Original Article

Predictive factors for lymph node positivity in patients undergoing extended pelvic lymphadenectomy during robot assisted radical prostatectomy

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ABSTRACT

Introduction: Pelvic lymphadenectomy during radical prostatectomy (RP) improves staging and may provide a therapeutic benefit. However, there is no clear consensus on the selection criteria for subjecting patients to this additional procedure. With a growing adoption of robot assisted radical prostatectomy (RARP) in India, it has become imperative to study the incidence and predictive factors for lymph node involvement in our patients.

Materials and Methods: From February 2010 to February 2014, 452 RARP procedures were performed at our institution. A total of 100 consecutive patients from July 2011 to August 2012 were additionally subjected to a robotic extended pelvic lymphadenectomy (EPLND). Lymph node positivity rates and lymph node density were analyzed on the basis of preoperative prostate specific antigen (PSA), Gleason score, clinical stage, D'Amico risk category and magnetic resonance imaging (MRI) findings. Multivariate analysis was performed to ascertain factors associated with lymph node positivity in our cohort.

Results: The mean age of the patients was 65.5 (47–77) years and the body mass index was 26.3 (16.3–38.7) kg/m^2. The mean console time for EPLND was 45 (32–68) min. A median of 17 (two to 40) lymph nodes were retrieved. Seventeen patients (17%) had positive lymph nodes (median of 1, range 1–6). Median lymph node density in these patients was 10%. When stratified by PSA, Gleason score, clinical stage, D'Amico risk category and features of locally advanced disease on MRI, a trend towards increasing incidence of lymph node positivity was observed, with an increase in adverse factors. However, on multivariate analysis, clinical stage > T2a was the only significant factor impacting lymph node positivity in our cohort.

Conclusions: A significant proportion of men undergoing RARP in India have positive lymph nodes on EPLND. While other variables may also have a potential impact, a higher clinical stage predisposes to an increased incidence of lymph node metastases.

Key words: Extended pelvic lymphadenectomy, pelvic lymphadenectomy, prostate cancer, radical prostatectomy, robot assisted radical prostatectomy

INTRODUCTION

Robot assisted radical prostatectomy (RARP) is now an established form of treatment for localized prostate cancer with equivalent, if not better, oncological and functional outcomes as compared to an open or a standard laparoscopic approach.[1-5] It is currently being offered to patients in India at multiple centers across the country. Pelvic lymph node dissection is an essential component of radical prostatectomy, especially in intermediate or high risk localized prostate cancer. Many radiological and less invasive methods (including sentinel node biopsy) are described to determine lymph node involvement in prostate cancer.[6,7] However, till date, pelvic lymph node dissection is the only reliable and effective method to ascertain the presence of lymph node metastases in patients undergoing radical prostatectomy. Various nomograms, based on pre-operative parameters, have been described to predict the probability of lymph node positivity.[8-10] The National Comprehensive Cancer Network (NCCN) guidelines recommend an extended pelvic lymph node dissection (EPLND) during radical prostatectomy in patients

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who have a greater than 2% nomogram-derived risk for pelvic lymph node metastases.[11]

While data derived from western populations is now available for assessing lymph node positivity rates and related pathological parameters in patients undergoing pelvic lymphadenectomy, the same may not apply to Indian patients.[12-17] We evaluated a contemporary cohort of 100 consecutive patients undergoing RARP at our center to gain greater insight regarding the role of EPLND in Indian patients.

MATERIALS AND METHODS

Patients

Data was extracted from the prospective database of patients undergoing RARP at our institution. A total of 452 RARPs have been performed at our institution since February 2010. One hundred consecutive patients undergoing RARP from July 2011 to August 2012 by two surgeons (RA and GG) were subjected to extended pelvic lymphadenectomy and formed the cohort of this study. Preoperatively, all patients had a 99mTechnetium methylene di-phosphonate (99mTc MDP) bone scan and a dynamic magnetic resonance imaging (MRI) of the pelvis to stage the disease.

Surgical technique

We perform EPLND as the initial step of RARP before creating the space of Retzius. The procedure entails the removal of lymph nodes and fibro fatty tissue in the external iliac, hypogastric and obturator regions [Figure 1]. The boundaries are the external iliac artery laterally, the bladder medially, the lymph node of Cloquet and circumflex branch of the external iliac vein distally, the endopelvic fascia caudally and the bifurcation of the common iliac artery proximally and cranially. At the end of the procedure, the obturator nerve and vessels, the external iliac vein and the hypogastric artery are completely cleared of the overlying tissue [Figure 2]. The obturator vessels may sometimes be sacrificed. Lymph nodes are sent in two separate packets (one for each side) for permanent section. Frozen section is performed only if there is evidence of bulky gross lymphadenopathy.

