Suboptimal use of pelvic lymph node dissection: Differences in guideline adherence between robot-assisted and open radical prostatectomy

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Abstract

Introduction: Our aim was to assess adherence to National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) guidelines for pelvic lymph node dissection (PLND) at the time of either robot-assisted (RARP) or open radical prostatectomy (ORP).

Methods: We relied on the Surveillance, Epidemiology, and End Results-Medicare linked database and focused on localized prostate cancer (PCa) patients who were treated with either RARP or ORP between October 2008 and December 2009. Categorical and multivariable logistic regression analyses targeted two endpoints: 1) probability of guideline-recommended PLND; and 2) probability of no PLND, when not guideline-recommended.

Results: Among 5268 PCa patients, adherence to NCCN PLND guideline was 56.9% during RARP and 76.5% during ORP (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.3–0.6). AUA PLND guideline adherence was 68.1% during RARP and 82.4% during ORP (OR 0.7, 95% CI 0.5–0.9). When PLND was not recommended, it was more frequently performed during ORP according to either NCCN (OR 3.7, 95% CI 3.5–3.9) or AUA (OR 2.7, 95% CI 2.6–2.8). According to the NCCN guideline, at recommended PLND in ORP patients, 6.3% harboured lymph node invasion (LNI) (number needed to treat [NNT] 16) vs. 3.2% at RARP (NNT 31). According to the AUA guideline, at recommended PLND in ORP patients, 12.3% harboured LNI (NNT 8) vs. 5.1% RARP (NNT 19).

Conclusions: Adherence to NCCN and AUA PLND guidelines was lower during RARP than during ORP when PLND was recommended. The rate of non-recommended PLND was also higher during ORP than during RARP. Technical considerations may be at play.
Oncology [ICD-O] site code 61.9, histologic code 8140) aged 65 years or older treated with RP from October 1, 2008–December 31, 2009 were identified. This time frame was selected as a specific modifier code for robot-assisted approach (RARP), which was introduced on October 1, 2008 (ICD-9 Clinical Modification [ICD-9-CM] procedure code: 17.42). Patients with unknown clinical characteristics were excluded (n=1042). This resulted in 5268 assessable patients.

**Covariates**

Age, race, population density (urban vs. rural), marital status (married vs. unmarried), 2000 census tract percent with four-year college education (very low ≤14.3; low 14.4–25.4; high 25.5–42.2; and very high ≥42.3%), 2000 census tract annual median income, region of residence, pathological Gleason score, preoperative prostate-specific antigen (PSA), clinical and pathological tumour stage, nodal stage, surgical volume (low ≤2; intermediate 3–6; high ≥7 cases/year), and Charlson comorbidity index (CCI) were assigned.

**Statistical analyses**

Our statistical analyses consisted of two steps. First, we quantified the rate of adherence to PLND recommendations according to either the NCCN or AUA guidelines. The contemporary NCCN guideline recommends PLND in patients with a nomogram-calculated LNI risk of ≥2%.

Second, we relied on two separate multivariable logistic regression analyses for predicting PLND when PLND was recommended according to either the NCCN or AUA guidelines. Then, two additional models were fitted to predict no PLND when it was not recommended according to either NCCN or AUA guidelines. All statistical tests were performed using R. All tests were two-sided, with a significance level set at p<0.05.

**Results**

**Baseline descriptives**

Of 5268 PCa patients, 3123 (59.3%) were treated with RARP and 2145 (40.7%) were treated with open radical prostatectomy (ORP), respectively. Significant differences between RARP and ORP patients were recorded for several characteristics (Table 1). Most importantly, PLND was significantly less frequent in RARP than in ORP patients (49.8 vs. 72.5%; p<0.001).

