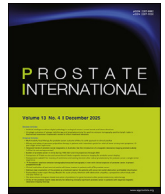




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Review article

Oncologic outcomes of salvage radiotherapy and lymphadenectomy for positron emission tomography–positive lymph nodes in biochemical recurrence: A systematic review to inform treatment decisions

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ABSTRACT

Introduction: Positron emission tomography (PET) scans are widely used for detecting biochemical recurrence (BCR) in prostate cancer, yet evidence for salvage treatments of PET-positive lymph nodes remains limited. This study aimed to analyze the oncologic outcomes of salvage treatments, specifically lymph node dissection (LND) and radiotherapy (RT), in patients with BCR and PET-positive lymph node recurrence.

Methods: Systematic reviews and meta-analyses were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search of PubMed, Cochrane, and Web of Science databases up to June 2023 was conducted. Inclusion criteria encompassed patients with BCR and PET-positive lymph node recurrence following definitive prostate cancer treatment, who underwent salvage LND or RT.

Results: A total of 38 publications involving 3,559 patients (1391 LND, 2168 RT) were included. Pooled incidence rates after LND and RT were as follows: prostate-specific antigen (PSA) response (56.4% vs. 78.9%), PSA progression (61.3% vs. 36.0%), image progression (44.9% vs. 34.9%), systemic progression (41.3% vs. 35.0%), overall mortality (3.0% vs. 4.8%), and cancer-specific mortality (8.4% vs. 4.1%). Subgroup analyses by prostate-specific membrane antigen (PSMA) PET scan, PSA level ≤ 2 ng/ml at PET scan, and androgen deprivation therapy usage with salvage therapy revealed varied outcomes.

Conclusions: Despite salvage LND or RT, about half of BCR patients with PET-positive nodal recurrence showed disease progression, suggesting limited effectiveness of focal therapies alone. RT appeared to provide better short-term disease control than LND, highlighting the importance of treatment selection. The study underscores the necessity for further investigation into optimal salvage management strategies for BCR using PET in prospective clinical studies.

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1. Introduction

Globally, the most common type of cancer among males is prostate, followed by lung, colorectal, and liver cancers.¹ Biochemical recurrence (BCR) remains common in approximately one-third of localized prostate cancer cases despite radical prostatectomy (RP) and radiotherapy (RT) being well-established treatment options.² BCR can be associated with local recurrence or an increased risk of metastasis and cancer-specific mortality (CSM) in patients, making it an important prognostic indicator for disease control with the goal of cure.³ A 2.0 ng/ml increase in prostate-specific antigen (PSA) above the nadir is observed in cases after RT; however, PSA ranges from 0.1 ng/ml to 0.4 ng/ml in cases after RP, regardless of the consensus about BCR. This is because BCR definitions slightly differ depending on the medical society.²

Conventional image modulations such as computed tomography (CT), magnetic resonance imaging, and bone scans, detect radiologic recurrence; however, they are limited in diagnosis with low sensitivity for BCR status.⁴ Therefore, next-generation imaging using positron emission tomography (PET) is recommended for patients with negative BCR results to overcome these limitations.⁵ Prostate-specific membrane antigen (PSMA), particularly overexpressed in prostate cancer cell membranes and radioactive tracers such as choline, with increased metabolism in the membranes of malignant cells, and fluciclovine—an upregulated amino acid in prostate cancer cells—excreted less in urine, have been approved by the Food and Drug Administration.⁶ Notably, centralized productions for 68Ga-PSMA, a widely used tracer for PET-CT and 18F-PSMA, with a long half-life, have increased.⁷ In BCR status, PSMA tracers were better at diagnosis than choline or fluciclovine tracers.⁸

Post-diagnostic treatments for BCR remain inadequate despite substantial evidence detailing the diagnostic accuracy of PET/CT. Recurrence in lymph nodes after primary treatment is challenging. Two focal salvage treatments for recurrent lymph nodes are lymph node dissection (LND) and RT. Therefore, this meta-analysis aimed to analyze the pooled incidence of oncologic outcomes in patients with BCR and PET-positive lymph node recurrence who underwent focal salvage treatment.

2. Evidence acquisition

2.1. Study protocol and registration

Systematic reviews and meta-analyses were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹ The protocol was registered with the International Prospective Register of Systematic Reviews (CRD42023489456).¹⁰

2.2. Search strategy

Studies from PubMed, Cochrane, and Web of Science databases were reviewed. All publications up to June 15, 2023, were included. A literature search was conducted on June 23, 2023. The inclusion criteria were studies involving patients with BCR and PET-positive lymph node recurrence after definitive prostate cancer treatment and salvage LND or RT. Those involving patients who underwent primary RT or RP and patients with N1 or M1a disease were also included. Studies on M1b or M1c diseases without separate reports on lymph nodes were excluded. Keywords included prostate cancer, BCR, PET, salvage RT, and salvage LND. [Supplementary Table 1](#) summarizes the full search strategy.

Two authors (S.Y.C. and J.C.) independently screened the titles and abstracts of the retrieved studies for eligibility. Conference

abstracts, review articles, editorials, comments, and letters to the editor were excluded. Disagreements were resolved through discussion between the authors or via consultation with a third author (Y-J.Y.).

2.3. Data extraction

Data were independently extracted by two authors (S.Y.C. and J.C.), and disagreements were discussed with a third author (Y-J.Y.). Study characteristics, including the author, year, primary treatment, PET type, use of androgen deprivation therapy, PSA level, and salvage treatment type, were the data extracted for this study. Oncological outcomes included PSA response and progression, imaging progression, systemic progression, overall mortality (OM), and CSM. The outcomes reported for each treatment were analyzed separately.

