Extended pelvic lymph node dissection in prostate cancer: a 20-year audit in a single center

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Background: We set to assess the impact of stage migration in prostate cancer (PCa) on the evolution of the pN1 rate and tumor characteristics in pN1 patients over the last two decades.

Patients and methods: We evaluated 5274 PCa patients treated with radical prostatectomy and anatomically extended pelvic lymph node dissection (ePLND) between 1990 and 2010. Year-per-year trends of clinical and pathological characteristics were examined. Logistic regression analyses addressed predictors of pN1.

Results: The median number of lymph nodes (LNs) removed was 16.0. Overall, the pN1 rate was 13.8% and it decreased from 26.1% to 15.6% between 1990 and 2010 (P < 0.001). For the same period, the pN1 rate changed from 0% to 3% in the low-risk PCa, from 20% to 7% in the intermediate-risk PCa, and from 33% to 44% in the high-risk PCa (P ≤ 0.01). In pN1 patients, pre-operative cancer characteristics and the median number of positive LNs (three in 1990 versus two in 2010) did not significantly change overtime (all P ≥ 0.1). Year of surgery was not an independent predictor of pN1 (all P ≥ 0.06).

Conclusion: Based on ePLND outcomes, contemporary patients with intermediate- and high-risk PCa’s still harbor a significant LNI risk. In consequence, stage migration does not justify omitting or limiting the extent of PLND in these individuals.

Key words: extended pelvic lymph node dissection, lymph node invasion, prostate cancer, risk groups, stage migration

introduction

The widespread use of the prostate-specific antigen (PSA) in clinical practice has lead to an important shift in prostate cancer (PCa) characteristics at diagnosis [1, 2]. Contemporary PCa patients are indeed often diagnosed with less aggressive disease when compared with their historic counterpart [1, 2]. However, the impact of this phenomenon usually referred to as ‘stage migration’ on node-positive disease has been poorly addressed.

Recent reports showed a progressive decrease in the rate of lymph node invasion (LNI) over time among surgically treated patients [3, 4]. Prevalence of LNI in the most contemporary patients was as low as 3% [3]. However, all these studies are limited by two main drawbacks: (1) not all men included received pelvic lymph node dissection (PLND) and (2) when PLND was performed, this consisted of a suboptimal, limited dissection [3–6]. For these reasons, nodal status might have been non-adequately staged in a significant proportion of these patients. From this premise, the real changes in LNI rates as well as in cancer characteristics of patients with LNI remain unknown. These observations could only be reliably addressed if consecutive patients treated with anatomically defined extended PLND (ePLND) were considered, given the well-known association between the extent of PLND and the rate of LNI [7–11].

Although the therapeutic role of ePLND has been a subject of continuous debate, its importance as an accurate staging procedure has always been recognized. As such, at our institution, anatomically ePLND has been always performed as an integral part of retro-pubic radical prostatectomy (RRP), regardless of cancer features. From this premise, the purpose of this study was to examine the evolution of LNI rates as well as the changes in cancer features among LNI patients treated with ePLND overtime. Indeed, given the standardized use of anatomically defined ePLND in all patients, any changes in LNI rates and features are likely to be attributed to changes in tumor characteristics over the study period.

materials and methods

patient population

We analyzed 6393 consecutive PCa patients treated with open RRP and anatomically ePLND at a single institution between 1990 and 2010.
Patients who did not receive an ePLND (n = 627) and/or received any neo-adjuvant treatment (n = 492) were excluded. These selection criteria yielded 5274 assessable patients.

All patients were pre-operatively staged with bone scan and abdomino/pelvic computerized tomography or abdominal ultrasound. Surgical procedures were performed by 10 different surgeons, using a standardized retro-pubic approach. ePLNDs consisted of the excision of fibrofatty tissue along the external iliac vein, the distal limit being the deep circumflex vein, and the femoral canal. Proximally, ePLND was performed up to and including the bifurcation of the common iliac artery. Furthermore, all fibrofatty tissue within the obturator fossa was removed to completely skeletonize the obturator nerve. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat. Lymph nodes (LNs) along the internal iliac vessels were invariably dissected. In some cases, LNs located in the pre-sacral and common iliac areas were also removed (Figure 1). For each patient, six separate LN packets were sent, one for each of the following anatomical regions: the obturator (right and left), the external iliac (right and left), and the internal iliac (right and left) area. Additional packets were sent when the pre-sacral and/or common iliac node was dissected. Such approach has been shown to improve the quality of specimen assessment [12].

