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Adequacy of lymphadenectomy among men undergoing robot-assisted laparoscopic radical prostatectomy

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Study Type – Therapy (case series)
Level of Evidence 4

OBJECTIVE

To compare rates of lymph node dissection (LND) and nodal yields between patients treated with open radical retropubic prostatectomy (ORRP) and robot-assisted RRP (RARP) in a contemporary single-institution series.

PATIENTS AND METHODS

Data from 1278 consecutive patients (716 ORRP and 562 RARP) from one institution were accrued prospectively in an institutional database, and the data analysed retrospectively. Disease risk was assessed

using the Cancer of the Prostate Risk Assessment (CAPRA) score. The likelihood of LND, nodal yield, and likelihood of node positivity were compared between ORRP and RARP.

RESULTS

Of patients treated with ORRP and RARP, 47.8% and 31.8% had LND, respectively, with more receiving LND over time in both surgical approaches. Men undergoing LND had a higher disease risk than those not undergoing LND (mean CAPRA score 4.3 vs 2.1, $P < 0.01$), and there was no difference in risk between those undergoing ORRP or RARP (mean CAPRA score 3.0 vs 2.9, $P = 0.29$). The mean (SD) nodal yield was 14.4 (8.7) for ORRP and 9.3 (5.4) for RARP

($P < 0.01$). Among patients undergoing LND, 5.8% of ORRP and 4.1% of RARP patients had positive nodes ($P < 0.01$).

CONCLUSIONS

The indications for LND and template dissection should be the same regardless of surgical approach. The nodal yield was adequate using both approaches; the yield was higher among ORRP than RARP patients, but the difference was not large, and is less remarkable than the wide variation in yield within each approach. Several factors might explain this variation.

KEYWORDS

prostatectomy, prostate neoplasms, lymphadenectomy, robotics, laparoscopy

INTRODUCTION

Recent evidence from several radical prostatectomy (RP) series suggests that a wider lymph node dissection (LND), particularly extended to include the tissue around the internal iliac vessels, will improve lymph node yield, resulting in more accurate tumour staging [1,2] and potentially improved outcomes for patients with limited nodal disease [3,4]. Although these findings are not entirely consistent, increasing attention is being paid to the extent of LND and nodal yield, particularly for higher-risk patients undergoing RP. However, relatively few data have been published on the adequacy of LND in association with laparoscopic RP with or without robot assistance.

At our institution, as at many others, robot-assisted RP (RARP) [5] is rapidly replacing open retropubic RP (ORRP) as the procedure selected by both surgeons and most men opting for surgical extirpation of localized prostate cancer. We therefore reviewed our experience with both procedures over the past 5 years for the indications for LND, nodal yield and outcomes.

PATIENTS AND METHODS

All patients treated surgically for prostate, renal or bladder cancer at the University of California, San Francisco (UCSF) Comprehensive Cancer Center are approached prospectively for consent to be registered in the UCSF Urologic Outcomes Data Base

(UODB), under supervision of the UCSF institutional review board. The UODB was queried for patients diagnosed between January 2003 and November 2008 who had ORRP or RARP. Risk factors for cancer recurrence and/or progression were assessed using the Cancer of the Prostate Risk Assessment (CAPRA) score, a well-validated instrument which calculates risk on a 0–10 score based on age at diagnosis, PSA level, biopsy Gleason score, clinical T stage, and percentage of biopsy cores positive. The CAPRA score has been associated with likelihood of lymph node involvement in several validation studies [6].