2.4. Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to systematically evaluate the risk of bias in each eligible study.¹¹ The risk index included six items, with each item assigned one point, excluding the non-exposed cohort and comparability. Therefore, the maximum possible score was 6 points. In this study, NOS scores of ≥ 5 and ≥ 3 but < 5 were rated as “good” and “fair,” respectively. The literature quality was evaluated independently by two researchers (S.Y.C. and J.C.). In cases of inconsistent results, both authors discussed or consulted a third author (Y-J.Y.).

2.5. Statistical analysis

The overall incidences of PSA response and progression, image progression, systemic progression, OM, and CSM were estimated in the RT and LND groups using a random effects model. A planned subgroup analysis was performed on the outcomes of PSMA PET scan, PSA ≤ 2 , and androgen deprivation therapy (ADT). Data were expressed as proportions with 95% confidence intervals (CIs). Heterogeneity was evaluated based on I^2 and Chi-square-based Q-test values. High heterogeneity was defined as $I^2 > 50\%$ with $P < 0.10$.¹² Funnel plots and Egger’s test were used to assess the publication bias. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using STATA/MP v18 (StataCorp., College Station, TX, USA).

3. Results

3.1. Literature retrieval

We initially retrieved 1,609 articles, and 785 duplicates were eliminated. In addition, 786 articles were excluded to comply with the inclusion criteria. Finally, 38 articles were included in the systematic review and meta-analysis ([Fig. 1](#)).

3.2. Study characteristics

We identified 38 eligible publications, including 3559 patients (1391 and 2168 for LND and RT, respectively; [Fig. 1](#)).^{13–50} [Table 1](#) summarizes the reviewed studies. Except for nine prospective studies, all other included studies were retrospective in design. PSMA PET scan was performed in 21 studies, and PET scan was performed in 19 studies at a PSA of ≤ 2 ng/mL. Fifteen studies involved patients who underwent ADT concomitantly with LND or RT.

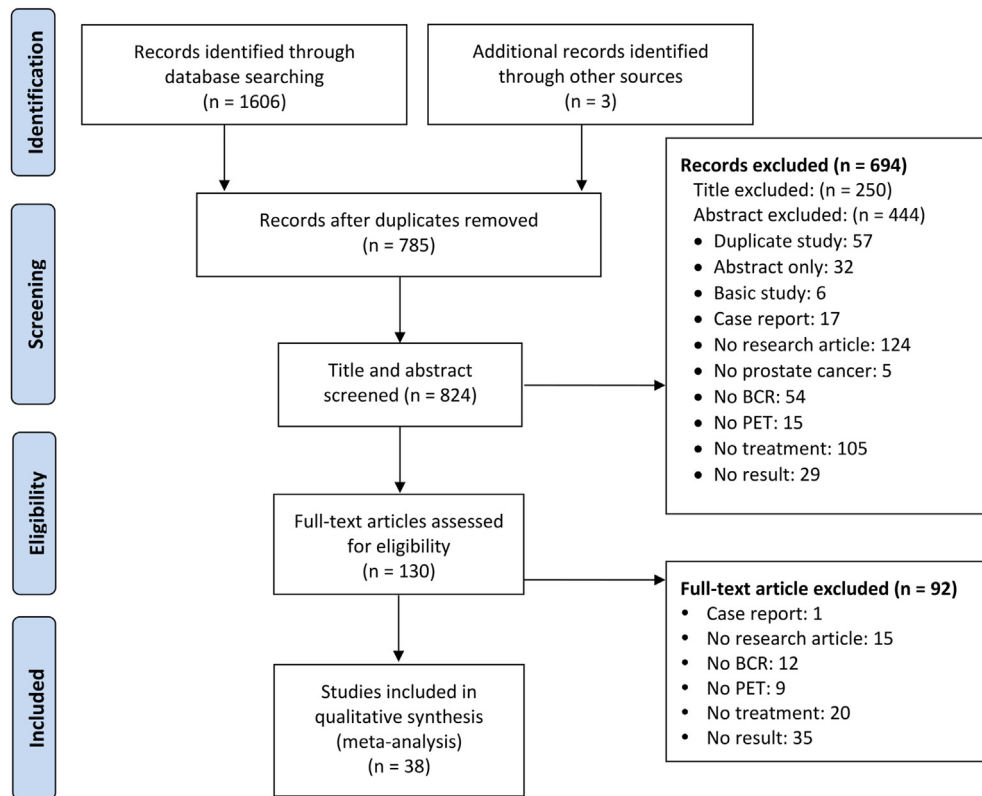


Figure 1. Flow chart of the study design.

3.3. Risk of bias

The risk of bias was assessed in the included studies. Risk scores of 6 and 5 were allotted to 19 and 13 of the 38 studies, respectively (Supplementary Table 2). The remaining six studies had scores of 3 or 4. Thus, all the participants were categorized as having a “good” or “fair” risk of bias.

3.4. Oncologic outcomes

3.4.1. Overall outcomes

The PSA response and progression, image progression, systemic progression, OM, and CSM were quantitatively analyzed (Table 2 and Supplementary Table 3). The overall proportions of PSA responses and mortality in the LND-treated group were lower than those in the RT-treated group (Fig. 2A and Supplementary Fig. 1A–6A). The pooled results of all outcomes, excluding CSM of RT in the LND and RT groups, revealed high heterogeneity. The results of all outcomes in the RT, excluding systemic progression, and the result of CSM in the LND showed publication bias (Table 2 and Supplementary Fig. 1B–6B).

