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PROSTATE CANCER TOPOGRAPHY AND PATTERNS OF LYMPH NODE METASTASIS

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Abstract

Pelvic lymph node (LN) metastasis is a well-recognized route of prostate cancer spread. However, the relationship between topography and pathologic features of primary prostatic cancers and patterns of pelvic LN metastasis has not been well studied. We reviewed original slides of radical prostatectomies and pelvic LN dissections from 125 patients with LN metastasis and recorded total # of LN excised / laterality of positive LN, as well as localization, staging parameters, lymphovascular invasion and tumor volume of primary tumors.

LN Quantity and Distribution—14.6 (mean) and 13 (median) LN were resected. 76 (61%), 33 (26%) and 16 (13%) cases had 1, 2 and > 2 positive LN, while 58, 44 and 20 cases had LN metastasis on the right (R), left (L), and bilaterally.

Pathologic Features—86% (108/125) and 37% (46/125) demonstrated extraprostatic extension and seminal vesicle invasion, while 64% showed lymphovascular invasion. Mean and median total tumor volume was 6.39 and 3.92 cc, with 50% and 90% Gleason patterns 4/5 in 105 (84%) and 73 (58%) cases, respectively.

Correlation with Dominant Tumor Location—Dominant lesions on RP: 50 R lobe, 44 L lobe, 31 bilateral. 15/50 (30%) R lobe and 18/44 (41%) L lobe dominant tumors had LN metastasis on the contralateral side. Only 4% (5/125) of cases were associated with anterior dominant tumors. 30–40% of LN metastases occur contralateral to the dominant tumor. LN metastasis is overwhelmingly associated with high grade, high stage and large volume disease. LN positivity is rarely associated with anterior dominant tumors.

Keywords

prostate; pelvic lymph node; topography; anterior tumor; lymphovascular invasion

INTRODUCTION

Pelvic lymph node dissection (PLND) is the standard means for detecting lymph node (LN) metastasis in prostate cancer (15). Over the past three decades, the manner in which urologists and oncologists view the finding of LN positivity in relation to patient management has evolved. While finding LN metastasis on frozen section analysis was once

a contraindication to radical prostatectomy (RP) (12) more recent studies have recognized the curative potential of PLND (2, 4). Over the past few years, evidence from groups such as CaPSURE suggests a steady decline in the performance of PLND, especially for patients in low and intermediate risk groups (15). This has coincided with the advent of risk stratification tools, which aid in selecting/avoiding intervention (8, 19), and the increasing popularity of minimally-invasive surgery.

Consequently, great variation exists in determining which risk categories warrant PLND (15) and the extent of LN sampling that should be routinely performed (2–3). The latter is compounded by difficulties in determining the relationship of primary prostate cancers with the location of positive LNs, which if known, may help govern extent of resection. Although a number of groups (10, 12, 26, 29) have reported variable incidence of unilateral v. contralateral LN metastasis in patients with prostate cancer, primary tumor location was assessed on digital rectal examination (DRE), transrectal ultrasound (TRUS) and/or prostatic needle biopsy (PNB) findings. In the current study therefore, we aimed to comprehensively evaluate primary prostate cancer topography, as seen in RP specimens, and the distribution of positive LNs, to further elucidate the patterns of LN metastasis in prostate cancer.

MATERIALS AND METHODS

This retrospective, Institutional Review Board-approved study included 125 patients with LN metastasis treated with open or laparoscopic RP and bilateral PLND by three of our busiest surgeons (JAE, BG, PTS) over a six year period. Prior to surgery, seven patients received radiation therapy, five received androgen deprivation therapy, and one patient received both therapies.

