	–; <0.001	74.3	–; <0.001	–; <0.001	–; –	–; –
7 vs 2–6	5.5; <0.001		4.5; <0.001	5.2; <0.001	–; –	–; –
8–10 vs 2–6	2.5; <0.001		8.3; <0.001	9.5; <0.001	–; –	–; –
Number of removed LNs	1.09; <0.001	71.0	–; –	–; –	1.09; <0.001	1.05; 0.01
ECE	1.4; 0.2	52.8	–; –	–; –	5.7; <0.001	6.3; <0.001
SVI	23.0; <0.001	78.7	–; –	–; –	28.2; <0.001	30.0; <0.001
Pathological Gleason sum	–; <0.001	79.5	–; –	–; –	–; 0.005	–; 0.002
7 vs 2–6	8.7; <0.001		–; –	–; –	2.8; 0.1	2.8; 0.1
8–10 vs 2–6	61.6; <0.001		–; –	–; –	6.2; 0.007	7.2; 0.004
Continent of origin	8.2; <0.001	67.5	–; –	8.9; <0.001	–; –	7.3; <0.001
Multivariable PA, %	–	–	80.0	84.7	91.8	93.3

The four columns for the multivariate models represent four different prognostic models; two include preoperative variables (without and with the continent of origin, left two columns) and two represent postoperative models (without and with the continent of origin, right two columns).

and a higher rate of LNI persisted after adjusting for ECE, SVI, pathological Gleason sum, and PSA level and age. Finally, in models that included age, PSA level, clinical stage and biopsy Gleason sum (Table 2), considering the continent of origin resulted in 4.7% increase in PA (from 80.0% to 84.7%; $P < 0.001$). The increase in PA was smaller when the variable representing the continent of origin was added in a multivariate model including age, PSA level, number of removed LNs, ECE, SVI and pathological Gleason sum (from 91.8% to 93.3%; $P = 0.1$).

DISCUSSION

In patients with localized prostate cancer, LNI is almost invariably associated with clinical disease progression. However, the existing tools used to predict LNI are still relatively inefficient in their ability to identify those who harbour metastases [1–5]. The earliest possible identification of patients with LNI would be helpful for many reasons. First, those with LNI could be spared from potential local therapies, which offer a limited probability of cure. Alternatively, those with high index of suspicion for the presence of occult metastases could be included in clinical trials of early systemic intervention. Therefore, identifying men with LNI before treatment represents an important consideration. Unfortunately, currently existing predictive tools are incapable of providing perfect predictions. The limitations in their predictive accuracy stem from many sources. Existing markers such as serum PSA level, clinical stage and biopsy Gleason sum are accurate but not perfect for predicting the rate of LNI. Biomarkers, such as nuclear factor-κB, are still in their infancy and have not been tested in large cohorts to warrant their standard inclusion [11]. Finally, other variables, which might modify the relation between established clinical predictors of LNI and their ability to predict the rate of LNI, are under investigation [12].

Cagiannos *et al.* [8] identified the institution of origin as a statistically significant predictor of LNI in 5510 patients; its statistical significance persisted after accounting for serum PSA level, clinical stage and biopsy Gleason sum. Moreover, including the variable accounting for institutional differences increased the PA by 2%. These findings suggest that institutional differences affect the rate of LNI, despite controlling for PSA level, clinical stage and biopsy Gleason sum. The inter-institutional differences reported by Cagiannos *et al.* are even more interesting, as this series included men from six institutions who were treated on three different continents [8]. Of the centres included, one was in Australia, one in Europe, and the remaining four in four different parts of the USA. In that context, the presence of inter-institutional differences suggests that the biological characteristics of prostate cancer might differ among regions and might impart different risks of LNI, despite the same clinical characteristics.

However, it could also be argued that in the reports of Cagiannos *et al.* other variables might have accounted for the observed effect of the institution of origin. These variables might include the extent of PLND or differences in pathological stages of prostate cancer. Extended PLND is associated with a higher yield of LNI [3,4]. Similarly, pathological tumour characteristics might differ despite similar clinical characteristics. At some institutions different selection criteria for RP might translate into differences in pathological stages at RP. Thus, when the association between clinical variables and the rate of LNI is considered, it is imperative to account for sources of potential bias, such as the extent of PLND, as well as the pathological tumour stage and grade.

In the present study we examined the relation between established clinical predictors and the rate of LNI in men from two large academic centres in Italy and the USA. Our objective was to test whether the rate of LNI was the same in European and North American patients, after accounting for pretreatment PSA level, clinical stage and biopsy Gleason sum. Our analyses relied on multivariate logistic regression models, which predicted the rate of LNI. The predictors in these models consisted of clinical stage, PSA level and biopsy Gleason sum. Moreover, the continent of origin (Europe vs America) and the extent of PLND, expressed as the number of removed and examined LNs, were added. The variable representing the extent of PLND was not included in the model by Cagiannos *et al.* [8].

The present results showed a significant association between the continent of origin and the rate of LNI in univariate analyses ($P < 0.001$); the same statistical significance ($P < 0.001$) persisted when the effect of the continent of origin was adjusted for the effect of preoperative PSA level, clinical stage and biopsy Gleason sum. European patients were nine times more likely to have LNI ($P < 0.001$), after accounting for all covariates. Moreover, when further adjusting for pathological variables (including pathological Gleason sum, ECE, SVI, the number of removed and examined LNs, and age and preoperative PSA level) there was seven times the rate of LNI ($P < 0.001$). These findings have important implications, as they show that PSA level, clinical stage, biopsy Gleason sum and the extent of PLND cannot fully discriminate between LNI-positive and -negative patients, when continent of origin differences are considered. Moreover, further adjustment for pathological Gleason sum, ECE and SVI also failed to annul these differences and suggests that not even pathological variables can fully account for the discrepancy in LNI rates between Europe and the USA.