pathological work-up of LNs

Fat tissue containing LNs were fixed in 10% buffered formalin. For each anatomic group, the number of nodes, the size of the largest node, and any gross features were described. The macroscopic specimen assessment was based on tactile and visual criteria. Large nodes (>2 cm) were sampled in multiple blocks. If no LNs were macroscopically detected, all fat tissue was processed. In particular cases, when an adequate number of LNs in large amount of fat tissue was not identified, an LN revealing solution based on acetic acid, alcohol, and formaldehyde (Carnoy clearing solution) was used. All blocks were embedded in paraffin, cut at 3 μm, and stained with hematoxylin–eosin. In selected cases, immunohistochemical stain for cytokeratin and multiple sections were analyzed.

variable definitions

Patient data included age at surgery (years), serum PSA value (ng/ml), clinical stage, biopsy Gleason score, pathological stage at RRP, pathological Gleason score, number of removed LNs, number of positive LNs (either used as continuously coded variable or dichotomized into the following categories: 1 versus 2 versus >2), and year of surgery (either continuously coded or grouped into: 1990–1995 versus 1996–2000 versus 2001–2005 versus 2006–2010). Pre-operative tumor risk was also classified into low, intermediate, and high according to the National Comprehensive Cancer Network (NCCN) guidelines definition [13].

We also reported post-operative complications potentially related to ePLND, consisting of: (i) clinically significant lymphoceles (CSLs), which was defined as the presence of a symptomatic lymphocele requiring any the type of invasive treatment (i.e. percutaneous drain, puncture, open or laparoscopic marsupialization), (ii) significant post-operative edema (of inferior limbs and/or genitals), and (iii) deep venous thrombosis (DVT) that occurred simultaneously, or was judged to be associated with post-operative lymph accumulation.

statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and ranges were reported for continuously coded variables. The year-per-year trend of clinical and pathological characteristics was reported in the overall population and in the subset of patients with LNI. The chi-square test and the one-way analysis of variance test were used to compare the differences in proportions and means, respectively.

The Kaplan–Meier curves were used to depict cancer-specific survival (CSS) rates in the overall cohort and in patients with LNI. Univariable and multivariable logistic regression models were used to test the relationship between the year of surgery and the LNI rate. Covariates consisted of the pre-operative PSA value, pathological stage, pathological Gleason score, and number of removed LNs.

All statistical analyses were performed using R statistical package system (R Foundation for Statistical Computing, Vienna, Austria) with a two-sided significance level set at P < 0.05.

results

Clinical and pathological data of the 5274 patients included in the study are summarized in Table 1. Overall, a significant increase in the proportion of patients with lower PSA values and less advanced clinical and pathological disease was noted over time (all P < 0.001). An opposite trend was instead seen for biopsy and pathological Gleason scores (all P < 0.001; Table 1).

The overall rate of CSLs, significant post-operative edema and DVT was 6.3%, 1.2%, and 0.3%, respectively. Higher rates of CSLs and significant post-operative edema were observed during the years 1990–1995 (7.8% and 1.7%, respectively) and 2006–2010 (8.3% and 2.1%, respectively). Conversely, lower rates of these complications were observed during the years 1996–2000 (3.5% and 0.3%, respectively) and 2001–2005 (5.2% and 0.6%, respectively). The rate of DVT did not significantly change overtime (Table 1).

Of all 5274 patients, 730 (13.8%) had LNI at ePLND. The rate of LNI decreased from 26.1% to 15.6% (P < 0.001) between 1990 and 2010 (Figure 2). For the same period, LNI rates changed from 0% to 3% in the low-risk, from 20% to 7% in the intermediate-risk, and from 33% to 44% in the high-risk group (all chi-square trend ≤0.01, Supplementary Figure S1A, available at Annals of Oncology online). When stratifying according to the clinical stage, the rate of LNI changed from 0% to 9% in T1, 33% to 19% in T2, and 0% to 53% in T3 cases (P = 0.2, P = 0.003, and P = 0.5, respectively; Supplementary Figure S1B, available at Annals of Oncology online). When stratifying according to the pathological stage, the rate of LNI

Figure 1. Graphical presentation of the PLND scheme: (1) The external iliac vessels region, (2) obturator fossa, (3) internal iliac vessels region, (4) common iliac vessels region, and (5) pre-sacral region.
changed from 9% to 1% in pT2, 50% to 18% in pT3a, and 33% to 59% in pT3b or higher cases (P = 0.001, P = 0.2, and P = 0.08, respectively; Supplementary Figure S1C, available at Annals of Oncology online).