All RP specimens were whole mounted and entirely-submitted according to previously published methods (1). Original H&E slides of all cases were re-evaluated by one of two genitourinary pathologists (VER, SWF) and tumor maps were constructed with annotation of low (Gleason pattern 3) and high grade (Gleason pattern 4) cancer. For each RP specimen, laterality, anterior-posterior and apex/mid/base localization of the tumor and the presence of extraprostatic extension (EPE), seminal vesicle invasion (SVI) and lymphovascular invasion (LVI) was recorded. RP slides were scanned as 300 dpi resolution digitalized tumor maps using an Epson Perfection 4990 PHOTO® digital scanner and Adobe Photoshop® Version 9.0. The JPEG formatted files were used to measure total tumor volume (TTV) and percentage of high grade tumor volume by Image-Pro® Plus 5.0, with the TTV being equal to the sum of section areas divided by 1.8797.

Frozen section analysis of LN was not performed. All LN specimens were fixed in 10% neutral buffered formalin and meticulously dissected by pathologists. Five µm H&E sections of each paraffin-embedded LN were examined microscopically. The PLND template included external iliac, obturator and hypogastric LN bilaterally. Approximately 25% of cases had LN submitted in 6 packets, while the remaining LN cases were submitted as right and left pelvic LN. Total number of LN and number of positive LN were recorded.

Student-t tests were performed to compare TTV, rate of high grade tumor and positive LN number between LVI positive and negative cases. Statistical analysis was performed using commercially available software.

RESULTS

Lymph Node Quantity and Distribution

The total number of LN dissected per case ranged from 4 to 48 (mean= 14.6; median=13). Seventy six of 125 (61%) cases had a single positive LN, 33 (26%) had 2 positive LNs and 16 (13%) had more than two positive LNs (range: 3 to 18). 58, 44 and 20 cases had positive LNs in the right pelvis, left pelvis, and bilateral pelves, respectively (in 3 cases laterality was unknown).

Eighty-nine cases had LN designated as “right and left pelvic”, while 33 cases were submitted in more detailed “packets” (for 3 cases, no designation other than “pelvic” LN was provided). Among these 33 cases, LN metastases were located in the obturator, hypogastric, external iliac, periprostatic and common iliac nodes in 16, 12, 8, 4, and 1 cases, respectively. Fourteen of 33 showed positive LNs in more than one site and 19 cases had metastasis in a single site only (obturator (10); external iliac (5); hypogastric (4)).

Pathologic Features of Primary Tumors

Pathologic features for the RP specimens are detailed in Table 1. Pathologic tumor stage was pT2, pT3a and pT3b in 13%, 50% and 37% of cases, respectively. Among these, 108 (86%) cases displayed EPE and 46 showed SVI (45 with concomitant EPE; 1 with SVI in the absence of EPE). Tumor involved the right seminal vesicle in 17 cases, the left seminal vesicle in 12 cases, and bilateral seminal vesicles in 17 cases. Among cases without SVI, 22 of 79 (28%) cases had multiple positive lymph nodes, compared with 27 of 46 cases (59%) with SVI ($p < 0.001$).

Tumor Volume Studies

Mean and median TTV were 6.39 and 3.92 cc, respectively (range 0.03 to 45.7 cc). Predominantly high grade tumor foci (Gleason pattern 4–5) accounted for 50% of TTV in 105 (84%) cases, and 90% in 73 (58%) cases. A nearly linear relationship between TTV and percentage of high grade tumor was observed (results not shown).

Lymphovascular invasion

We evaluated the presence of lymphovascular invasion in 115 cases in which all original whole mount slides could be obtained. Assessment of LVI was on H&E sections alone, without immunohistochemistry for endothelial markers. Care was taken to exclude retraction artifacts, tumor within prostatic ducts and tumor within perineural spaces. We did not attempt to differentiate blood vessels from lymphatics.

Lymphovascular invasion was detected in seventy four (64%) cases. As summarized in Table 2, the mean number of positive LNs, TTV and percent high grade tumor were all significantly higher in cases with LVI than in those without ($p = 0.011$, 0.008 and 0.013, respectively).