**Adherence to guidelines**

First, we examined adherence to the NCCN PLND guideline. PLND was recommended in 73.7% of RARP and 73.7% of ORP patients (Fig. 1). PLND was performed in 56.9% of RARPs and 76.5% of ORPs when recommended by the NCCN guideline (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.3–0.6; p<0.001). Conversely, PLND was not recommended by the NCCN guideline in 26.3% of RARPs and 26.3% of ORPs. PLND was indeed not performed in 70% of RARPs and 38.8% of ORPs (OR 3.7, 95% CI 3.5–3.9; p<0.001). LNI was recorded in 3.2% of RARP and in 6.3% of ORP patients when PLND was recommended by the NCCN guideline. The number needed to treat (NNT) was 31 vs. 16 in RARP and ORP patients, respectively (Fig. 1).

Second, we examined adherence to the AUA PLND guideline. According to the AUA guideline, PLND was recommended in 13.8% of RARP and 17.4% of ORP patients. PLND was performed in 68.1% of RARPs and 82.4% of ORPs when recommended by the AUA guideline (OR 0.7, 95% CI 0.5–0.9). Conversely, PLND was not recommended by the AUA guideline in 86.2% of RARPs and 82.6% of ORPs. PLND was indeed not performed in 53.1% of RARPs and 29.6% of ORPs (OR 2.7, 95% CI 2.2–3.3; p<0.001). PLND was performed in 68.1% of RARPs and 82.4% of ORPs when recommended by the NCCN guideline in 73.7% of RARP and 73.7% of ORP patients when PLND was recommended by the AUA guideline. The NNT was 19 vs. 8 in RARP and ORP patients, respectively (Fig. 1).

**Multivariable logistic regression analyses predicting PLND when PLND is recommended by guidelines**

The first set of multivariable logistic regression analyses focused on predictor variables that are associated with adherence to recommended PLND according to the NCCN guideline. Within these analyses, five variables achieved independent predictor status: surgical approach, region of residence, surgical volume, education, and marital status. Specifically, patients treated by high-volume surgeons were more likely to undergo PLND when recommended than those treated by low-volume surgeons (OR 1.3, 95% CI 1.0–1.7; p=0.048). Additionally, patients residing on the Pacific coast (OR 1.3, 95% CI 1.1–1.7; p=0.002) were more likely to undergo PLND when recommended than those residing in the East. Similarly, patients from the high education category were more likely to undergo PLND when recommended than those from the very low education category (OR 1.5, 95% CI 1.0–2.1; p=0.04). Conversely, patients treated with RARP were less likely to undergo PLND when recommended than ORP patients (OR 0.4, 95% CI 0.3–0.5; p<0.001). Finally, unmarried patients were also less likely to undergo PLND when recommended compared to those who were married (OR 0.8, 95% CI 0.6–0.96; p=0.03) (Table 2).
Guideline adherence for PLND during radical prostatectomy

The second set of multivariable logistic regression analyses focused on variables that are associated with adherence to recommended PLND according to the AUA guideline. Within these analyses, two variables achieved independent predictor status: surgical approach and region of residence. Specifically, patients treated with RARP were less likely to

<table>
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<tr>
<th>Parameter</th>
<th>Overall n=5268</th>
<th>ORP n=2146 (40.7%)</th>
<th>RARP n=3123 (59.3%)</th>
<th>p value</th>
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<td>69.0 (68.0)</td>
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<td>66.0–71.0</td>
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<td>571 (26.6)</td>
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<td>50 955–69 389</td>
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<td>417 (19.4)</td>
<td>898 (28.8)</td>
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<td>Charlson comorbidity index, n (%)</td>
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<td>Preoperative serum PSA, ng/ml</td>
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<td>Mean (median)</td>
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<td>&lt;10</td>
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<td>≥T3a</td>
<td>140 (2.7)</td>
<td>71 (3.3)</td>
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IQR: interquartile range; ORP: open radical prostatectomy; PSA: prostate-specific antigen; RARP: robot-assisted radical prostatectomy; SEER: Surveillance, Epidemiology, and End Results.
Table 1. Descriptive statistics of 5268 patients treated with either RARP or ORP for localized prostate cancer between October 1, 2008 and December 31, 2009 within the SEER-Medicare-linked database (cont’d)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall n=5268</th>
<th>ORP n=2145 (40.7%)</th>
<th>RARP n=3123 (59.3%)</th>
<th>p value</th>
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<td>Pelvic lymph node dissection, n (%)</td>
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<td>Not performed</td>
<td>2157 (40.9)</td>
<td>590 (27.5)</td>
<td>1567 (50.2)</td>
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<tr>
<td>Performed</td>
<td>3111 (59.1)</td>
<td>1555 (72.5)</td>
<td>1556 (49.8)</td>
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<td>Gleason score, n (%)</td>
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<td>≤6</td>
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<td>660 (30.8)</td>
<td>864 (27.7)</td>
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<td>7</td>
<td>2916 (55.4)</td>
<td>1118 (52.1)</td>
<td>1798 (57.6)</td>
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<td>8–10</td>
<td>828 (15.7)</td>
<td>367 (17.1)</td>
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<td>pT2</td>
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<td>pN0/NX</td>
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<td>pN1</td>
<td>122 (2.3)</td>
<td>77 (3.6)</td>
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<td>Organ-confined tumour (≤pT2, N0/NX), n (%)</td>
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<td>Intermediate</td>
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<td>234 (23.9)</td>
<td>526 (41.7)</td>
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IQR: interquartile range; ORP: open radical prostatectomy; PSA: prostate-specific antigen; RARP: robot-assisted radical prostatectomy; SEER: Surveillance, Epidemiology, and End Results.