In general, indications for LND at the time of ORRP or RARP included a serum PSA level of

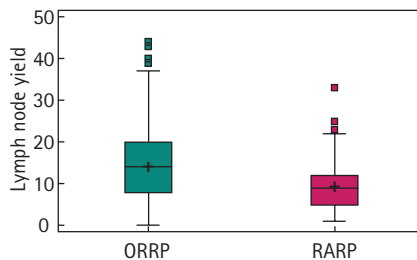
TABLE 1 The number of operations each year, with the percentage of ORRP and RLRP in each year, and overall, with the mean CAPRA score in each year

Surgical approach	Year of treatment						Total
	2003	2004	2005	2006	2007	2008	
ORRP, n (%)	190 (97.9)	214 (90.3)	142 (80.7)	89 (42.0)	66 (25.8)	15 (7.4)	716 (73.1)
Mean CAPRA score	2.68	2.90	2.77	3.20	4.43	5.82	3.02
RARP, n (%)	4 (2.1)	23 (9.7)	34 (19.3)	123 (58.0)	190 (74.2)	188 (92.6)	562 (26.9)
Mean CAPRA score	2.00	2.86	2.91	2.72	2.95	3.00	2.88
Total	194	237	176	212	256	203	1278
Mean CAPRA score	2.67	2.90	2.80	2.92	3.33	3.21	2.96

TABLE 2 The likelihood of undergoing LND by surgical approach, as n (%) of patients undergoing LND or not and the mean CAPRA score for each group

LND	Surgical approach		
	ORRP	RARP	Total
No, n (%)	379 (52.9)	421 (74.9)	800 (62.6)
Mean CAPRA score	1.9	2.3	2.1
Yes, n (%)	337 (47.1)	141 (25.1)	478 (37.4)
Mean CAPRA score	4.2	4.4	4.3

FIG. 1. A box plot of lymph node yield among ORRP and RARP patients. The box indicates the interquartile range, the horizontal line the median, the plus sign the mean, and the dots outlier values.



>10 ng/mL, biopsy Gleason sum ≥ 7 and/or clinical stage >T2a. However, the decision to perform LND was ultimately at the discretion of the surgeon. For patients undergoing ORRP, LND precedes RP. The limits of the dissection by either technique are the external iliac vein laterally, the circumflex iliac vein distally, the obturator nerve caudally and the bifurcation of the common iliac vein proximally. We have noted a trend toward a more extended LND for high-risk patients undergoing ORRP or RARP, but the anatomical extent of LND is not entered into the UODB, so this trend could not be analysed beyond the trend in nodal yield.

For the patients undergoing RARP, the LND typically follows the transperitoneal RARP, usually before but sometimes after the vesico-urethral anastomosis. This allows the surgeon and assistant to retract more vigorously on the bladder medially without fear of disrupting the anastomosis, and takes advantage of the full mobilization of the anterior bladder and peritoneum for an optimal LND. The nodal tissue can be removed in an Endocatch bag separately to optimize the nodal count, or together with the prostate to minimize the cost of several bags. However, the nodes are not divided into separate packets.

Mean CAPRA scores between ORRP and RARP patients and between those undergoing or not undergoing LND were calculated and compared using the *t*-test. The proportion of patients undergoing LND was compared between ORRP and RARP patients using the chi-square test. The likelihood of LND among ORRP and RARP patients was corrected for the CAPRA score and year of surgery using logistic regression, and the odds ratio calculated with the 95% CI. Trends over time in likelihood of RARP vs ORRP, mean CAPRA score, and mean nodal yield were assessed with the Cuzick nonparametric test for trend. Finally, the percentage of LND patients with positive nodes was compared with the *t*-test.

RESULTS

Between January 2003 and December 2008, 1451 men had RP for prostate cancer, and 1278 (88%) consented to be registered in the UODB; 716 (56.0%) had ORRP and 562 (44.0%) RARP. Over the study period, the proportional representation of RARP among RP cases in the UODB increased rapidly ($P < 0.01$, Table 1); 47.8% of ORRP and 31.8% of RARP patients had a concurrent LND ($P < 0.01$, Table 2).

As assessed by the CAPRA score, men undergoing LND presented with higher risk features than those not undergoing LND (mean CAPRA score 4.3 vs 2.1, $P < 0.01$). There was no significant difference in risk between those undergoing ORRP and those undergoing RARP (CAPRA score 3.0 vs 2.9, $P = 0.29$, Table 1). The risk was likewise similar between those undergoing ORRP and RARP stratified by LND status (Table 2). The increase in CAPRA scores over time was statistically significant among ORRP patients ($P < 0.01$) but not RARP patients ($P = 0.76$).