Correlation of Dominant Tumor Location and Positive Lymph Node Location

On review of RP specimens, 50 dominant tumor masses were located in the right lobe, 44 in the left lobe and 31 in bilateral lobes. Fifteen of 50 (30%) right lobe dominant cases showed positive LNs on the left side (10 exclusively left, 5 bilateral LN metastases). Conversely, 18 of 44 (41%) left lobe dominant cases showed positive LNs on the right side (9 exclusively right, 9 bilateral LN metastases) [Figures 1–2].

Dominant tumors were located in posterior/posterolateral prostate in 102 (82%), both anterior and posterior in 18 (14%) and anterior only in 5 (4%) cases, respectively. Sixty

dominant RP tumors extended from apex through base, 45 cases were located primarily in the apex to mid gland and 19 cases in the mid to base. Thirteen of 16 cases without EPE or SVI (otherwise organ-confined) had dominant tumors localized to the apex-mid prostate.

DISCUSSION

A number of prior studies have attempted to determine patterns of prostate cancer spread to lymph nodes, reporting a 10 to 46% incidence of LN metastasis contralateral to the dominant tumor mass among LN positive cases (10, 12, 26, 29). Since these investigations encompass different eras in the clinical application of PLND, the conclusions drawn from the data have varied. Harrison et al writing at a time when LN metastasis detected at frozen section was cause for aborting RP, argue that since only eleven of 100 cases showed exclusively contralateral LN metastasis to DRE-detected dominant masses, ipsilateral LNs should be sampled first (12). Spiess et al evaluated the ability of DRE, TRUS and/or PNB to predict side of pelvic LN metastasis. They found a 10–17% rate of contralateral-only LN metastasis and false negative predictive rates between 14 to 29% with these modalities and conclude that they are not accurate enough to reliably guide physicians (26). Similarly, Weckermann et al studied 564 men with negative or unilaterally positive DRE as well as PNB positive in one lobe only and found up to 30% contralateral-only positive LNs (29). Results from imaging studies are conflicting, with some reporting little “crossover” of injected contrast medium to contralateral LN (24), others demonstrating some lymphatic crossover on lymphoscintigraphy (30), and a general consensus that standard imaging techniques consistently fail to identify pelvic lymph node spread with sufficient specificity (21, 25). Given these findings, a number of authors (10, 26, 29) have recommended complete bilateral PLND as the only appropriate LN staging method.

A drawback of previous studies, however, is the use of surrogates (DRE, TRUS, PNB and/or imaging findings) for determination of primary tumor location. To our knowledge, this is the first study to comprehensively assess prostate cancer topography, as seen in RP specimens, and corresponding lymph node metastasis. Herein, we demonstrate that, in the setting of standard (external iliac, obturator and hypogastric) LN dissection, 15% of metastasis occurs exclusively contralateral to the dominant prostatic tumor mass. Including cases with bilateral LN metastasis, over 25% of prostate cancers associated with positive LNs show contralateral spread. These findings are similar to those demonstrated by Leissner et al who recommend extended radical lymphadenectomy to all patients undergoing radical cystectomy for bladder cancer, based on ~ 20% risk of contralateral LN metastasis (17) and may suggest that a unilateral lymph node dissection for prostate cancer staging is unwise.

Evidence to support a therapeutic benefit of PLND in prostate cancer comes from studies showing that standard dissection (including external iliac, obturator, and hypogastric LN packets) results in detection of more positive LNs than limited (external iliac packet only) dissection (2, 27) and others demonstrating that the number of LN dissected correlates with time of PSA recurrence, relapse of symptoms, and prostate cancer-related mortality (4). Furthermore, Burkhard et al have reported that meticulous LN dissection results in a 7% rate of LN metastasis even in patients with PSA less than 10 ng/ml and GS less than 7 (7).