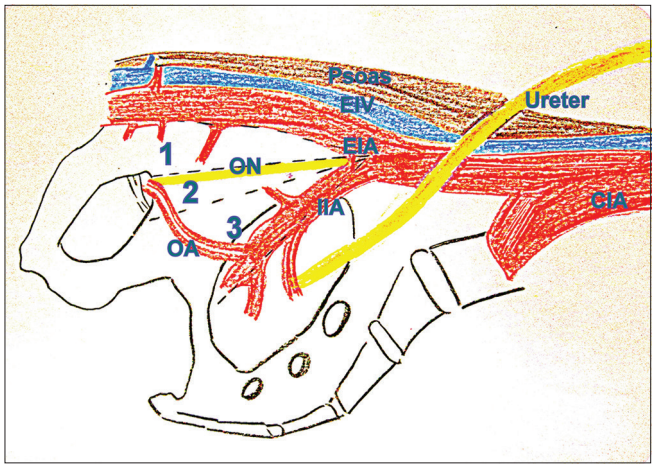

Figure 1: Extended pelvic lymphadenectomy template (right side) including the external iliac (zone 1), obturator (zone 2) and hypogastric (internal iliac) (zone 3) group of lymph nodes. CIA: Common iliac artery, EIV: External iliac vein, EIA: External iliac artery, IIA: Internal iliac artery, ON: Obturator nerve, OA: Obturator artery

Pathological processing

Pathological processing and reporting is performed as per the latest recommendations of the College of American Pathologists (CAP).[18] The surgical specimen is fixed overnight in 10% formalin. The lymph nodes are isolated and put in separate cassettes. The cassettes are then taken for further processing in the automatic processor, where steps of dehydration, clearing and impregnation with embedding media take place overnight, using graded alcohol, xylene and paraffin wax. Individual blocks are prepared on the next day, followed by sectioning, slide preparation, hematoxylin and eosin staining and examination under the microscope. Each lymph node is examined for the presence of lymph node involvement with prostate cancer. Extranodal extension is noted, if present.

Statistical analysis

Basic demographic data and preoperative, operative and postoperative data points were noted, along with complications within 30 days after surgery. Pre-operative and post-operative histopathological details also formed a part of the database. The data was stratified by prostate specific antigen (PSA), Gleason score, clinical stage, D'Amico risk category and features of locally advanced disease on pelvic MRI (extraprostatic extension, seminal vesicle invasion and pelvic lymphadenopathy). Lymph node positivity and lymph node density (percentage of the number of positive lymph nodes divided by the total lymph node yield in a particular patient) were calculated for each data set. Statistical analysis was performed by the SPSS software version 17.0 for Windows. Data was checked for normality before statistical analysis using the

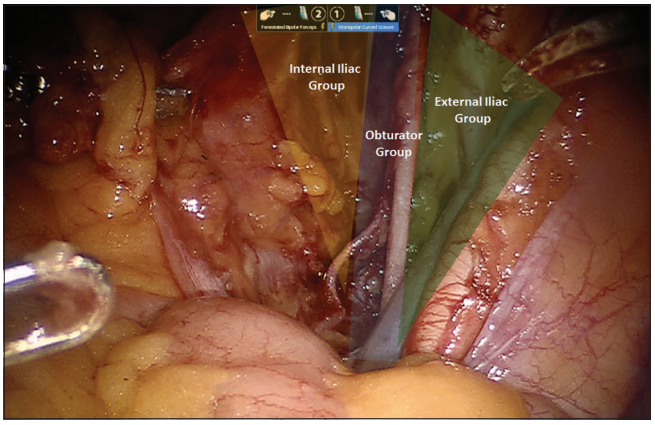

Figure 2: Intraoperative picture of robotic extended pelvic lymphadenectomy (right side) showing important anatomical landmarks and zones of dissection

Shapiro Wilk test. Kruskal–Wallis and Mann–Whitney U tests were used for those variables that were not normally distributed. Categorical variables were analyzed using the chi square test. Continuous variables are presented as mean ± SD, while those with a skewed distribution are described as a median (IQR). Categorical variables are presented as absolute numbers and percentage. For all statistical tests, a $P < 0.05$ was taken to indicate a significant difference. Univariate and multivariate logistic regression models were used to predict the probability of positive pelvic lymph nodes and lymph node density as a function of biopsy Gleason score, clinical stage, initial PSA, radiological staging and the D'Amico risk category. Sensitivity and specificity were calculated. Possible cut-off scores were evaluated, as shown by a receiver operating characteristics (ROC) curve.