Table 2. Multivariable logistic regression analyses A: adherence to PLND recommendation according to NCCN guideline; B: adherence to PLND recommendation according to AUA guideline, in 5268 patients treated with either RARP or ORP for localized prostate cancer between October 1, 2008 and December 31, 2009 within the SEER-Medicare-linked database

<table>
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<tr>
<th>Parameter</th>
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<th>Multivariable analyses B</th>
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<td>p value</td>
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<td>1 (ref.)</td>
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<td>Southwest</td>
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<td>1.2 (0.6–2.8)</td>
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<td>1 (ref.)</td>
<td></td>
<td>1.4 (0.7–2.8)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.2 (0.9–1.5)</td>
<td>0.2</td>
<td>1.2 (0.6–2.5)</td>
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</tr>
<tr>
<td>High</td>
<td>1.3 (1.0–1.7)</td>
<td>0.048</td>
<td>1.2 (0.6–2.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Education</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Very low</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td></td>
<td>0.7 (0.3–1.5)</td>
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<tr>
<td>Low</td>
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<td>0.6</td>
<td>2.1 (0.8–5.4)</td>
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<tr>
<td>High</td>
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<td>0.04</td>
<td>2.9 (0.8–9.9)</td>
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<tr>
<td>Very high</td>
<td>1.4 (0.9–2.1)</td>
<td>0.2</td>
<td>2.9 (0.8–9.9)</td>
<td>0.1</td>
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<tr>
<td>Marital status</td>
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<td></td>
</tr>
<tr>
<td>Married</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td></td>
<td>0.6 (0.3–1.1)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>0.8 (0.6–0.96)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All analyses were also adjusted for prostate-specific antigen, population density (rural vs. urban), patient age categories (65–66, 67–68, 69–71, ≥72 years), Charlson comorbidity index categories (0, 1, 2, ≥3), race (White, Black, other), and annual income categories (<38 012, 38 013–50 954, 50 955–69 389, ≥69,390 US$), which failed to reach insignificant predictor status. AUA: American Urological Association; CI: confidence interval; NCCN: National Comprehensive Cancer Network; OR: odds ratio; ORP: open radical prostatectomy; PLND: pelvic lymph node dissection; RARP: robot-assisted radical prostatectomy; SEER: Surveillance, Epidemiology, and End Results.
undergo PLND when recommended than those treated with ORP (OR 0.2, 95% CI 0.1–0.5; p<0.001). Finally, patients residing in the Northern plains were more likely to undergo PLND when recommended than those residing in the East (OR 4.6, 95% CI 1.4–15.2; p=0.01) (Table 2).