3.4.2. PSA response

The overall rate of PSA response was 66.1% [95% CI: 58.0–74.1%], with high heterogeneity ($I^2 = 92.73\%$, $P < 0.001$). No publication bias existed in the PSA analysis results (Egger's test, $t = -1.94$, $P = 0.066$). In the LND-treated group, the pooled proportion of PSA response was 56.4% (95% CI: 45.9–66.8%), with high heterogeneity ($I^2 = 90.71\%$, $P < 0.001$). Additionally, the PSA response rate was 78.9% (95% CI: 71.4–86.4%), with high heterogeneity ($I^2 = 82.22\%$, $P < 0.001$). A small sample bias was not detected in the LND treatment group (Egger's test, $t = -0.49$,

$P = 0.635$); however, it was observed in the RT treatment group (Egger's test, $t = -2.63$, $P = 0.030$).

3.4.3. PSA progression

The overall proportion of PSA progression was 46.6% (95% CI: 37.7–55.4%), with high heterogeneity ($I^2 = 96.20\%$, $P < 0.001$). No small study bias was detected (Egger's test, $t = 0.41$, $P = 0.684$). The overall proportion in the LND-treated group was 61.3% (95% CI: 47.3–75.3%), with high heterogeneity ($I^2 = 96.54\%$, $P < 0.001$). In contrast, the overall proportion was 36.0% (95% CI: 27.5–44.5%) in the RT treatment group, with high heterogeneity ($I^2 = 92.32\%$, $P < 0.001$). Publication bias was identified in the RT-treated group (Egger's test, $t = 2.28$, $P = 0.037$), but not in the LND-treated group (Egger's test, $t = -0.76$, $P = 0.464$).

3.4.4. Image progression

The overall proportion of image progression was 38.7% (95% CI: 31.1–46.4%), with high heterogeneity ($I^2 = 95.44\%$, $P < 0.001$). A small publication bias was not detected (Egger's test, $t = 2.02$, $P = 0.054$). In the LND-treated group, the overall proportion was 44.9% (95% CI: 32.1–57.7%), with high heterogeneity ($I^2 = 93.57\%$, $P < 0.001$). The pooled proportion in RT treatment was 34.9% (95% CI: 25.7–44.2%), with high heterogeneity ($I^2 = 95.64\%$, $P < 0.001$). Publication bias was detected in the RT-treated group (Egger's test, $t = 4.15$, $P = 0.001$); but not in the LND-treated group (Egger's test, $t = -0.34$, $P = 0.740$).

3.4.5. Systemic progression

The overall proportion of systemic progression was 38.5% (95% CI: 31.2–45.7%), with high heterogeneity ($I^2 = 82.23\%$, $P < 0.001$). No publication bias was identified (Egger's test, $t = 1.47$, $P = 0.168$). The pooled analysis of systemic progression revealed a proportion

Table 1
Demographic characteristics of the included studies

Study	Year	Design	Primary treatment	Type of PET	Usage of ADT at PET	PSA at PET (ng/mL)	Salvage treatment	Enrolled number	Outcomes	Follow-up period (months)
Bolton ¹³	2022	Retrospective	RARP (75%), RT (25%)	68Ga-PSMA-11 PET-CT	No	2.49	LND	20	PSA progression	3
Bravi ¹⁴	2023	Retrospective	RP	68Ga-PSMA PET-CT	No	1.1	LND	164	PSA response, PSA progression, image progression	12
Glicksman ¹⁵	2021	Prospective	RP	18F-DCFPyL PSMA PET-MR/CT	No	1.0	LND	10	PSA response	17.7
Karnes ¹⁶	2015	Prospective	RP	11C choline PET-CT	19.3%	2.2	LND	52	PSA response, systemic progression, OM, CSM	20
Knipper ¹⁷	2023	Retrospective	RP	99mTc-PSMA-I&S or 111In-PSMA-I&T	No	1.0	LND (radio-guided)	364	PSA response, systemic progression, OM	24
Kretschmer ¹⁸	2021	Retrospective	RP	68Ga-PSMA PET-CT	No	2.6	LND (+ADT 5.6%)	71	PSA response, PSA progression, image progression	33
Rischke ¹⁹	2015	Retrospective	RP, RT	11C-choline or 18F-fluoroethylcholine PET-CT	N/R	N/R	LND	46	PSA response, PSA progression, image progression, CSM	28.7
Bobrowski ²⁰	2021	Retrospective	RP (86.4%), RT (13.6%)	68Ga-PSMA PET/CT or 18F-DCFPyL PSMA PET/CT	No	1.5	LND	22	PSA response, PSA progression, image progression, systemic progression	23.1
Devos ²¹	2019	Retrospective	RP	11C-choline PET-CT or 68 Ga PSMA-11 PET/CT	N/R	N/R	LND (open)	60	PSA progression, systemic progression	53
Devos ²¹	2019	Retrospective	RP	11C-choline PET-CT or 68 Ga PSMA-11 PET/CT	N/R	N/R	LND (robot)	30	PSA progression, systemic progression	15
Farolfi ²²	2020	Retrospective	RP	68Ga-PSMA-11 PET/CT	N/R	1.2	LND	16	PSA response, image progression	3.5
Herlemann ²³	2017	Prospective	RP	18F-fluoroethylcholine or 68Ga-PSMA-HBED-CC PET/CT	N/R	4.1	LND	104	PSA response, PSA progression, image progression, systemic progression, OM, CSM	39.5
Osmonov ²⁴	2016	Retrospective	RP, RT	11C-choline PET/CT	No	>0.5	LND (+ADT 88.9%)	45	PSA response, PSA progression, image progression, OM, CSM	42.7
Rauscher ²⁵	2017	Retrospective	RP (93.5%), RT (3%), HIFU (3%)	68 Ga-HBED—CC—PSMA PET	N/R	1.3 (at LND)	LND (radio-guided)	31	PSA response, systemic progression, OM	11.2
Rinnab ²⁶	2008	Prospective	RP, RT	11C-choline PET/CT	N/R	2.34	LND	15	PSA response, systemic progression	13.7
Zattoni ²⁷	2016	Retrospective	RP	11C-choline PET/CT	N/R	2.3	LND	117	PSA progression, image progression, CSM	20.2
Schmidt Hegemann ²⁸	2020	Retrospective	RP	68Ga-PSMA PET/CT	No	3.07 (before LND)	LND	33	PSA response, PSA progression, image progression, OM, CSM	17
Boeri ²⁹	2021	Retrospective	RP (96.9%), RT (3.1%)	11C-choline PET/CT	No	2.3 (at LND)	LND (+bicalutamide)	191	Image progression, systemic progression, CSM	51.8
Ben Shimol ³⁰	2022	Retrospective	RT	68Ga-PSMA PET/CT	54%	N/R	RT	113	OM	29.2
Caroli ³¹	2020	Retrospective	RT (28.9%), RP + RT (71.1%)	68Ga-PSMA-11 PET/CT	No	1.1	RT	38	PSA response, PSA progression, image progression	15
D'Angelillo ³²	2014	Retrospective	RP	18F-Choline PET-CT	31.7%	0.9	RT (+ADT 31.7%)	60	PSA progression	31.2
Emmett ³³	2017	Prospective	RP	68Ga-PSMA PET-CT	No	0.23	RT	26	PSA response, PSA progression	10.5
Hölscher ³⁴	2022	Prospective	RP, RT	68Ga-PSMA PET-CT/MR	No	2.2	RT (linear-accelerator-based radiotherapy)	72	PSA progression, systemic progression, OM	37.2
Kretschmer ¹⁸	2021	Retrospective	RP	68Ga-PSMA PET-CT	No	1.3	RT (elective nodal radiotherapy)	67	PSA response, PSA progression, image progression	47
Pêtre ³⁵	2023	Retrospective	RP (69.8%), RT (31.2%)	18F-fluorocholine or 68 Ga PSMA PET-CT	N/R	3.1	RT (+ADT 37.2%) (salvage nodal involved-field radiation therapy or salvage nodal extended-field radiation therapy)	86	PSA progression, image progression, systemic progression, OM, CSM	41.9

Scharl ³⁶	2023	Retrospective	RP	68Ga-PSMA-11, 18F-PSMA-1007, 68Ga-PSMA-I&T, 18F-PSMA-DCFpyL or 18F-PSMA-rhPSMA-7/-7.3	No	N/R	RT	168	PSA progression, image progression, OM	28
Zamboglou ³⁷	2022	Retrospective	RP	68Ga-PSMA-11, 68Ga-PSMA-I&T, 18F-PSMA-1007, 18F-PSMA-DCFpyL, 18F-siPSMA-14, or 18F-PSMA-rhPSMA-7/-7.3	30.8%	N/R	RT (+ADT 30.8%)	275	Image progression	36
Schmidt Hegemann ³⁸	2020	Retrospective	RP	8F- or 11C-choline PET/CT or 68Ga-HBED-CC PSMA PET/CT	No	0.69	RT (+ADT 38%)	257	Image progression	30
Schmidt Hegemann ³⁹	2020	Retrospective	RP	68Ga-PSMA PET/CT or PET/MRI	No	1.09	RT (+ADT 35%)	224	PSA response, PSA progression	16
Schmidt Hegemann ⁴⁰	2019	Retrospective	RP	68Ga-PSMA PET/CT	No	0.78	RT (+ADT 60%)	42	PSA response, PSA progression, image progression, OM, CSM	23
Spohn ⁴¹	2023	Retrospective	RP	68Ga-PSMA 11-PET/CT	No	N/R	RT (+ADT 47.5%)	99	PSA progression, OM	29
Supiot ⁴²	2021	Prospective	RP, RT	Fluorocholine PET/CT	No	N/R	RT (+ADT 100%)	67	Progression, image progression	49.4
Garcia ⁴³	2016	Retrospective	RP	11C-choline PET/CT	N/R	N/R	RT	37	PSA response, image progression	36
Henkenberens ⁴⁴	2017	Retrospective	RP, RT	68Ga-PSMA ligand PET/CT	No	2.75	RT	23	PSA response, PSA progression, image progression, OM	12.4
Incerti ⁴⁵	2015	Retrospective	RP, RT	11C-choline PET/CT	N/R	2.42	RT (helical tomotherapy)	68	PSA response, PSA progression, OM	20
Ingrosso ⁴⁶	2020	Retrospective	RP, RT	Choline PET, PSMA PET	N/R	2.0	RT (elective nodal radiotherapy + ADT 83%)	41	PSA progression, image progression, OM, CSM	33.6
Lawal ⁴⁷	2023	Prospective	RP	18F-fluciclovine PET/CT	N/R	0.32	RT (+ADT 34.7%)	60	PSA progression	48
Oehler ⁴⁸	2019	Retrospective	RP	18F-Choline PET/CT	No	3.53 (at RT)	RT (SBRT)	25	PSA response, systemic progression	18
Rogowski ⁴⁹	2022	Retrospective	RP	68 Ga-PSMA-11, 18F-PSMA-1007 PET-CT	N/R	1.4	RT (+ADT 83%)	100	PSA progression, image progression	37
Werensteijn-Honingh ⁵⁰	2021	Prospective	RP, RT	68Ga-PSMA-PET/CT	No	1.3 (before RT)	RT (SBRT)	90	Image progression, systemic progression, OM	21
Schmidt Hegemann ²⁸	2020	Retrospective	RP	68Ga-PSMA PET/CT	No	1.3	RT (elective nodal radiotherapy)	67	PSA response, PSA progression, image progression, OM, CSM	31
Boeri ²⁹	2021	Retrospective	RP (88.8%), RT (11.2%)	11C-choline PET/CT	No	2.0 (at RT)	RT(SBRT 28%/+ADT 79.8%)	63	Image progression, systemic progression, CSM	38.1

ADT, androgen deprivation therapy; CSM, cancer-specific mortality; LND, lymph node dissection; N/R, not reported; OM, overall mortality; HIFU, high-intensity focused ultrasonography; PET, positron emission tomography; PSA, prostate-specific antigen; RARP, robot-assisted radical prostatectomy; RT, radiation therapy; RP, radical prostatectomy; SBRT, stereotactic body radiotherapy.

Table 2

Summary of the meta-analysis on oncologic outcomes in patients who underwent LND and RT using the random effect model

Outcome measures	Treatment type	Studies (n)	Total (n)	Event (n)	Proportion (%; 95% CI)	Heterogeneity				Egger's test	P	Ref
						Q	df	P _{hetero}	I ² (%)	t-value		
PSA response	LND	13	973	517	56.4 (45.9-66.8)	159.40	12	<0.001	90.71	−0.49	0.635	14–20,22–26,28
	RT	10	617	477	78.9 (71.4-86.4)	47.53	9	<0.001	82.22	−2.63	0.030	18,28,31,33,39,40,43–45,48
PSA progression	LND	12	1076	648	61.3 (47.3-75.3)	420.01	11	<0.001	96.54	−0.76	0.464	13,14,17–21,23,24,27,28
	RT	17	1308	447	36.0 (27.5-44.5)	215.91	16	<0.001	92.32	2.28	0.037	18,28,31–36,39–42,44–47,49
Image progression	LND	10	809	373	44.9 (32.1-57.7)	194.52	9	<0.001	93.57	−0.34	0.740	14,18–20,22–24,27–29
	RT	16	1489	485	34.9 (25.7-44.2)	392.61	15	<0.001	95.64	4.15	0.001	18,28,29,31,35–38,40,42–46,49,50
Systemic progression	LND	8	765	316	41.3 (30.0-52.6)	67.67	7	<0.001	88.42	1.35	0.224	16,17,20,21,25,26,29
	RT	5	336	119	35.0 (26.9-43.2)	10.02	4	0.040	59.87	0.08	0.943	29,34,35,48,50
OM	LND	5	525	15	3.0 (−0.1-6.0)	11.93	4	0.018	59.07	2.55	0.083	16,17,24,25,28
	RT	11	869	46	4.8 (1.7-7.8)	47.60	10	<0.001	92.13	6.08	<0.001	28,30,34–36,40,41,44–46,50
CSM	LND	7	588	53	8.4 (3.1-13.7)	26.77	6	<0.001	86.16	3.38	0.019	16,19,23,24,27–29
	RT	5	299	16	4.1 (0.2-7.9)	10.89	4	0.028	74.57	3.26	0.047	28,29,35,40,46

CI, confidence interval; CSM, cancer-specific mortality; LND, lymph node dissection; OM, overall mortality; df, degrees of freedom; PSA, prostate-specific antigen; P_{hetero}, probability level associated with Q-test; Q, homogeneity test; RT, radiation therapy.

of 41.3% (95% CI: 30.0–52.6%), with high heterogeneity ($I^2 = 88.42\%$, $P < 0.001$) and 35.0% (95% CI: 26.9–43.2%) with high heterogeneity ($I^2 = 59.87\%$, $P = 0.040$) in the LND- and RT-treated groups, respectively. Publication bias was not detected in the LND- and RT-treated groups (Egger's test, $t = 1.35$, $P = 0.224$ and $t = 0.08$, $P = 0.943$, respectively).

3.4.6. Overall mortality

The pooled result of death risk was 4.2% (95% CI: 2.0–6.5%), with high heterogeneity ($I^2 = 91.13\%$, $P < 0.001$). Publication bias was also detected (Egger's test, $t = 6.57$, $P < 0.001$). The rate of OM in the LND-treated group was 3.0% (95% CI: −0.1–6.0%), with high heterogeneity ($I^2 = 59.07\%$, $P = 0.018$). In contrast, a relatively higher death proportion was observed in the RT-treated group, at 4.8% (95% CI: 1.7–7.8%), with high heterogeneity ($I^2 = 92.13\%$, $P < 0.001$). Publication bias was detected in the RT-treated group (Egger's test, $t = 6.08$, $P < 0.001$); but not in LND-treated group (Egger's test, $t = 2.55$, $P = 0.083$).

3.4.7. Cancer-specific mortality

A pooled analysis revealed that the rate of CSM was 6.7% (95% CI: 3.2–10.3%), with high heterogeneity ($I^2 = 85.50\%$, $P < 0.001$). Publication bias was detected (Egger's test, $t = 5.46$, $P < 0.001$). The LND-treated group had a 8.4% rate of CSM (95% CI: 3.1–13.7%), with high heterogeneity ($I^2 = 86.16\%$, $P < 0.001$). This result contrasted substantially with that of the RT treatment group, which exhibited a 4.1% rate of CSM (95% CI: 0.2–7.9%), with high heterogeneity ($I^2 = 74.57\%$, $P = 0.028$). Small publication biases were observed in the LND-treated group (Egger's test, $t = 3.38$, $P = 0.019$) and RT-treated group (Egger's test, $t = 3.26$, $P = 0.047$).

3.5. Subgroup analysis

3.5.1. PSMA PET scan

The overall proportion of PSA responses was 47.0% and 79.1% for the LND- and RT-treated groups, respectively (Table 3A and Supplementary Fig. 7A–12A). The pooled rates of PSA progression were 56.5% and 30.4%, and systemic progressions were 45.0% and 36.6% for the LND- and RT-treated groups, respectively. The image progression and OM rates were 32.9% and 28.2% and 0.9% and 2.0% in the LND- and RT-treated groups, respectively. The pooled rates of CSM were 1.5% and 1.3% in LND and RT, respectively. The results of the oncological outcomes, excluding systemic progression and OM in LND, and CSM in RT, showed substantial heterogeneity. Heterogeneity could not be analyzed because the results of CSM after LND were included in two studies. A small study bias was detected in the

results of OM in RT-treated group (Table 3A and Supplementary Figs. 7B–12B).

3.5.2. PSA ≤ 2 at PET scan

The overall proportions of PSA responses were 50.3% and 76.3% in the LND- and RT-treated groups, respectively (Table 3B and Supplementary Fig. 13A–18A). The risks of PSA progression, image progression, systemic progression, and OM were 48.7%, 24.7%, 45.0%, and 0.9%, respectively, with LND, and 30.5%, 36.7%, 27.4%, and 7.5% with RT, respectively. The overall rate of CSM reported only in RT was 5.7%. The pooled results of oncological outcomes, excluding image progression, systemic progression, and OM in LND, and PSA progression and systemic progression in RT, revealed high heterogeneity. Publication bias was observed in the image progression results after RT (Table 3B and Supplementary Fig. 13B–18B).

3.5.3. ADT usage with salvage therapy

The pooled proportions of PSA response, PSA progression, image progression, systemic progression, OM, and CSM were 58.1%, 62.2%, 40.5%, 24.1%, 20.0%, and 12.0%, respectively, with LND, and 73.9%, 36.1%, 32.7%, 28.6%, 9.1%, and 8.0% with RT (Table 3C and Supplementary Fig. 19A–23A), respectively. High heterogeneity was detected in the LND- and RT-treated groups, excluding PSA response in the RT-treated group. Due to the insufficient number of studies, it was not possible to identify heterogeneity in the results of systemic progression in LND and RT, as well as OM in LND. A small study bias was observed only in the results of image progression with RT (Table 3C and Supplementary Fig. 19B–23B).

4. Discussion

The timing and management of BCR after definitive therapy remain controversial based on the limited evidence in the conventional imaging era. The development of next-generation imaging modalities is influencing the therapeutic landscape with changing clinicians' intent.⁵¹ A higher detection rate of PET scans might clinically impact BCR because the localization of recurrent tumors before metastasis would be related to focal treatment with less systemic adverse effects and a high possibility of complete cure.⁸ We collected oncological outcomes of focal salvage treatment for LND and RT. The primary findings of this meta-analysis were a pooled incidence of 56.4% and 78.9% for PSA response, 61.3% and 36.0% for PSA progression, 44.9% and 34.9% for image progression, 41.3% and 35.0% for systemic progression, 3.0% and 4.8% for OM, and 8.4% and 4.1% for CSM after LND and RT, respectively. The disease progression after LND remains high compared

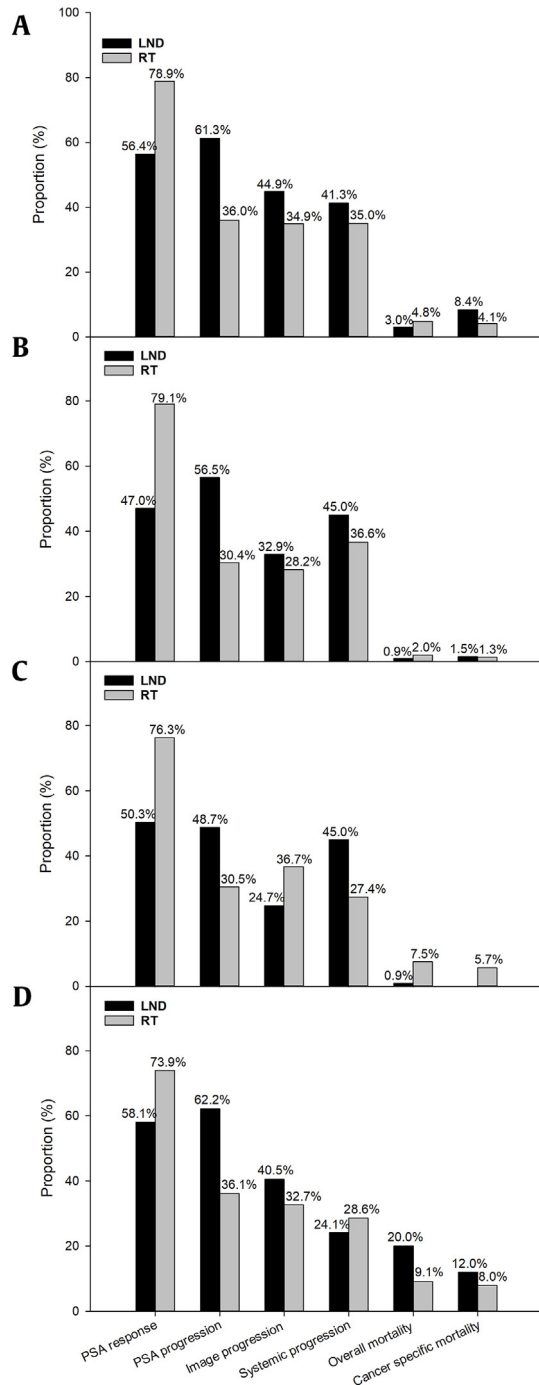


Figure 2. Proportion of oncologic outcomes according to salvage LND and RT (A) total (B) PSMA PET scan, (C) PSA 2 or less, and (D) concomitant ADT. LND, lymph node dissection; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RT, radiotherapy.

with that after early salvage RT treatments in the conventional imaging era.^{52,53}

Controversy regarding salvage treatments in BCR persists because of the paucity of high-level comparative studies, rarity of PET-positive lymph nodes, and heterogeneity of outcomes. Only three retrospective studies have compared salvage LND and RT.^{18,28,29} Boeri *et al.*²⁹ Reported no difference in survival outcomes between LND and RT, but both salvage therapies showed benefits in image, systemic progression compared with ADT. Two studies

might have involved common (shared) participants.^{18,28} Patients' characteristics (pathologic T stage and nodal stage) were favorable for the LND-treated group in both studies; however, the RT-treated group had a greater PSA progression.^{18,28} Kretschmer *et al.*¹⁸ Reported no difference in image progression rate. However, Schmidt Hegemann *et al.*²⁸ Reported lower rates of image and systemic progression in the RT-treated group compared with that of the LND-treated group. A median of eight or nine lymph nodes using standard extended LND were removed; however, only one pathologically positive lymph node was observed in both studies.^{18,28} Karnes *et al.*¹⁶ Removed a median of 21.5 lymph nodes, including a median of 3.5 positive lymph nodes, with a reasonable rate (25.0%) of systemic progression during a median of 20 months. Osmonov *et al.*²⁴ Removed a median of 20 lymph nodes, including a mean of 4.1 positive lymph nodes, and observed a reasonable incidence rate (22.2%) of image progression during a mean of 42.7 months. For effective salvage LND, an appropriate number of lymph nodes must be carefully removed and must contain substantial metastatic lesions. Hence, radio-guided surgery using PSMA could provide high value for the intraoperative detection of small metastatic lesions.^{17,25} Nevertheless, previous inadequate outcomes of disease progression revealed that patient selection is important when performing radio-guided surgery.^{17,25}

The pooled PSA response results (66.1%) were relatively high for both salvage treatments. Herlemann *et al.*²³ Reported a high PSA response of 86.5%, comprising complete and partial responses of 29.8% and 56.7%, respectively, for LND treatment. However, image progression was detected via PET/CT in 70.2% of all patients in 39.5 months.²³ In RT, Henkenberens *et al.*⁴⁴ Showed a high PSA response of 95.7% to RT treatment; however, cases requiring RT were insufficient ($n = 23$). PSA and systemic progression rates of 27.9% and 15.2%, respectively, were observed during a short-term follow-up of 12.4 months.⁴⁴ PSA or image progression frequently occurred during long-term follow-up despite the considerable PSA response reported in the early phase after salvage treatment. These results, therefore, led to the initiation of systemic therapy.

Treatment choice is known to influence the side-effects. Adverse effects were acceptable in studies that reported salvage treatment toxicity compared with studies without this report. Approximately, 10–40% of toxicity has been reported, and side-effects graded ≥ 3 were limited.^{16–18,20,21,23–28,31,32,35,39,40,42,44,46,50} In LND, lymphatic complications were the most common and some complications graded ≥ 3 were ureter stricture, rectovesical fistula, or pulmonary embolism.^{24,25,28} LND reduces hospital stay and lowers blood loss and complication rates than open LND.²¹ In RT, genitourinary toxicity is the most common, and other toxicities graded ≥ 3 include erectile dysfunction, radiation cystitis, and rectal bleeding.^{32,39,40,42}

The PET scan is not the gold standard for curing BCR; however, we derived three conclusions from our results. Therefore, selecting appropriate and effective treatment methods will increase treatment efficiency. First, most studies reviewed were single-armed, making direct comparison difficult; however, the overall pooled results of RT were greater than those of LND. Additionally, concomitant ADT and RT use were reported by several studies. Conventional imaging of intermediate-to-high-risk localized prostate cancer revealed using PSMA PET-CT that approximately 27% and 6% were upstaged and metastasized, respectively, which was associated with BCR prediction.⁵⁴ These situations indicate the presence of a metastatic burden beyond the regional area in BCR cases; thus, regional salvage treatment might be effective. Systemic therapy using androgen receptor-targeted agents with ADT significantly improved metastasis in high-risk patients with BCR.⁵⁵ Therefore, novel systemic agents targeting nonvisible metastatic lesions with focal salvage treatment are required for better

Table 3
Summary of the meta-analysis on oncologic outcomes in (A) PSMA PET scan, (B) PSA ≤ 2 ng/mL, and (C) patients treated with concomitant ADT, LND, and RT using the random effect model