Overall, the mean number of removed LNs was 17.4 (median, 16.0; range, 5.0–64.0; Table 1). Year-per-year trend analysis showed that the mean and the median number of removed LNs decreased between 1990 and 2000 (from 20.2 to...
13.8 and from 20 to 13, respectively) and then increased between 2001 and 2010 (from 14.2 to 18.7 and from 13 to 17, respectively; Figure 3). These trends were statistically significant ($P < 0.001$). When patients were stratified according to the nodal status (pN0 versus pN1, respectively), significant changes in the median number of LNs removed was seen in both node-negative and node-positive patients (all $P < 0.001$; Supplementary Figure S2A, available at *Annals of Oncology* online). This trend was also seen when men were divided according to the pre-operative risk group ($P < 0.001$; Supplementary Figure S2B, available at *Annals of Oncology* online).

In patients with LNI ($n = 730$), the mean and the median number of positive LNs were 3.5 and 2 (range, 1.0–59.0), respectively. These numbers did not significantly change over the study period (mean and median number of positive LNs: 3 and 3 in 1990 versus 4.2 and 2 in 2010, respectively; $P = 0.1$; Figure 4). The same trends were observed, when the median number of positive LNs was assessed according to PCa risk groups (all $P ≥ 0.4$, Supplementary Figure S3, available at *Annals of Oncology* online). Interestingly, 46% of LNI patients had more than two positive LNs in 2010 (Supplementary Figure S4, available at *Annals of Oncology* online). The year-per-year trend analysis focusing on patients with LNI showed that between 1990 and 2010, the pre-operative cancer characteristics did not significantly change over time ($P = 0.2$; Supplementary Figure S5A and B, available at *Annals of Oncology* online). Interestingly, 48% of LNI patients had a PSA between 4 and 10 ng/ml in 2010 (Supplementary Figure S5A, available at *Annals of Oncology* online). Overall, the vast majority of LNI patients had pT3b or higher disease (range, 33%–89%), whereas pT2 decreased from 17% in 1990 to 5% in 2010 ($P = 0.2$; Supplementary Figure S5C, available at *Annals of Oncology* online). Finally, pathological Gleason score of $\leq 6$ decreased from 33% to 0%, whereas a significant increase in the rates of Gleason 4 + 3 and 8–10 was noted ($P < 0.001$; Supplementary Figure S5D, available at *Annals of Oncology* online).

The mean and the median follow-up were 62.6 and 55.2 months, respectively. Overall, the mean CSS time was 235.2 months and the median was not achieved. Likewise, in patients with LNI, the mean CSS time was 181.4 months, and the median was not achieved. At 10- and 15-year postoperatively, the CSS rate was 95% and 92%, respectively, in the overall cohort (Supplementary Figure S6A, available at *Annals of Oncology* online) and 83% and 79%, respectively, in patients with LNI (Supplementary Figure S6B, available at *Annals of Oncology* online).

At multivariable logistic regression analyses (Table 2), the year of surgery category was not an independent predictor of LNI (all $P ≥ 0.06$). Conversely, the pre-operative PSA value, pathological tumor stage, pathological Gleason score, and the number of removed LNs were independently associated with the rate of LNI at ePLND (all $P ≤ 0.005$).
LNI is an important adverse pathological feature in patients with PCa, being associated with a detrimental impact on cancer control outcomes [14, 15]. Our purpose was to explore the evolution of LNI rates and cancer characteristics in patients treated with RP and ePLND over a period of two decades.
Several results of our study deserve attention. First, we demonstrated that in the ePLND setting, the rate of LNI is not negligible (13.8%). Although the highest LNI rates were observed during the most historic year category (1990–1995), 10.6%–15.6% of men treated in more recent years (2006–2010) still had node-positive disease. One might argue that such high LNI rates can be explained by the relatively large proportion of high-risk patients treated in this period (23%). In fact, 34%–44% of men with high-risk PCa treated between 2006 and 2010 had LNI. However, the proportion of high-risk patients in the most recent years was comparable with what reported in recently published series [16, 17]. Moreover, the use of an ePLND was also a key in the high rates of nodal metastases found among contemporary high-risk patients. Indeed, studies reporting lower rates of LNI among high-risk patients did not include the standardized use of ePLND [3, 6, 7, 18, 19]. This is also true among intermediate-risk patients where the rates of LNI were invariably lower in previously published limited PLND series when compared with our report (LNI rate range: 6%–14% in 2006–2010) [3, 6, 7]. This implies that contemporary intermediate-/high-risk patients still harbor a considerable risk of LNI if treated with ePLND. This has been further confirmed at multivariable analyses, where PCa characteristics and number of LNs, but not year of surgery, represented independent predictors of LNI. Therefore, the observed changes in LNI rates are mainly attributed to changes in tumor characteristics over time and not to the year of surgery and/or other unobserved confounders.