Table 3 summarizes the use of LND among ORRP and RARP patients. The likelihood of LND increased over time; the trend was statistically significant among ORRP patients ($P < 0.01$) but not RARP patients ($P = 0.07$). Controlling for year of surgery and CAPRA score, RARP patients were less likely to undergo LND than ORRP patients (odds ratio 0.18, 95% CI 0.11–0.32). The mean (sd) lymph node yield was 14.4 (8.7) among ORRP and 9.3 (5.4) among RARP patients ($P < 0.01$). Since 2006 the difference narrowed but was still statistically significant (12.5 vs 9.4 nodes, $P < 0.01$). There was a significant trend over time in the number of nodes recovered among ORRP ($P < 0.01$) but not RARP patients ($P = 0.45$). Fig. 1 is a box plot of lymph node yield by type of surgical approach, showing

TABLE 3 The percentage of patients undergoing LND in each year of treatment and overall, with the mean (SD) lymph node yield

Surgical approach	Year of treatment						Total
	2003	2004	2005	2006	2007	2008	
ORRP							
LND, %	28.4	47.2	47.9	64.0	65.2	93.3	47.8
LND yield	11.2 (8.7)	15.9 (9.8)	17.4 (9.0)	12.1 (6.1)	13.0 (6.6)	18.6 (3.3)	14.4 (8.7)
RARP							
LND, %	0.0	13.0	32.4	30.1	18.4	29.3	31.8
LND yield		11.0 (5.3)	9.5 (6.2)	9.8 (6.7)	8.9 (4.7)	9.1 (4.9)	9.3 (5.4)
Total							
LND, %	27.8	43.9	44.9	44.3	30.5	34.0	41.8
LND yield	11.2 (8.7)	15.8 (9.8)	16.3 (9.0)	11.2 (6.4)	11.2 (6.2)	11.0 (6.0)	14.4 (8.5)

the median and considerable spread in terms of yield for each approach.

There were two symptomatic lymphoceles in the RARP group and three in the ORRP group. There were no other complications attributable to LND. Among patients undergoing LND, 35 ORRP (7.3%) and five RARP (1.1%) patients had positive nodes ($P = 0.02$). The mean CAPRA score for lymph node-positive patients was 5.8, vs 4.1 for those undergoing LND but with no positive nodes ($P < 0.01$). The mean percentage of nodes positive among node-positive men was 10.6% among ORRP and 17.2% among RARP patients ($P = 0.05$).

DISCUSSION

In recent years, concurrent with the rapid spread and adoption of robot-assisted surgery in urological oncology, increasing attention has been paid to the effect of LND on outcomes of the surgical management of pelvic urological malignancies. The extent of the template and the nodal count or yield have both been the subject of many studies in those undergoing ORRP. However, relatively few reports have examined the quality of LND in emergent RARP programmes.

Multivariable risk-prediction systems have been used to stratify patients according to likelihood of lymph node metastases [6–8]. The actual node-positive rate in the series used to build these instruments was consistently <5%, with most patients in the series managed with a standard LND template. Using a more extensive dissection template (median 21 nodes recovered), Burkhard *et al.* [9] reported a 24% node

positive rate; 12% of patients with a preoperative PSA level of <10 ng/mL and a well-differentiated tumour on prostate biopsy were found to have nodal metastases (0–13% of similar patients, depending on clinical stage, would be predicted by the Partin tables to have nodal disease [7].) Heidenreich *et al.* [10], reporting another large European experience, found a 26% overall node-positive rate with an extended template dissection (mean 28 nodes recovered, vs 11 for the standard template), but only a 2% rate among patients with a PSA level of <10 ng/mL and Gleason grade of <7. A contemporary mapping study in a small series based on nodal radiolabelling and intraoperative γ -probe identification found that in two-thirds of patients, the sentinel node, presumably reflecting the primary tumour landing site, was located outside the standard LND dissection template.