RESULTS

A total of 100 consecutive men with clinically localized prostate cancer operated by two surgeons (RA and GG) from July 2011 to August 2012 formed the cohort for this study. Data was extracted from our prospectively maintained database to evaluate the correlation of lymph node positivity rates with various clinical and pathological variables. All patients underwent an extended pelvic lymphadenectomy performed robotically prior to proceeding with radical prostatectomy. All patients proceeded to a radical prostatectomy, irrespective of the presence or absence of gross lymphadenopathy. The mean age was 65.5 years (range, 47–77) and the body mass index was 26.3 kg/m^2 (range, 16.3–38.7). The mean console time for EPLND was 45 min (range, 32–68). A median of 17 (range, two to 40) lymph nodes were retrieved in the 100 patients undergoing EPLND. Seventeen patients (17%) had positive lymph nodes (median of one positive lymph node, range 1–6). A total of 33 lymph nodes were found to be positive in 17 patients. The median lymph node density in these patients was 10% (range, 2.5–28.5%) [Table 1].

When stratified by PSA, Gleason score, clinical stage, D'Amico risk category and features of locally advanced disease on MRI, a trend towards increasing incidence of lymph node positivity was observed with an increase in adverse factors [Tables 2–6].

On univariate analysis, there was no significant difference between various PSA groups for lymph node positivity and density rates. Similarly, no difference was noted among patients in different D'Amico risk categories and Gleason score cohorts for either of these measures. However, a significant increase in lymph node positivity was observed with increasing clinical stage. The probability of lymph node involvement increased from 8.1% in patients with ≤T2a disease to 42.9% in those with a stage ≥T2c. Similarly, evidence of locally advanced disease on MRI was predictive of increased probability of lymph node involvement. Patients with organ-confined disease on MRI had an 8.6% chance of lymph node involvement as compared to 26.3% in patients with suspected extracapsular spread or seminal vesicle involvement.

Table 1: Demographics and characteristics of patients undergoing extended pelvic lymph node dissection

n	100
Mean age (range), years	65.5 (47-77)
Mean BMI (range), kg/m^2	26.3 (16.3-38.7)
Mean PSA (range), ng/mL	17.6 (0.5-68)
Median biopsy Gleason score (range)	7 (6-9)
Median lymph nodes retrieved (range)	17 (2-40)
Total positive lymph nodes	33
Patients with nodal involvement	17
Median positive lymph nodes in patients with node involvement (range)	1 (1-6)
Median lymph node density in patients with node involvement (range), %	10 (2.5-28.5)
Mean console time for EPLND (range), min	45 (32-68)
Clinical stage	
T1c	44
T2a	18
T2b	24
T2c	12
T3	2
D'Amico risk category	
Low	7
Intermediate	47
High	46

EPLND=Extended pelvic lymphadenectomy

Table 2: Lymph node positivity stratified by prostate specific antigen

PSA (ng/mL)	<10	10-20	>20	*P*
*n**	34	33	27	
Patients with nodal involvement (%)	5 (14.7)	6 (18.2)	5 (18.5)	0.676
Median lymph node density (range), %	5.6 (2.5-28.5)	10.8 (4.5-16.6)	9.1 (3.1-19.1)	0.34

*Six patients received androgen deprivation therapy in the form of LHRH analogues or anti-androgen therapy prior to surgery and were excluded

Table 3: Lymph node positivity stratified by magnetic resonance imaging

MRI	T2	T3a/T3b	N+	*P*
n	58	36	6	
Patients with nodal involvement (%)	5 (8.6)	10 (26.3)	2 (33.2)	0.03
Median lymph node density (range), %	5.6 (2.5-10.0)	8.9 (3.1-18.2)	11.3 (11.1-11.5)	0.07

MRI=Magnetic resonance imaging

On multivariable logistic regression analysis, lymph node positivity was significantly correlated to stage progression beyond T2a (OR 4.01, CI 1.64–9.77, $P = 0.002$). No other prognostic factor was found to be significant. ROC curve analysis showed highest sensitivity and specificity for clinical stage (70.6 and 69.1, respectively) with an area under the curve of 0.71 (CI 0.62–0.80) [Figure 3].