Second, despite the overall decrease in LNI rates over the study period, the average number of positive LNs in LNI patients remained virtually stable. This observation was confirmed, when patients were classified according to tumor risk. Even in more recent years (2006–2010), 54%–67% of LNI patients had at least two positive LNs at ePLND. This may imply that when LNI takes place, it does not occur as a gradual phenomenon, where tumor cells invade one LN per time. Instead, tumor cells tend to invade multiple LNs simultaneously. This further emphasizes the importance of performing an anatomically ePLND, especially when the pre-operative LNI risk is high.

Third, the rate of LNI in our contemporary patients treated with ePLND was almost 3-fold higher than their American counterparts receiving a limited PLND [3, 6, 7]. Although tumor characteristics in our cohort might have been more aggressive than those observed in these studies, we cannot exclude that the low rates of LNI reported in previous limited PLND series might have been due to inadequate nodal dissection. Indeed, several studies showed a direct relationship between the extent of PLND and LNI rates in PCa, regardless of disease characteristics [3, 7–11]. Thus, it is possible that a considerable proportion of contemporary patients enrolled in limited PLND series were under-staged regarding nodal invasion. This may represent an important quality of care concern. Specifically, a correct LN staging at RRP may allow for a prompt adjuvant therapy administration in pN1 patients, which may improve their cancer control outcomes [20, 21].

Fourth, it appears that among contemporary LNI patients (2006–2010), 21%–37% had intermediate-risk PCa at diagnosis. This is the key, since previous studies have shown a significant decrease in PLND performed in this patient group, especially when treated with minimally invasive procedures [5, 6]. In this context, the use of accurate and reliable prediction models developed on ePLND series is mandatory for the correct selection of patients suitable for ePLND.

Fifth, intuitively, the CSS rate was less favorable in patients with LNI when compared with the overall cohort. Nonetheless, at 15 years of follow-up, the CSS rate in patients with LNI was roughly 80%. Although these data derive from a retrospective analysis, such high rates of CSS might imply that a certain proportion of these patients might benefit from RRP and...

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**Table 2.** Univariable and multivariable logistic regression analyses predicting LNI in 5274 patients treated with radical prostatectomy and ePLND for PCa between 1990 and 2010 at a single institution

<table>
<thead>
<tr>
<th>Year of surgery category</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990–1995</td>
<td>1.00 (Ref.)</td>
<td>—</td>
<td>1.00 (Ref.)</td>
<td>—</td>
</tr>
<tr>
<td>1996–2000</td>
<td>0.68 (0.5–0.91)</td>
<td>&lt;0.001</td>
<td>0.83 (0.57–1.21)</td>
<td>0.3</td>
</tr>
<tr>
<td>2001–2005</td>
<td>0.54 (0.41–0.71)</td>
<td>0.009</td>
<td>0.76 (0.53–1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>2006–2010</td>
<td>0.61 (0.46–0.79)</td>
<td>&lt;0.001</td>
<td>0.68 (0.47–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>PSA level (ng/ml)</td>
<td>1.04 (1.03–1.04)</td>
<td>&lt;0.001</td>
<td>1.02 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.00 (Ref.)</td>
<td>—</td>
<td>1.00 (Ref.)</td>
<td>—</td>
</tr>
<tr>
<td>T3a</td>
<td>8.58 (6.31–11.67)</td>
<td>&lt;0.001</td>
<td>5.32 (3.85–7.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T3b or higher</td>
<td>58.59 (44.77–76.67)</td>
<td>&lt;0.001</td>
<td>25.87 (19.25–34.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathological Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>1.00 (Ref.)</td>
<td>—</td>
<td>1.00 (Ref.)</td>
<td>—</td>
</tr>
<tr>
<td>3 + 4</td>
<td>2.55 (1.92–3.38)</td>
<td>&lt;0.001</td>
<td>1.62 (1.16–2.25)</td>
<td>0.005</td>
</tr>
<tr>
<td>4 + 3</td>
<td>6.71 (5.03–8.96)</td>
<td>&lt;0.001</td>
<td>2.60 (1.83–3.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥8</td>
<td>23.62 (18.19–30.66)</td>
<td>&lt;0.001</td>
<td>4.68 (3.37–6.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of removed LNs</td>
<td>1.05 (1.04–1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.001</td>
</tr>
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OR, odds ratio; 95% CI, 95% confidence interval.
ePLND. This has been also demonstrated in a recent randomized trial, which showed that ePLND was associated with more favorable biochemical-free survival rates when compared with limited PLND, especially in patients with intermediate-/high-risk PCa [22].