Touijer *et al.* [11] found that among patients predicted by the Partin tables to have a >1% likelihood of positive lymph nodes, an extended template dissection (mean nodal yield 13, vs 10 for standard dissection) increased the likelihood of lymph node positivity by seven times. Joslyn and Konety [4] analysed over 13 000 men included in the Surveillance, Epidemiology, and End Results (SEER) database, finding that more nodes were removed among men with positive nodes identified (mean 13, vs nine for negative nodes).

Improved accuracy of staging would presumably benefit patients by guiding those with metastatic disease to early adjuvant therapy. Moreover, there is limited evidence that some patients with minimal nodal metastatic burden were apparently cured by

RP and LND alone [3,12,13]. For example, Messing *et al.* [14] found that among patients randomized to observation for node-positive disease detected at the time of ORRP (median 12 nodes examined), 16% had no evidence of disease at a median of 7 years; the progression-free survival was \approx 30% at 10 years. More recently, Bader *et al.* [3] found that among patients with only one positive node, the progression-free and cause-specific survival were 39 and 81%, respectively, at 5 years. Their median (range) nodal yield using an extended template was 21 (6–50). Overall outcomes were strongly associated with the number of positive nodes. The SEER analysis showed improved cancer-specific mortality rates for men whose lymph node yield was at least four nodes at the time of surgery; among node-negative patients, those with >10 nodes examined (51% of the 71% of patients undergoing LND) had improved cause-specific survival [4].

Other reports do not substantiate these findings; e.g. a multi-institutional study from the CaPSURE registry found no effect of obturator LND on outcomes after ORRP [15]. Similarly, DiMarco *et al.* [16] reported a series of >7000 ORRP patients from 1987 to 2000, finding that the median lymph node yield declined from 14 to five over the study period, and that in multivariable analysis nodal yield had no effect on the likelihood of recurrence-free survival among pathological NO patients. Clark *et al.* [17] analysed 123 ORRP patients randomized to right side-extended and left side-standard LND vs the reverse. They found a 6.5% rate of node-positive disease, with no difference in positive nodes and a trend toward more complications on the side of the extended dissection. In a series of >5000 men, Masterson *et al.* [18] found that extended LND

improved the accuracy of staging, but did not modify biochemical outcomes after ORRP. It should be stressed that the differences in findings might reflect differences in screening practices and patient risk distribution among the cohorts, and it remains unclear to what extent the effect of the nodal dissection template on outcomes reflects a real effect, as opposed to the so-called 'Will Rogers' phenomenon (i.e. improved staging with extended LND, but no actual improvement in outcomes) [19]. Furthermore, the extent of LND has been associated with increased complications, at least in some series [20].

While the lymph node yield for RARP has not been widely reported, previous series have examined outcomes from unassisted laparoscopic LND with RP. In an older laparoscopic series, Stone *et al.* [11] compared non-randomized outcomes from standard vs extended LND, with a mean of nine vs 18 nodes dissected. They also found more positive node cases with extended dissection (23% vs 7%), but no statistically significant differences when controlling for level of cancer risk; moreover, their rate of complications was much higher with extended (36%) than standard (2%) dissection. More recently, Wyler *et al.* [21] analysed their series of 123 patients undergoing non-robotic laparoscopic RP and extended-template LND. They removed a mean of 21 nodes, found metastases in 17% of cases, and reported a 4% complication rate. In a report including both ORRP and laparoscopic cases, Toujier *et al.* [11] assessed 177 laparoscopic cases, finding a median of nine and 14 nodes after obturator and extended LND, respectively. Lattouf *et al.* [22] reported a technique of extended LND among 35 patients (23 of whom had unilateral dissection only), and obtained a median yield of 13 nodes; 31% of the patients had positive nodes. Notably in that report the dissection was extended anteriorly over the external iliac vessels, rather than posteriorly to include the tissue around the internal iliac vessels; while both regions might be 'landing sites' for prostate cancer cells, the latter generally appears to be the more important region for extended LND [23].

