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ORIGINAL ARTICLE

Is More Always Better? An Assessment of the Impact of Lymph Node Yield on Outcome for Clinically Localized Prostate Cancer with Low/Intermediate Risk Pathology (pT2-3a/pN0) Managed with Prostatectomy Alone

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Abstract The clinical impact of lymph node dissection extent remains undetermined in the contemporary setting, as reflected in care pattern variations. Despite some series demonstrating a direct relationship between number of lymph nodes identified and detection of nodal involvement, the correlation between lymph node yield and disease control or survival outcomes remains unclear. Patients with clinically localized prostate cancer, pre-RP PSA <30, and pT2-3a/N0 disease at RP were retrospectively identified from two databases for inclusion. Those who received pre- or post-RP radiotherapy or hormone therapy were excluded. Kaplan-Meier method was employed for survival probability estimation. Cox regression models were used to assess bRFS differences between subsets. From 2002 to 2010, 667 eligible patients were identified. The median age was 61 yrs. (range, 43–76), with median PSA 5.6 ng/dL (0.9–28.0). At RP, most patients had pT2c (64%) disease with Gleason Score (GS) ≤6 (43%) or 7 (48%); 218 (33%) patients had positive margins (M+). At median clinical and PSA follow-up of 96 and 87 months, respectively, 146 patients (22%) experienced PSA failure with an estimated bRFS of 81%/76% at 5/8 years. For patients who underwent LND, univariable analysis identified PSA (at diagnosis), higher GS (≥7, at biopsy or RP), intermediate/high risk stratification, M+ as adversely associated with bRFS (all $p < 0.01$). A higher number of LNs excised was not associated with improved bRFS for the entire cohort (HR = 0.97, $p = 0.27$), nor for any clinical risk stratum, biopsy GS, or RP GS subgroup. This study did not demonstrate an association between LN yield and bRFS in patients with clinically localized pT2-3a/pN0 prostate cancer managed with RP alone, either in the entire population or with substratification by clinical risk stratum or GS.

Keywords Radical prostatectomy · Lymph node dissection · Localized prostate cancer · Biochemical relapse free survival

Introduction

Prostate cancer is the second most prevalent cancer in men worldwide with approximately 1.1 million new cases diagnosed each year [1]. Since introduction of PSA screening, the incidence of early stage prostate cancer has increased, resulting in a higher number of curative-intent interventions, including radical prostatectomy (RP) [2]. However, the clinical impact of limited versus extended lymph node dissection (LND) remains undetermined in the contemporary setting, as reflected in variations of pattern of care [3]. Despite extended LND series demonstrating a direct relationship between number of lymph nodes identified (LN yield) and detection of LN involvement [4, 5], the correlation between LND and disease control or survival outcomes remains unclear, with

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retrospective studies presenting inconsistent results [6–8]. Further, these studies have included heterogeneous populations of patients, including those with clinically locally advanced disease, very high PSA levels, clinically-evident LN involvement, and pathologically involved LNs, often with confounding pre- or post-RP treatments such as hormone and/or radiotherapy. The present study seeks to determine whether a correlation exists between bRFS and either performance of LND or number of LNs excised in the setting of clinically localized prostate cancer with pT2-3a disease at RP.

Methods

Study Cohort Following IRB approval at the study institutions, patients who underwent curative-intent RP for clinically organ-confined prostate adenocarcinoma from 2002 to 2010 were identified. The following criteria were used for exclusion: clinical or pathologic lymph node or seminal vesicle involvement, pre-prostatectomy PSA >30 ng/dL, incomplete surgical records, missing pathological data, less than 12 months of post-RP PSA follow-up, and patients who received pre- or post-operative radiation therapy, chemotherapy or hormone therapy.

Treatment, Pathologic Evaluation and Follow-up All patients underwent RP with extent of LN dissection at the discretion of the managing urologist. All pathological specimens were prepared and reviewed in accordance with standard techniques [9]. Information regarding pathologic staging, margin involvement, and number of lymph nodes sampled was obtained from pathology reports. Surveillance included clinical assessment with PSA at least every 3 to 6 months for the first two years post-RP, then every 6 to 12 months through 5 years and annually thereafter.