In spite of this data, selective application of PLND is currently the norm owing to the low reported contemporary incidence of positive LNs (2% to 6%), the rise of minimally-invasive surgery and the development of risk stratification tools to better identify men at risk for advanced disease (8, 11, 13, 15, 19). As highlighted by Kawakami et al in their review of an observational disease registry (CaPSURE), marked variation among institutions and individual surgeons exists in the selection of patients for and anatomic extent of PLND in prostate cancer. These authors report that although fewer overall patients underwent PLND

in the ten year period from 1992–2001, LN dissection was still performed in 75% and >80% of low and intermediate risk patients in whom the actual incidence of LN metastasis was < 1% and 2%, respectively. Importantly, they question the adequacy of PLND in achieving accurate staging, based on the small mean number of LN dissected in CaPSURE-enrolled patients (15). While it is clear from these collective analyses that the application of PLND remains controversial, our median of 13 lymph nodes dissected per case as well as high incidence of positive LNs in the obturator and hypogastric LN packets (among those cases with available data), supports the contention that standard PLND yields higher LN counts and will detect more metastatic foci than dissections limited to external iliac LNs (2–3, 27).

It is rather intuitive that the large – 6.39 cc mean and 3.92 cc median – tumor volumes seen presently would be associated with pelvic LN metastasis. However, it is interesting to note that more extensive breakdown of this data reveals 6, 12 and 26% of the cohort with <0.5 cc, <1 cc, and < 2 cc TTV, respectively. The relationship of tumor volume and pelvic LN metastasis has previously been explored by McNeal who reported that the volume of Gleason patterns 4 or 5 cancer (i.e. multiplying TTV by % high-grade tumor) was most strongly predictive of LN metastasis. In their hands, tumors with greater than 3.2 cc Gleason grade 4/5 cancer showed a 100-fold increase in the proportion of cases with nodal spread (20). Although we found predominantly Gleason grade 4/5 encompassed 50% of TTV in 84% of cases and 90% of TTV in 58% of cases, more than half of our cohort (65/125; 52%) had volumes of Gleason grade 4/5 less than 3.2 cc. In a similar vein, though the majority of our cohort displayed EPE, SVI, or both, 13% showed otherwise organ-confined primary tumors, the majority of which were located in the apex-mid prostate. It is apparent therefore, that LN positivity is not uniformly associated with tumors exhibiting high TTV, large volumes of high grade disease or stage pT3a.

A remarkable finding that emerges from this topographic analysis is the small number (4%) of LN positive cases associated with an anterior dominant tumor. Contemporary studies have shown an increasing rate – up to 20–25% – of anterior dominant tumors (1, 5) and no significant difference in the rate of LN metastasis compared with posterior tumors generally (16, 18). However, no prior study has focused exclusively on LN positive patients to discern these patterns. This result raises a number of interesting possibilities regarding anterior dominant tumors and PLND. First is the suggestion that anterior dominant cancers do not exhibit LN metastasis as frequently as posterior tumors. While there is some evidence that anterior tumors are typically of lower stage due to stromal boundaries of the transition zone (20) and/or a relative paucity of nerves in the anterior prostate leading to less perineural invasion and EPE (23, 28), this does not adequately account for the dearth of LN metastasis observed in the present study. A review of the LN data from our previous report on a large series of anterior dominant tumors reveals that 139 of 167 patients (97 anterior peripheral zone tumors and 70 transition zone tumors) underwent PLND (mean and median LN dissected: 10.4 and 10, respectively). While it was not the study's focus, we found that only 3 of 139 (2.2%) cases displayed LN metastases, providing further evidence of the paucity of LN metastasis in the setting of anterior dominant tumors (1). In the present study, we also note that the mean TTV among the five anterior dominant tumors is 14.1 cc, a value well beyond the mean TTV for all cases in this series, suggesting that only exceptionally large anterior tumors may metastasize to pelvic LNs. Another intriguing possibility is that the standard PLND performed in all of our patients does not include the main drainage pathways of the anterior prostate. Investigations of prostate lymphatic drainage have shown that removing external iliac, obturator, and hypogastric LNs covers the major regions to which the prostatic parenchyma empties, but not LN zones such as presacral nodes which may contain a small, but significant number of metastases (6). Further study with increased limits of dissection may be necessary to determine whether anterior dominant tumors have a divergent pattern of LN drainage compared with the majority of the prostate.