Multivariable logistic regression models predicting absence of PLND when PLND is not recommended by guidelines

The third set of multivariable logistic regression analyses focused on predicting no PLND when it was not recommended according to the NCCN guideline. Within these analyses, three variables achieved independent predictor status: surgical approach, region of residence, and surgical volume. Specifically, patients treated with RARP were more likely to not undergo PLND when not recommended than ORP patients (OR 3.0, 95% CI 2.4–3.7; p<0.001). Conversely, patients residing at the Pacific coast were less likely to not undergo PLND when not recommended than those residing in the East (OR 0.8, 95% CI 0.6–1.0; p=0.02). Finally, patients treated by high-volume surgeons were also less likely to not undergo PLND when not recommended than those treated by low-volume surgeons (OR 0.7, 95% CI 0.6–0.9; p=0.003) (Table 3).

Discussion

Recommendations for PLND at RP differ according to the source of the guideline.1,13 Additionally, PLND rates might vary according to surgical approach.5,6,9 The objective of the present study was to assess differences in NCCN and
AUA guideline adherence to PLND recommendations during RARP or ORP. Our analyses detected several important findings.

First, according to the NCCN guideline, the rates of PLND recommendation were not significantly different between RARP and ORP patients (73.7 vs. 73.7%; p=1.0). However, RARP patients less frequently underwent PLND when recommended (56.9 vs. 76.5%, OR 0.4; p<0.001). Conversely, RARP patients more frequently did not undergo PLND when PLND was not recommended (70 vs. 38.8%, OR 3.7; p<0.001).

Second, according to the AUA guideline, the rates of PLND recommendation were significantly lower for RARP than ORP patients (13.8 vs. 17.4%; p=0.001). Despite this difference, RARP patients underwent PLND less frequently than ORP patients when recommended (68.1 vs. 82.4%, OR 0.7; p=0.01). As for NCCN guidelines, RARP patients more frequently did not undergo PLND when not recommended than ORP patients (53.1 vs. 29.6%, OR 2.7; p<0.001).

When the first and second points are taken together, they indicate that the threshold for PLND varies according to guideline. The NCCN guideline is more stringent and leads to more frequent PLND then the AUA guideline. However, regardless of the guideline, RARP patients were invariably less frequently treated with PLND than ORP patients.

Third, we examined the rates of LNI according to recommended rates of PLND and found higher rates and lower NNT values when the AUA guideline was followed. However, such trade-off was associated with higher number of missed patients with LNI. In consequence, clinicians need to decide which approach is preferred.

Fourth, we examined predictors of recommended PLND and predictors of no PLND when not recommended by guidelines. In these analyses, surgical approach (ORP) was invariably associated with higher PLND rates. The region of residence also affected PLND rates. Pacific coast residents were more likely to undergo PLND when recommended by the NCCN guideline. Similarly, patients from Northern plains more frequently underwent PLND when it was recommended by the AUA guideline. Conversely, patients from the Pacific coast were less likely not to have a PLND when it was not recommended according to the AUA guideline. Surgical volume affected the rate of recommended PLND and, invariably, no PLND when not recommended according to guidelines. High-volume surgeons were more likely to perform a PLND when recommended according to the

### Table 3. Multivariable logistic regression analyses C: adherence to no PLND recommendation according to NCCN guidelines; and D: adherence to no PLND recommendation according to AUA guideline in 5268 patients treated with either RARP or ORP for localized prostate cancer between October 1, 2008 and December 31, 2009 within the SEER-Medicare-linked database