Endpoints and Statistical Analysis The primary endpoint of this investigation was biochemical relapse free survival (bRFS) which was defined as the time from RP to PSA failure date or last follow-up if disease free. PSA failure date was recorded as the initial date of two consecutive PSA elevations greater than 0.1 ng/ml of the recorded initial value after RP. The Kaplan-Meier method was used to construct survival curves for bRFS. Estimates of bRFS and OS along with 95% pointwise confidence intervals were reported. To adjust for potential selection bias, an inverse probability score weighted Cox regression model was fit to evaluate bRFS differences by receipt of nodal excision. Propensity scores were derived from a model adjusting for patient age at diagnosis, overall Gleason score at biopsy, clinical risk stratum, and pre-RP PSA. Among nodal excision patients, Cox regression models were used to assess whether the effect of nodal yield on bRFS varied by clinical risk stratum (low/intermediate/high, as per D'Amico criteria [10]) or overall Gleason score of initial biopsy and RP specimen. A sensitivity analysis was performed with and without a potential statistical outlier for number of nodes excised (33); this value was excluded. All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Results

Study Population Demographics Between 2002 and 2010, 1009 patients underwent RP, of whom 667 were eligible for the present analysis. The median age was 61 (range, 43–76), and median PSA was 5.6 ng/dL (0.9–28.0). The majority of men had Gleason score ≤ 7 at biopsy (91%). Of the 667 patients who underwent RP, 444 (67%) had pelvic LNs excised, of whom 393 had a specific number of LNs recorded. A median of 5 LNs were identified at specimen analysis (range, 1–33), with 83 patients (21%) having ≥10 LNs identified in the specimen. When evaluated by clinical factors, 9 of 45 patients (20%) with biopsy Gleason score ≥ 8 had 10 or more lymph nodes excised, as compared with 28/201 (14%) and 46/421 (11%) for Gleason 7 and ≤6, respectively. At RP specimen analysis, these rates were 8/59 (14%), 40/321 (12%), and 35/287 (12%) for final pathologic Gleason scores ≥8, 7, and ≤6, respectively. Approximately one-third of patients had positive surgical margins (n = 218/667; 33%). Complete study population data are described in Table 1.

General Population Outcomes At a median clinical follow-up of 96.1 months (range, 13.4–178.4), 626 patients were alive (491 without recurrence, 55 without disease following salvage radiotherapy, and 80 with active recurrence) and 41 had died (5 of prostate cancer, 22 of non-prostate cancer cause, and 14 of undetermined cause). The estimated 5-, 8-, and 10-year overall survival rates were 98% (95% C.I., 97–99%), 96% (93–97%), and 93% (90–95%), respectively. At a median PSA follow-up of 87.3 months (range, 12.8–175.4), 146 patients (22%) experienced PSA failure. The estimated 5-, 8-, and 10-year bRFS rates were 81% (77–83%), 76% (72–79%), and 73% (69–77%), respectively (Fig. 1).

Performance of Lymph Node Dissection Association with bRFS Univariable analysis identified higher Gleason score at biopsy, higher clinical risk stratum, higher PSA, and performance of LND as associated with worse bRFS (all $p < 0.01$). Owing to concern that LND performance was biased toward higher risk cases, a second analysis was performed, adjusting for these factors; however, patients undergoing some extent of LN removal remained at increased risk of biochemical relapse (HR = 1.52, 95% CI 1.25–1.85, $p < 0.01$), potentially reflecting other unmeasured variables.

Table 1 Population characteristics

	Entire Population (n = 667)		Population with Known #LNs Excised (n = 393)	
	N	%	N	%
Age (at diagnosis)				
Median (Range)	61 yrs. (43–76)		62 yrs. (44–75)	
Race				
White	653	98	388	99
PSA				
Median (Range)	5.6 ng/dL (0.9–28.0)		6.0 ng/dL (1.2–28.0)	
Staging				
CT Scan	73	11	38	10
Bone Scan	223	33	120	31
Gleason Score at Biopsy				
4–5	5	1	2	1
6	416	62	216	55
7	201	30	134	34
8	35	5	32	8
9–10	10	1	9	2
T stage (Clinical)[$]				
1a–b	3	<1	2	1
1c	551	83	314	80
2a	86	13	55	14
2b	15	2	13	3
2c	6	1	4	1
Interval Biopsy to RP				
Median (Range)	54 days (11–512)		48 days (11–512)	
>365 days*	3	<1	3	1
Surgical Margin				
Negative	449	67	247	63
Positive	218	33	146	37
T stage (Pathologic)[$]				
2a	63	9	36	10
2b	23	3	13	3
2c	425	64	229	58
3a	154	23	114	29
Gleason Score at RP				
5	3	<1	3	1
6	284	46	158	40
7	321	48	185	47
8	39	6	29	7
9	20	3	18	5

RP = Radical prostatectomy; LN = lymph node. [$] American Joint Committee on Cancer, TNM Staging Manual, version 7.0. *Reasons for delay included: patient indecision (2) and unknown/not specified (1)

Lymph Node Yield and bRFS For patients who underwent LND and had the number of LNs recorded, univariable results identified Gleason score at biopsy and prostatectomy, clinical risk stratum, margin status, and pre-RP PSA as associated with bRFS; the number of LNs excised was not associated with bRFS (Table 2). No relationship was observed between lymph node yield and bRFS. A secondary analysis was performed to identify a subgroup for whom an interaction was observed. When stratified by Gleason score at biopsy, Cox regression hazard ratios were not able to demonstrate a relationship between bRFS and number of excised LNs as a continuous variable (Table 3).

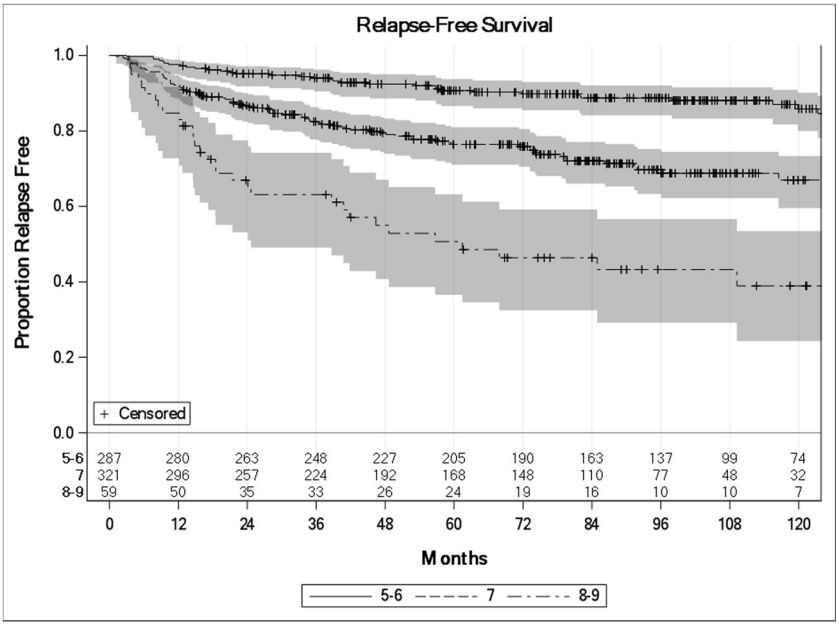

Fig. 1 Relapse-free survival by gleason score at prostatectomy

Discussion

Series of extended pelvic LN dissection have demonstrated correlations between higher LN yield and improved bRFS [11], as well as cancer-specific survival [12]; however, the most common practice pattern in the United States remains local or regional LN sampling [13, 14]. As such, we sought to determine whether the LN yield would remain correlative with bRFS in this setting, as generalizable data are needed for guidance of therapeutic decision-making in this area. In this study, we were unable to demonstrate an association between LN yield and bRFS in the context of lower-risk (pT2-3a / pN0) disease at RP with variable extent LND, either in the overall population or in pre-RP Gleason score subgroups. These findings are supported by others, including a large database series evaluating 5-year bRFS outcomes for patients who underwent limited LND versus no LND [15]. Of the 4693 patients in the CaPSURE database, in which a mean of 5.8 LNs were identified (range 0 to 71), no differences in bRFS were noted by either clinical risk stratification or by dichotomization of <9 versus ≥10 LNs removed. Despite limitations of treatment heterogeneity (inclusion of patients receiving hormone therapy and/or radiotherapy) and inclusion of patients with LN involvement (2% of total), these results generally align with the present study.

Table 2 Univariate analysis of PSA relapse free-survival for patients with known number of LNs excised*

Covariate	Level	N	Hazard Ratio	95% CI	*p*
Age at Diagnosis	(per year)	392	1.01	0.98–1.04	0.64
Clinical Risk Stratum (D'Amico)[22]	Low	184	Ref	-	<0.01
	Intermediate	151	2.31	1.46–3.66	
	High	52	4.52	2.67–7.66	
Gleason Score at Biopsy	4–6	218	Ref	-	<0.01
	7	134	2.42	1.57–3.72	
	8–10	40	3.50	2.02–6.08	
% Cores Involved		214	3.16	0.92–10.91	0.07
Gleason Score at RP	5–6	161	Ref	-	<0.01
	7	185	2.95	1.78–4.88	
	8–9	46	7.05	3.97–12.51	
Margin Status	Negative	246	Ref	-	<0.01
	Positive	146	3.17	2.13–4.72	
#LNs Excised	(per LN)	392	0.97	0.93–1.02	0.27

LN = Lymph Node; RP = Radical Prostatectomy. *One case with 33 lymph nodes sampled was excluded as a statistical outlier (adjusted range 1–24)

Table 3 bRFS in relation to number of lymph nodes sampled stratified by gleason score at biopsy

Biopsy GS	HR	95% CI
4–6	0.92	0.84–1.00
7	1.00	0.94–1.07
8–10	1.07	0.95–1.19

GS = Gleason score; HR = Hazard ratio, reflecting risk per each additional lymph node excised; 95% CI = 95% confidence interval. *One case with 33 lymph nodes sampled was excluded as a statistical outlier (adjusted range 1–24)

A second large, multi-institutional retrospective series reported by Kluth et al. described findings very similar to ours [8]. In a population of 6540 eligible pN0 patients (with median 6 LNs removed) who underwent RP between 2000 and 2011, a higher number of LNs removed correlated with worse bRFS at univariable analysis. Noting that LN yield was directly related to higher pre-RP PSA and Gleason score, a multivariable analysis ultimately determined that none of the study nodal stratifications (≥6, ≥10, or ≥20) was associated with bRFS. The findings of this retrospective study are most applicable to the current investigation, as patients with high pre-RP PSA (defined as >50 ng/mL), positive LNs and pre- or post-RP hormone therapy were excluded, though a small number of patients who received adjuvant radiotherapy were included (n = 164; 2.5%). The primary weakness of the study was the short follow-up (median 21 months), which limits determination of the true impact of LN yield over time. In this way, the presented study builds upon the findings of Kluth et al., demonstrating that long-term bRFS remains independent of nodal yield in the setting of pN0 disease.

The present study did not demonstrate correlation between LN yield and bRFS, which is supported by a single-institution study reported by investigators at Columbia University [16]. In a population of 964 patients with median LN yield of 7 and median follow-up 59 months, LN yield (measured in 5 subgroups) was not correlated with bRFS, even after correction into low- and high-risk subgroups (by clinicopathologic factors). However, these data conflict with other reports, which have correlated higher LN yield as independently associated with bRFS, attributed primarily to increased identification of LN involvement [4, 17]. The reasons for this discordance may be generally divided into two primary issues: 1) selection biases, in both physician practice and study population, and 2) limitations of detection.

With respect to selection bias, the impact of clinical factors (e.g., higher PSA and/or Gleason score) likely influences the extent of lymph node dissection a surgeon elects to perform as studies have shown that extended LND for intermediate-high risk disease yields higher rates of LN involvement [3, 17, 18]. This finding was observed within the present study, with stepwise higher nodal yields in higher Gleason score patients, and likely contributed to the correlation between higher LN yield and increased risk of recurrence in the Gleason 8–10 subset (Table 3). Further, whereas prior series have included patients with a wide variety of presenting clinical factors and pathologic findings (e.g., seminal vesicle involvement and/or very high PSA), we elected to focus on a pre-defined subset of patients with clinically localized presentations and low- to intermediate-risk pathologic findings, more reflective of contemporary prostate cancer presentation [19]. Additionally, by excluding patients who received pre- or post-RP treatment and maintaining long duration of follow-up, we sought to describe the natural history of patients who may be at risk for harboring residual nodal disease, to determine whether the increased LN yield would be associated with differences in PSA relapse.

With respect to limitations of detection, several studies have demonstrated that extended LND demonstrates superior ability to detect LN involvement as compared with limited LN sampling [6, 7, 20]. However, even when extended LND is performed, the false negative rate may exceed 10%, and the impact on disease control and survival outcomes remains uncertain [11, 12, 20, 21]. As an example, in a recent series evaluating sentinel lymph node scintigraphy, an estimated 13% of LN metastases would have been undetected by extended LND [22]. This discrepancy appears primarily related to variant lymphatic drainage (e.g., rectal); however, the clinical impact of these remains to be determined. A further limitation in detection is the insensitivity of standard hematoxylin and eosin staining to detect clinically significant nodal metastasis. Investigators at the University of Southern California assessed the rate of occult (microscopic) lymph node metastasis, using immunohistochemistry (IHC) in a high-risk subset of patients with pT3N0 disease at RP plus extended LND [23]. With a median of 22 LNs identified per case, 24 of 180 patients (13%) initially diagnosed with pN0 disease were subsequently found to harbor occult tumor cells using cytokeratin antibody-based IHC with PSA IHC confirmation. In reviewing cancer control and survival outcomes, patients with occult LN metastases demonstrated inferior recurrence-free and overall survivals as compared to those without occult tumor cells. Importantly, the outcomes of patients with occult LN metastases more closely reflected those of patients with overt LN metastasis, suggesting that underdetection of occult LN involvement could have both prognostic and therapeutic implications.

These results raise questions regarding the potential impact of advanced staging imaging techniques and/or less invasive sampling techniques in selectively identifying patients for whom an extended LND may be indicated, in order to minimize potential morbidity (e.g., edema, thrombosis, lymphocele) [3]. Recently, a positron emission tomography (PET) tracer specific to prostate cancer has been developed, by attaching a radioactive gallium isotope (^{68}Ga) to a ligand which binds prostate membrane specific antigen (PSMA). In a

study evaluating 130 patients with intermediate- to high-risk prostate cancers, ^{68}Ga-PSMA PET scan demonstrated superior sensitivity and specificity in correctly identifying LN metastases as compared with magnetic resonance imaging (MRI) plus computed tomography (CT) (66% versus 44% and 99% versus 85%, respectively) [24]. In addition, sentinel lymph node techniques are being explored in prostate cancer, and appear to show promise [25, 26], potentially with selective therapeutic implications [26].

While retrospective in nature, the present series has several strengths, including size, length of follow-up, and uniformity of management (i.e., elimination of potential confounding variables, such as pre- or post-operative radiation or hormone therapy). While the LN yield in the present study (median, 5) is less than that described in extended LND series (median, 15–18) [3], our population appears reflective of national practice patterns (e.g., median 3–6) [13, 14, 18] and compares well with other similarly-designed series [8], and as a result may be more relevant to contemporary clinical situations.

Conclusions

Within a large population of clinically localized, pT2-3a/pN0 prostate cancer patients with long-term follow-up and absence of confounding treatments before or after RP, higher LN yield was not associated with improvement in bRFS. While specific higher-risk subsets of patients may benefit from extended LND, and several studies have suggested greater detection of nodal burden, the overall impact on cancer control and survival remain uncertain, and must be balanced against the risk of morbidity. Innovative techniques, such as sentinel lymph node dissection and prostate-specific radiotracer-based imaging, may provide opportunities for individualization of diagnostic and therapeutic interventions.

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Compliance with Ethical Standards

Conflict of Interest None of the authors declares that he or she has any potential or actual conflicts of interest with respect to the present investigation.

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