Complications were recorded in 11 patients [Table 7]. Apart from transient scrotal edema due to suspected lymphatic obstruction in four patients, none of the complications were directly attributable to the lymphadenectomy component of RARP. In one patient, there was a ureteric injury during seminal vesicle dissection via a posterior approach. It was identified intraoperatively and managed with a ureteric reimplant over a double J stent during the same procedure. None of the patients developed symptomatic lymphocele. None of the patients required blood transfusions during or after the procedure.

Table 4: Lymph node positivity stratified by Gleason score

Gleason score	6	7	8-10	*P*
n	38	45	17	
Patients with nodal involvement (%)	4 (10.6)	11 (24.4)	2 (11.8)	0.199
Median lymph node density (range), %	6.1 (2.9-18.2)	7.4 (2.5-28.5)	10.7 (5.5-15.7)	0.97

Table 5: Lymph node positivity stratified by clinical staging

Clinical stage	≤T2a	T2b	≥T2c	*P*
n	62	24	14	
Patients with nodal involvement (%)	5 (8.1)	6 (25)	6 (42.9)	0.004
Median lymph node density (range), %	5.6 (2.5-28.5)	10.2 (3.1-18.2)	13.7 (4.1-19.1)	0.25

Table 6: Lymph node positivity stratified by D'Amico risk category

D'Amico risk category	Low	Intermediate	High	*P*
n	9	46	45	
Patients with nodal involvement (%)	1 (11.1)	7 (15.2)	9 (20)	0.736
Median lymph node density (range), %	2.9	10.2 (2.5-28.5)	11.5 (3.1-19.1)	0.25

Table 7: Intraoperative and post-operative complications

Intraoperative complications	2
Bladder injury	1
Ureteric injury	1
Post-operative complications	9
Grade 1 and 2	8
Transient scrotal edema	4
Transient femoral nerve paresis	1
Epididymo-orchitis	3
Grade 3 and 4	1
Pulmonary thromboembolism	1
Total	11

DISCUSSION

We evaluated a 100 consecutive patients undergoing RARP with extended pelvic lymphadenectomy at our center over a 14-month period and assessed the rates of lymph node positivity and density in these patients based on several pre-operative parameters, including clinical stage, PSA, biopsy Gleason score, MRI and D'Amico risk category. 17% of our patients were detected with lymph node-positive disease. We found that, although statistical trends indicated an increasing probability of lymph node positivity with an increase in adverse features of the disease, the only significant criteria for pelvic lymph node involvement was pre-operative clinical stage.

The last 5 years have witnessed a rapid expansion of robotic surgery all over the world, and India has not been left untouched by it. At present, around 25 robotic surgical systems have been installed in the country and many more are on the anvil. This has resulted in a significant increase in the number of RARP procedures being performed in India. In contrast to the West, where most tumors are detected by screening programs, a vast majority of Indian patients have higher stage disease with a greater propensity for lymph node involvement. In our own cohort, only 7% of patients fell into the low-risk D'Amico category and 45% had high-risk disease. 20% of these high-risk patients had positive lymph nodes on EPLND. This underlines the importance of pelvic lymphadenectomy in patients undergoing RARP in this part of the world.

The controversy regarding the optimal extent of pelvic lymphadenectomy during RP is now almost settled, with most

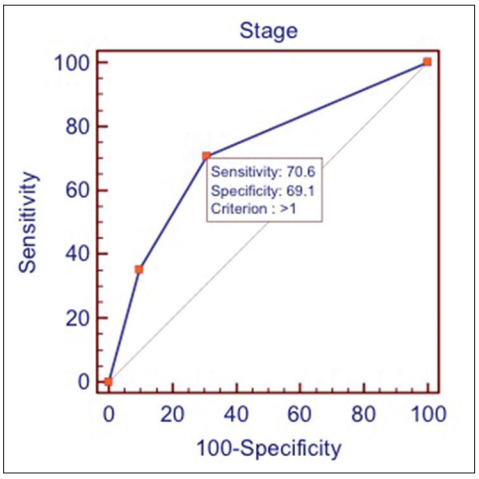

Figure 3: Receiver operating characteristics curve analysis of lymph node positivity in relation to clinical stage