Several variables predisposed European patients to a higher rate of LNI. Europeans had more advanced disease characteristics, i.e. higher PSA levels and a higher rate of palpable cancer. Moreover, PLNDs in European men were more extensive, at 14.9 vs 7.8 nodes. After controlling for these differences, the rate of LNI was still nine times higher in Europeans. The increased rate of LNI was not accounted for by including pathological tumour characteristics, as the odds ratio of 7.3 persisted when these were included in multivariate analyses.

The cause of this disparity in LNI rate between Europe and America cannot be explained with certainty. However, the effect of these dissimilarities can be approximated using the continent of origin as a proxy variable. Its use is therefore recommended when rates of LNI from different regions or institutions are analysed. In the present study, adding the variable defining the continent of origin into the multivariate model was associated with a 4.7% gain in PA. Thus, institution of origin is not only significantly related to the rate of LNI, but also improves the overall model accuracy, which represents an important statistical consideration.

Our findings on intercontinental differences in LNI rates are in agreement with Graefen *et al.* [13], who reported significant differences in clinical characteristics between European and North American patients. For example, the PSA level was ≤4 ng/mL in 23% of North Americans, vs 9% of Europeans. Furthermore, Europeans were more frequently diagnosed with a biopsy Gleason score of ≥7. Intercontinental differences in pathological variables were also reported; the rate of clinically insignificant prostate cancer (defined as a tumour volume of <0.5 mL and no Gleason 4 or 5) was lower among Europeans (5.8%) than North Americans (range 10–30.7%) [14,15]. Taken together, these data suggest that, in general, European patients might harbour less favourable prostate cancer variants than their American counterparts.

These findings are important, as they suggest that variables that have not yet been identified might account for observed differences in LNI rates. Moreover, our findings suggest that predictive models for LNI developed within North American cohorts might not be applicable in European patients, unless there is a statistical adjustment for the continent of origin. Many hypotheses might be postulated to explain the differences between European and North American patients. PSA screening might be more heavily enforced in the USA than in Italy. Moreover, early detection of prostate cancer might be more rigorously enforced in the USA. The combination of screening and early detection might lead to an earlier diagnosis, where fewer men have LNI. Alternatively, a selection bias might account for the observed differences, whereby North American surgeons might suggest treatments other than RP for men with less favourable clinical characteristics. Moreover, socio-economic status and cultural differences among the two populations might further bias the results. The socio-economic status can affect the proportions of patients seeking medical advice for prostate problems, which might trigger PSA testing and prostate biopsies. Finally, the observed differences might be explained by third variables, e.g. genetic, where the phenotypes of tumours found in European men have a greater propensity for nodal spread. Unfortunately, the present study cannot identify or confirm a causal relationship, nor can it exclude that the aforementioned biases are operational.

There are other limitations; first, our findings need to be confirmed with data from other European and North American centres to further validate the observed intercontinental differences. Second, several limitations are related to differences between the number of LNs removed and the number of LNs that are actually examined by the pathologist. Possibly fewer nodes might have been examined in American patients, which might have led to a lower LNI rate. Differences in patient anatomy, specifically the LN to fibrofatty tissue ratio, might vary among patients. This could have affected the LN yield and the LNI rate. Lack of central pathological review represents another limitation. At some institutions a more rigorous search for LNs within the surgical specimen might yield more nodes and a higher rate of LNI. Finally, the reported differences in LNI rate might be universal, or they might only apply to men treated in the specific period at the two treatment institutions. Indeed the observed differences might not be generally applicable to other European and/or North American populations (Table 3) [3–5,16–20].

In conclusion, our study shows that, after accounting for clinical and pathological variables, the continent of origin represents a highly statistically significant and informative predictor of LNI; European men have nine times the risk of LNI. Clinical and pathological variables, e.g. PSA level, clinical stage, biopsy Gleason sum and the extent of PLND, cannot completely explain this difference. Novel variables are needed to explain this discrepancy.

Origin/study	PLND, % overall	extended	limited
Europe			
Conrad *et al.* [17]	5.8	–	5.8
Jeschke *et al.* [18]	12.6	12.6	–
Heidenreich *et al.* [3]	19.2	26.2	12
Bader *et al.* [2]	24	24	–
Weckermann *et al.* [19]	8.5	8.5	–
North America			
Clark *et al.* [16]	6.5	4	3.2
Palapattu *et al.* [7]	4.4	4.4	–
Allaf *et al.* [4]	2.3	3.3	1.2
Stone *et al.* [5]	12.2	23.1	7.3
Daneshmand *et al.* [20]	12.1	–	12.1

TABLE 3
Reported prevalence of LNI in extended or limited PLND in European and North American men

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **PLND**, pelvic lymphadenectomy; **RP**, radical prostatectomy; **LN(I)**, lymph node (invasion); **OR**, odds ratio; **ECE**, extracapsular extension; **SVI**, seminal vesicle invasion; **PA**, predictive accuracy.