Another notable feature of this analysis is the high incidence of LVI detected. A wide selection of RP-based studies have reported an incidence of LVI ranging from 5% to 53%, data which is confusing due to non-uniform criteria for its evaluation as well as marked variation in the cohorts studied (9). Even with strict criteria that required unequivocal identification of tumor within endothelial-lined spaces and excluded suspicious lesions within the tumor mass, we were still able to identify LVI in 64% of patients on H&E alone. LVI was noted not only in the immediate periphery of tumors but frequently in the posterior periurethral region and within/around the ejaculatory duct complex. While statistical associations with larger TTV and volumes of high grade tumor are similar to those reported previously (14), the potential role of LVI in select patient groups is informative. For example, four of 5 anterior dominant tumors displayed LVI, suggesting that intraprostatic lymphatic infiltration plays a key role in anterior tumor metastasis to LN. Additionally, LVI was present in four of the otherwise organ-confined primary tumors with an additional four of these cases being among the 13 pre-operatively treated cases (which may have increased the difficulty of evaluation for LVI). The association of LN metastasis in these cases with intraprostatic LVI mirrors the phenomenon of SVI in cases lacking tumor contiguous to the ejaculatory duct complex or in the peri-seminal vesicle extraprostatic space (22). Finally, while the finding of multiple LN metastases in those patients with SVI was double that of patients without SVI, it is possible that the markedly different rates of LVI among these groups (83% of patients with SVI v. 46% of patients without SVI) largely accounts for this discrepancy.

In this large, well-annotated cohort of patients with pelvic LN metastasis, we have demonstrated that 30–40% of LN metastases occur contralateral to the dominant prostatic tumor mass. Moreover, while LN positive cases are overwhelmingly associated with high grade, high stage and large volume disease, subsets of patients with lower volume tumors or organ-confined primary disease may be identified in which intraparenchymal lymphovascular invasion likely plays a key role. LN positivity is rarely associated with anterior dominant tumors.

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Figure 1.

(a) 15/50 (30%) right lobe dominant cancers had positive lymph nodes in the left pelvis (10 exclusively left and 5 bilateral); (b) 18/44 (40%) left lobe dominant cancers showed positive lymph nodes in the right pelvis (9 exclusively right and 9 bilateral).

Figure 2.

(a) Unifocal (left-sided) large volume (TTV=7.85cc) high grade tumor (black) with lymph node metastasis only on the right side; (b) Multifocal (bilateral) small volume (TTV=0.06cc) low grade tumor (green) with bilateral lymph node metastases; (c) Anterior dominant, relatively small volume (TTV=1.91cc) grade 4+3=7 tumor with lymph node metastasis on the right side.

Table 1

Prostatectomy Pathologic Parameters for 125 Cases with Lymph Node Metastasis

	Number of Cases	Percentage (%)
Pathologic Stage		
pT2	16	13
pT3a	63	50
pT3b	46	37
Extraprostatic Extension *	108	86
Seminal Vesicle Invasion	46	37
Lymphovascular Invasion	74 **	64
Dominant Tumor Location		
Right	50	40
Left	44	35
Bilateral	31	25
Posterior/posterolateral	102	82
Anterior/posterior	18	14
Anterior only	5	4
Apex through base	60	48
Apex-mid	45	36
Mid-base	20	16

* with or without seminal vesicle invasion

** based on evaluation of 115 cases

Table 2

Association of Lymphovascular Invasion with Tumor Volume and Extent of Lymph Node Metastasis

	LVI positive (n=74)	LVI negative (n=41)	p value
Mean TTV (cc)	7.86	4.60	0.008
Mean % HG tumor	84.8	72.1	0.013
Mean # of positive lymph nodes	2.08	1.44	0.011

LVI: lymphovascular invasion; TTV: total tumor volume; HG: high grade (Gleason grade 4/5)