guidelines recommending an extended template dissection, including external iliac, internal iliac (hypogastric) and the obturator group of lymph nodes.[11,19] Superextended templates including the pre-sacral and common iliac groups have also been described, but their role in prostate cancer treatment is yet to be established.[14] On the other hand, lymphadenectomy may not be required in patients with a low risk of lymph node involvement. According to the latest update of Partin tables, lymphadenectomy may be omitted in men with Gleason 3 + 3 disease, unless they have a PSA > 10 ng/mL AND a clinical stage ≥ T2b. Even in Gleason 3 + 4 disease, PLND can be avoided in men with cT1c disease, unless PSA is greater than 10 ng/mL.[10]

While the role of extended pelvic lymphadenectomy in improving prostate cancer staging is well established, there is evolving evidence of a therapeutic benefit as well. Daneshmand *et al*. observed long-term therapeutic advantage in terms of overall, clinical recurrence-free and biochemical recurrence-free survival in a cohort of 163 lymph node-positive patients who did not receive any form of adjuvant therapy after surgery.[20] A Surveillance Epidemiology and End Results (SEER) database study demonstrated that excision of at least four lymph nodes improves cancer-specific survival, vis a vis no PLND.[21] In a recent study, Abdollah *et al*. demonstrated an improvement in cancer-specific survival of lymph node-positive patients with increasing number of removed lymph nodes during radical prostatectomy and EPLND. The 10-year cancer-specific survival was 74.7%, 85.9%, 92.4%, 96.0% and 97.9% for patients with 8, 17, 26, 36 and 45 lymph nodes removed, respectively.[22] Ji *et al*. recently reported the findings of the only prospective randomized study comparing the impact of limited PLND versus EPLND on survival outcome measures. At a median follow-up of 74 months, biochemical progression-free survival for limited PLND versus EPLND was 73.1% and 85.7% in intermediate-risk disease ($P = 0.042$) and 51.1% and 71.4% in high-risk disease ($P = 0.036$). EPLND was an independent prognostic factor for biochemical progression-free survival when adjusted for other clinical and pathologic features.[23] This accumulating evidence in favor of a therapeutic effect of EPLND in prostate cancer adds to the importance of performing a meticulous lymphadenectomy in patients undergoing RARP.

Several nomograms are currently available to assess the chances of lymph node invasion in clinically localized prostate cancer. These make use of pre-operative variables, including Gleason score, clinical stage, PSA and, in certain cases, percentage involvement and number of positive biopsy cores, to assess the risk of lymph node involvement.[8-10] These nomograms are derived mostly from western cohorts and therefore a direct extrapolation of these data to our part of the world may not be reasonable. While our study falls short of creating a nomogram for the Indian population, it does provide valuable insight regarding the chances of lymph node positivity and the factors impacting the same in a contemporary cohort of Indian men undergoing robotic EPLND. We believe that this is the first step in the procurement and analysis of larger volume, long-term robust data, which is essential for the creation of an India-specific nomogram.

Our study is not without its limitations. Our cohort of 100 patients operated by two surgeons in a single institution may not reflect the "real world" scenario of prostate cancer in India. Indeed, ours is a tertiary care center where patients come pre-selected for undergoing RARP. The pathological specimens were reported by a team of multiple pathologists with varying levels of experience in uro-pathology. Pre-operative prostate biopsies were also not standardized as they were an admixture of those performed in our institution and those performed and reported elsewhere.

In spite of the above shortcomings, we believe that our study does provide important information regarding the various aspects of lymph node positivity in clinically localized disease in the Indian prostate cancer population. It may serve as a decision making tool for clinicians regarding lymph node dissection and aid proper patient counseling prior to undergoing treatment for prostate cancer.

CONCLUSION

According to our study, patients undergoing RARP in India are likely to have more advanced disease at presentation. In these patients, robotic EPLND may have a significant role, as evidenced by a high proportion of these patients manifesting positive lymph nodes on final pathology. The chances of lymph node positivity are influenced by pre-operative clinical stage, although other factors may also contribute to the same. Further evaluation is warranted to compare EPLND with other templates for lymphadenectomy in the Indian context – not only in terms of lymph node yields and positivity rates but also in terms of its potential therapeutic benefit.

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