A recent analysis of Medicare data from 2003 to 2005 found that patients undergoing laparoscopic RP (with or without robotic assistance) only had LND 17% of the time, vs 83% of those undergoing ORRP, suggesting possible under-use of LND in the laparoscopic

setting and overuse in the open setting. In this analysis, high-volume laparoscopic surgeons were more likely to perform LND than low-volume surgeons, although the effect of volume was weaker than the effect of regional practice variation [24]. Another analysis of surgical volume and LND yield found that higher volume surgeons within a single group practice had higher nodal yields and higher rates of nodal involvement [25].

Case-to-case variation in lymph node yield reflects several overlapping factors, including technique and the extent of LND, individual patient lymphatic anatomy, and variability in pathological examination. The latter issue has been studied in particular with respect to radical cystectomy, for which nodal yield is more consistently associated with outcomes; several studies showed that submitting nodal tissue to pathologists in multiple rather than single packets produces markedly higher nodal counts [26,27]. In another study, variation in pathological technique (including serial step-sectioning and incorporation of immunohistochemistry) improved sensitivity for nodal metastases, but to a lesser degree than extension of the LND template beyond the obturator fossa [28].

While the overall nodal yields in the current analysis are lower than those reported by centres performing extended LND, they are comparable to other academic centres using a standard template dissection, and compare favourably to those reported, e.g. in SEER [4] and CaPSURE [15]. There are several possible explanations for the difference in nodal yield we observed between ORRP and RARP patients. It might be that the dissection is inherently more complete within a given template for ORRP patients. Risk has increased more among ORRP than RARP patients, and it is also possible that more ORRP patients are undergoing relatively extended template dissections. Our registry does not include detailed information on the borders of LND, therefore this question cannot be answered using this data source. Certainly we do not detect significant changes over time in nodal yield for either surgical approach to support this explanation. Finally, during open surgery it is simple to pass tissue for analysis in multiple packets, and during ORRP nodal tissue is sent in at least two (left and right) and sometimes four or more packets. Conversely, during RARP, to save on the cost of using several Endocatch

bags, the nodes are usually sent in a single packet. However, the use of multiple packets was not routine in the ORRP cases. This difference in procedure, as discussed above, could explain a potentially limited proportion of our observed variation in nodal yield.

The primary limitation of the present study is that the specific extent of LND was not recorded in the UODB for each case, so we cannot identify the intended template for each case as standard vs extended. Indications for LND also were not fully standardized. However, the templates for ORRP and RARP were generally similar over time for patients at similar levels of risk, and most operations in both cases used a standard template. These analyses were not corrected for multiple comparisons, which might have increased the overall likelihood of type I statistical error in the study. Patients in this series were more likely to receive LND if they had ORRP rather than RARP, even controlling for risk and year of surgery. We speculate that this bias might be seen among other programmes gaining experience in RARP, and we are currently working to standardize indications for LND across the urological oncology programme.

The nodal yield in this series is generally comparable to other reported academic series of ORRP and laparoscopic RP using a standard template, and rates of node positivity are comparable to others among patients with similar risk characteristics. The nodal yield was higher in association with ORRP rather than RARP, but the difference was not large, and is less striking than the range of variation within each surgical approach. Indications for LND and the dissection template should be consistent regardless of an open or laparoscopic approach.

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CONFLICT OF INTEREST

Christopher J. Kane is a consultant for Intuitive Surgical.

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Abbreviations: (RA)(OR)RP, (robot-assisted) (open retropubic) radical prostatectomy; CAPRA, Cancer of the Prostate Risk Assessment; SEER, Surveillance, Epidemiology, and End Results; LND, lymph node dissection; UODB, Urologic Outcomes Data Base; UCSF, University of California, San Francisco.