<table>
<thead>
<tr>
<th>Surgical approach</th>
<th>OR [95% CI]</th>
<th>p value</th>
<th>OR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>ORP</td>
<td>1 (ref.)</td>
<td></td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>RARP</td>
<td>5.0 (3.4–7.7)</td>
<td>&lt;0.001</td>
<td>5.0 (3.4–7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>1 (ref.)</td>
<td></td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>Northern plains</td>
<td>1.4 (0.8–2.7)</td>
<td>0.3</td>
<td>1.0 (0.7–1.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pacific coast</td>
<td>1.0 (0.7–1.6)</td>
<td>0.9</td>
<td>0.8 (0.6–1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Southwest</td>
<td>2.0 (0.9–4.3)</td>
<td>0.07</td>
<td>1.4 (0.9–2.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Surgical volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (ref.)</td>
<td></td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.0 (0.6–1.7)</td>
<td>0.9</td>
<td>0.9 (0.7–1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>High</td>
<td>0.5 (0.3–0.8)</td>
<td>0.007</td>
<td>0.7 (0.6–0.9)</td>
<td>0.003</td>
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<tr>
<td>Education</td>
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<tr>
<td>Very low</td>
<td>1 (ref.)</td>
<td></td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.8 (0.5–1.4)</td>
<td>0.5</td>
<td>0.8 (0.6–1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>High</td>
<td>0.9 (0.5–1.7)</td>
<td>0.7</td>
<td>0.8 (0.6–1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Very high</td>
<td>0.9 (0.4–1.8)</td>
<td>0.7</td>
<td>0.8 (0.6–1.2)</td>
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<tr>
<td>Marital status</td>
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<tr>
<td>Married</td>
<td>1 (ref.)</td>
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<td>1 (ref.)</td>
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<tr>
<td>Unmarried</td>
<td>1.4 (0.9–2.3)</td>
<td>0.1</td>
<td>1.3 (1.0–1.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

All analyses were also adjusted for prostate-specific antigen, population density (urban vs. rural), patient age categories (65–66, 67–68, 69–71, ≥72 years), Charlson comorbidity index categories (0, 1, 2, 3), race (White, Black, other), and annual income categories (<38 012, 38 013–50 954, 50 955–69 389, ≥69,390 US$), which failed to reach insignificant predictor status. AUA: American Urological Association; CI: confidence interval; NCCN: National Comprehensive Cancer Network; OR: odds ratio; ORP: open radical prostatectomy; PLND: pelvic lymph node dissection; RARP: robot-assisted radical prostatectomy; SEER: Surveillance, Epidemiology, and End Results.
NCCN guideline. Conversely, high-volume surgeons were less likely to perform PLND when it was not recommended by either the NCCN or AUA guidelines. Education category affected PLND rates; patients from the high education category were more likely to undergo PLND than those from the very low education category when PLND was recommended according to the NCCN guideline. Finally, marital status also affected PLND rates; unmarried patients were less likely to undergo PLND when recommended according to the NCCN guideline. Conversely, those patients were more likely to not undergo PLND when not recommended according to the AUA guideline. Together, these results show that besides surgical approach, other variables, such as patient characteristics or surgeon volume, may affect PLND rates.

Our results are in agreement with other studies that examined rates of PLND according to surgical approach.\textsuperscript{5,6,10-14} To the best of our knowledge, the current study represents the only contemporary assessment of adherence to NCCN and AUA guidelines that differentiated according to surgical approach and relied on the RARP-specific modifier that became available as of October 2008.

Despite its strengths, our study has limitations. First, our cohort exclusively originates from the Medicare database, with an age distribution of over 65 years. The results might not be generalizable to younger patients. Second, due to a lack of detailed information from SEER-Medicare-derived analyses, we relied on pathological Gleason score. Since high rates of upgrading were recorded between clinical and pathological Gleason score,\textsuperscript{15} a corresponding bias might exist in our analyses. Finally, other limitations known to affect SEER-Medicare-derived analyses are also operational, for example, use of claims data or lack of detailed parameters that are included in prospective trials.

**Conclusion**

Our data indicate that adherence to either NCCN or AUA guidelines remains suboptimal. The urological community should be sensitized about the staging impact of PLND\textsuperscript{16-19} and possible elimination of micrometastases,\textsuperscript{17,20-22} especially during RARP.\textsuperscript{23} On the other hand, it is also important to notice that a non-negligible percentage was exposed to the potential harm of PLND\textsuperscript{9,24,23} when it was not recommended. Followup studies are needed in more recently treated patients.

**Competing interests:** Dr. Lattouf has been an Advisory Board member for AbbVie, Amgen, Astellas, Novartis, and Pfizer; and has received an educational grant from Janssen. Dr. Zorn is a consultant and an Advisory Board member for Boston Scientific. Dr. Saad has been an Advisory Board member for Janssen and Sanofi; and has received research funding, as well as honoraria from Sanofi. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

**References**


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References: