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More Extensive Lymph Node Dissection at Radical Prostatectomy is Associated with Improved Outcomes with Salvage Radiotherapy for Rising Prostate-specific Antigen After Surgery: A Long-term, Multi-institutional Analysis

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Abstract

Up to 50% of patients recur after salvage radiation therapy (sRT) for prostate-specific antigen (PSA) rise following radical prostatectomy (RP). Notably, the importance of lymph node dissection (LND) at the time of RP with regard to recurrence risk following sRT has not been previously determined. Therefore, we evaluated the association between nodal yield at RP and recurrence after sRT. We performed a multi-institutional review of men with a rising PSA after RP treated with sRT. Clinicopathologic variables were abstracted, and the associations between lymph node yield and biochemical (BCR) as well as clinical recurrence (CR) after sRT were assessed using multivariable Cox proportional hazards regression models. In total, 728 patients were identified; of these, 221 and 116 were diagnosed with BCR and CR, respectively, during a median follow-up of 8.4 (interquartile range: 4.2–11.2) yr. On multivariable analysis, the risk of BCR after sRT was inversely associated with the number of nodes resected at RP (hazards ratio [HR]: 0.98; 95% confidence interval [CI]: 0.96–0.99; $p = 0.049$). Increased extent of dissection was also independently associated with a decreased risk of CR after sRT (HR: 0.97; 95%CI: 0.94–0.99; $p = 0.042$). These data support the importance of an extensive LND at surgery and may be used in prognosis assessment when sRT is being considered.

Patient summary: We found that patients who had increased number of lymph nodes resected at surgery had improved outcomes after the receipt of salvage radiation therapy. These findings support the use of the extended lymph node dissection at initial surgery and should serve to improve counseling among patients who require salvage radiation therapy.

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Salvage radiation therapy (sRT) is an alternative for the management of men with a rising or persistently elevated prostate-specific antigen (PSA) after radical prostatectomy (RP) [1,2]. The use of sRT has been supported by numerous retrospective studies [3,4]; nevertheless, recurrence after sRT has been reported in up to 50% patients [5]. Identified prognostic factors for men receiving sRT include Gleason score at surgery, pathologic tumor stage, surgical margin status, and PSA at radiation administration [6].

Interestingly, although such pathologic features have been used to inform prognosis, assessments to date have not included the extent of lymphadenectomy. While a therapeutic role for pelvic lymphadenectomy (PLND) in prostate cancer has not been definitively established, retrospective data support the oncologic efficacy of PLND at RP, with improved outcomes seen in patients undergoing more extensive nodal dissections [7]. Indeed, the potential remains for residual, unresected lymph node disease to be a source for recurrence after sRT [8]. Therefore, we investigated whether the extent of nodal dissection at RP is associated with oncologic outcomes following sRT for men with PSA relapse after surgery.

Following the institutional review board approval, a multi-institutional cohort of patients treated with sRT was generated. Radiation field for sRT (prostate fossa only versus whole pelvis, inclusive of pelvic nodal irradiation), as well as use of concurrent androgen deprivation therapy with sRT were at the discretion of the treating center and were noted for analyses. The outcomes of interest were biochemical recurrence (BCR) and clinical recurrence (CR), with the time-to-event calculated from the date of sRT, and with patients censored at the date of death or last follow-up if without the event. BCR was defined as PSA level >0.2 ng/ml and rising after sRT. CR was defined as the radiographic diagnosis of either local or distant metastatic disease.

In order to assess independent associations between the extent of PLND (number of nodes resected) with BCR and CR after sRT, multivariable Cox proportional hazards regression models were generated and summarized with hazard ratios (HR) and 95% confidence intervals (CI). Interactions between the extent of node dissection and previously identified prognostic variables such as Gleason score (>8 vs <8), pathologic T-stage (>pT3b vs <pT3b), and use of nodal irradiation were tested to evaluate potentially meaningful patient subgroups. To summarize the influence of nodal yield on survival outcomes, locally weighted 8-yr Kaplan-Meier estimated BCR-free survival and CR-free survival were plotted against the number of resected lymph nodes using the Lowess method. All analyses were performed using R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria), with two-sided p values reported, and a p value of <0.05 was considered significant.

A total of 728 patients were identified for analysis. Clinical characteristics are summarized in Supplementary Table 1. PLND was performed in 573 (79%) patients, with a median of nine (interquartile range [IQR]: 5–15) lymph nodes resected. Radiotherapy was delivered at a median of 13 (IQR: 4–37) mo after surgery; the median PSA at sRT was 0.3 (IQR: 0.15–0.7) ng/ml.

Median follow-up after sRT among patients alive at the last follow-up was 8.4 (IQR: 4.2–11.2) yr; during this time, 221 patients experienced BCR and 116 patients were diagnosed with CR. Estimated 8-yr BCR-free survival was 68% (95% CI: 64–72). Notably, we found that after adjusting for pathologic Gleason score, pT-stage, nodal involvement, PSA at sRT, use of concomitant hormonal therapy with sRT, and radiation field, the risk of BCR after sRT was inversely associated with nodal yield at RP (HR: 0.98; 95% CI: 0.96–0.99; $p = 0.049$; Table 1). When nodal yield was categorized in five lymph node increments, the association with BCR remained significant (HR: 0.91; 95% CI: 0.79–0.99; $p = 0.049$; Supplementary Table 2). The risk of BCR at 8 yr following sRT according to nodal yield, as estimated from the multivariable model, is depicted in Fig. 1.

Moreover, the estimated 8-yr CR-free survival in our overall cohort was 88% (95% CI: 85–91). We further determined that the extent of node dissection was likewise independently associated with an inverse risk of CR on multivariable analysis (HR: 0.97; 95% CI: 0.94–0.99; $p = 0.042$ for each additional node; Table 1). When the nodal yield was categorized in five lymph node increments, the association remained (HR: 0.86; 95% CI: 0.74–0.99; $p = 0.042$; Supplementary Table 2). The risk of CR as a function of nodal yield, as estimated from the multivariable model, is illustrated in Supplementary Figure 1.

To the best of our knowledge, we report the first assessment of the interaction between the extent of PLND at RP and the efficacy of sRT for patients with PSA rise after

Table 1 – Multivariable analysis of the association of clinicopathologic features with biochemical recurrence and clinical recurrence after salvage radiation therapy

	BCR			CR		
Variable	HR	95% CI	p value	HR	95% CI	p value
Gleason 8–10 (ref <7)	1.57	1.15–2.15	<0.01	2.47	1.63–3.72	<0.01
Positive margin	0.78	0.47–1.30	0.30	1.02	0.69–1.51	0.90
pT3b/4 (ref <pT3a)	2.49	1.82–3.40	<0.01	3.21	2.08–4.94	<0.01
pN1 (ref pN0/x)	0.81	0.62–1.07	0.14	1.14	0.61–2.13	0.70
Nodal yield (per node)	0.98	0.96–0.99	0.049	0.97	0.94–0.99	0.042
PSA at sRT (per ng/ml)	1.16	1.10–1.23	<0.01	1.21	1.12–1.31	<0.01
Whole pelvic sRT (ref fossa only)	0.76	0.51–1.13	0.20	1.13	0.69–1.86	0.60
Concomitant hormonal therapy	1.21	0.79–2.30	0.40	1.24	0.82–1.88	0.30

BCR = biochemical recurrence; CI = confidence interval; HR = hazards ratio; PSA = prostate-specific antigen; sRT = salvage radiation therapy.

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