Finally, the most frequent complication potentially related to ePLND was lymphocele formation. The rate of symptomatic lymphocele was 6.3%. Interestingly, the rates of CSL and post-operative edema fluctuated significantly overtime according to the number of nodes removed. Specifically, the higher rates were observed when the number of LNs removed was higher and vice versa (Table 1). These data corroborate several previous studies reporting a relationship between the extent of PLND and the rate of complications [10, 22, 23].

Our study is not the devoid of limitations. Our findings must be interpreted within the context of the limitations applicable to observational, retrospective data. Despite the fact that an anatomically ePLND is routinely offered to all RP patients in our institution, a fluctuation in the number of LNs removed overtime was seen in our series. This held true when patients were stratified according to either nodal status or PCa characteristics at diagnosis. This fluctuation might be derived by individual variability, which is inevitable especially in a large cohort that covers a long period, as in the case of our study. Moreover, many unobserved confounders, such as surgical expertise, pathological expertise, and/or patient variability, might have affected the LN count. Likewise, at surgeon discretion, a more ePLND that involves pre-sacral and/or common iliac LNs was performed in some patients. These unobserved confounders might explain, at least partially, the variability in the LN count over the study period. However, given the tertiary care center nature of our institute, all the surgeons and uropathologists that attributed to the data of this study benefited from a high expertise and standardized protocols. Moreover, virtually the same surgeons (10 in total) and pathologists (4 in total) performed, respectively, RP and RP specimen examination over the 20-year period of this study. Thus, it may be argued that the effect of these unobserved confounders is minimal. Indeed, the median number of LNs removed remained consistently high over the whole study period. This indicates that PLND was adequate in the vast majority of patients.

Increasing rates of high Gleason scores in more recent years might also be seen in the context of the grade inflation phenomenon described by Albertsen et al. [24]. According to the latter, pathologists are more reluctant to assign the low Gleason grade to contemporary patients. Therefore, we cannot exclude that low cancer grades assigned to historical patients might be reconsidered as higher Gleason scores if reevaluated now-a-days. It is noteworthy that PLND was omitted in 627 patients. These individuals harbored less aggressive tumor characteristics (the median PSA was 5.6 ng/ml, the clinical stage was T1–T2 in 81.7%, and the biopsy Gleason score was ≤6 in 88.5%) than their counterparts that were treated with PLND. Most of pNx patients (72.6%) were classified as low risk by the NCCN guidelines. These individuals are known to have a very low LNI risk. As such, it is unlikely that the exclusion of these individuals has biased our results. Finally, our cohort represents a single institution data. It remains to be tested whether our findings are applicable to other clinical settings or countries where PSA screening programs are more implemented.

conclusions
Stage migration in PCa patients was associated with a decrease in the overall LNI risk. However, in contemporary patients, the LNI risk is still significant, especially in patients with intermediate-/high-risk tumors. In consequence, stage migration does not justify omitting or limiting the extent of PLND in these individuals. It is also noteworthy that in contemporary pN1 patients, the volume of nodal invasion did not decrease when compared with their historic counterparts. This further emphasizes the need for performing an ePLND even in contemporary patients whenever a PLND is indicated.

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disclosure
The authors have declared no conflicts of interest.

references
Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy


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Background: To compare long-term, updated overall survival (OS) of patients with advanced transitional cell carcinoma of the urothelium (TCCU) treated with vinflunine plus best supportive care (BSC) or BSC alone, after failure of platinum-based chemotherapy.

Patients and methods: Three hundred and seventy patients were randomly assigned in a phase III trial and allocated (2:1) to vinflunine (320 or 280 mg/m2) plus BSC or BSC alone. The first report (Bellmunt J, Theodore C, Demkov T et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a