Outcome measures	Treatment type	Studies (n)	Total (n)	Event (n)	Proportion (%; 95% CI)	Heterogeneity				Egger's test		Ref
						Q	df	P _{hetero}	I ² (%)	t-value	P	
(A) PSMA PET scan												
PSA response	LND	8	711	320	47.0 (35.6–58.3)	29.78	7	<0.001	85.66	0.40	0.701	8 14,15,17,18,20,22,25,28
	RT	7	487	371	79.1 (71.4–86.8)	25.30	6	<0.001	75.88	–1.21	0.280	7 18,28,31,33,39,40,44
PSA progression	LND	6	674	379	56.5 (35.1–77.9)	279.84	5	<0.001	97.19	–0.02	0.983	6 13,14,17,18,20,28
	RT	11	926	272	30.4 (20.1–40.8)	132.55	10	<0.001	93.04	1.65	0.133	11 18,28,31,33,34,36,39–41,44,49
Image progression	LND	5	306	82	32.9 (19.7–46.0)	25.60	4	<0.001	79.84	1.31	0.280	5 14,18,20,22,28
	RT	9	870	240	28.2 (14.5–41.8)	235.85	8	<0.001	97.29	2.32	0.053	9 18,28,31,36,37,40,44,49,50
Systemic progression	LND	3	417	209	45.0 (32.6–57.4)	5.19	2	0.075	60.00	–0.99	0.504	3 17,20,25
	RT	2	162	58	36.6 (16.5–56.8)	7.50	1	0.006	86.67	–	–	2 34,50
OM	LND	3	428	4	0.9 (0.0–1.8)	0.64	2	0.727	0.09	0.75	0.590	3 17,25,28
	RT	8	674	18	2.0 (0.3–3.6)	16.22	7	0.023	69.56	3.39	0.014	8 28,30,34,36,40,41,44,50
CSM	LND	1	33	0	1.5 (–2.6–5.5)	0.00	0	–	–	–	–	1 28
	RT	2	109	1	1.3 (–0.8–3.5)	0.02	1	0.881	0.07	–	–	2 28,40
(B) PSA ≤2 at PET scan												
PSA response	LND	6	607	277	50.3 (36.3–64.3)	23.95	5	<0.001	87.33	0.41	0.705	6 14,15,17,20,22,25
	RT	6	464	349	76.3 (71.4–81.2)	7.91	5	0.161	28.48	–0.77	0.482	6 18,28,31,33,39,40
PSA progression	LND	3	550	288	48.7 (15.2–82.2)	196.70	2	<0.001	98.49	0.41	0.752	3 14,17,20
	RT	10	725	227	30.5 (21.0–40.0)	80.79	9	<0.001	88.72	1.82	0.107	10 18,28,31–33,39,40,46,47,49
Image progression	LND	3	202	39	24.7 (9.8–39.6)	5.76	2	0.056	63.88	1.68	0.341	3 14,20,22
	RT	9	765	276	36.7 (23.7–49.7)	272.93	8	<0.001	95.60	3.96	0.005	9 18,28,29,31,38,40,46,49,50
Systemic progression	LND	3	417	209	45.0 (32.6–57.4)	5.19	2	0.075	60.00	–0.99	0.504	3 17,20,25
	RT	2	153	42	27.4 (20.4–34.5)	0.07	1	0.796	0.00	–	–	2 29,50
OM	LND	2	395	4	0.9 (–0.1–1.8)	0.56	1	0.454	0.13	–	–	2 17,25
	RT	4	240	16	7.5 (–3.7–18.7)	16.59	3	0.001	96.77	3.81	0.062	4 28,40,46,50
CSM	RT	4	213	14	5.7 (–0.6–11.9)	10.89	3	0.012	85.07	3.27	0.082	4 28,29,40,46
(C) Concomitant ADT												
PSA response	LND	2	116	65	58.1 (37.5–78.7)	5.33	1	0.021	81.23	–	–	2 18,24
	RT	3	333	246	73.9 (69.2–78.6)	0.03	2	0.988	0.01	–0.11	0.928	3 18,39,40
PSA progression	LND	2	116	78	62.2 (15.0–109.4)	33.45	1	<0.001	97.01	–	–	2 18,24
	RT	8	700	245	36.1 (26.8145.4)	35.05	7	<0.001	85.24	1.47	0.191	8 18,32,39–42,46,49
Image progression	LND	3	307	153	40.5 (17.9–63.1)	35.39	2	<0.001	93.54	–5.87	0.107	3 18,24,29
	RT	8	912	301	32.7 (21.7–43.6)	223.34	7	<0.001	94.53	3.45	0.013	8 18,29,37,38,40,42,46,49
Systemic progression	LND	1	191	46	24.1 (18.0–30.1)	0.00	0	–	–	–	–	1 29
	RT	1	63	18	28.6 (17.4–39.7)	0.00	0	–	–	–	–	1 29
OM	LND	1	45	9	20.0 (8.3–31.7)	0.00	0	–	–	–	–	1 24
	RT	3	182	12	9.1 (–8.2–26.3)	16.28	2	<0.001	98.63	3.60	0.172	3 40,41,46
CSM	LND	2	236	21	12.0 (–1.3–25.2)	4.87	1	0.027	79.47	–	–	2 24,29
	RT	3	146	13	8.0 (–0.9–16.8)	10.03	2	0.007	79.89	3.16	0.194	3 29,40,46

ADT, androgen deprivation therapy; CI, confidence interval; CSM, cancer-specific mortality; df, degrees of freedom; LND, lymph node dissection; OM, overall mortality; PET, positron emission tomography; P_{hetero} , probability level associated with Q-test; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; Q, homogeneity test; RT, radiation therapy.

outcomes. Therefore, selecting appropriate patients for focal salvage treatment is important.

Second, proper timing of the PET scan and salvage treatment should be considered. The low PSA level observed in the BCR group was directly proportional to the diagnostic positivity rate of the PET scan.⁸ The detection rate of PSMA was higher than that of fluciclovine and choline in patients with PSA <2.0 ng/mL.⁸ Adequate outcomes from subgroup analysis were observed in studies that used PSMA scans and had cases with PSA ≤ 2.0 ng/mL compared with those in studies that met the total inclusion criteria. Earlier PSMA scans at very low PSA levels (<0.5 ng/mL) could distinguish local from distant lesions.⁵⁶ Moreover, PSA levels of 0.5 ng/mL were significantly associated with positive outcomes after salvage RT.⁵⁷ Therefore, positive PSMA scan results could determine treatment specialty and reduce the incidence of salvage treatment failure.⁵⁸ The European Association of Urology recently classified risk groups for disease progression during BCR using the Gleason score and PSA kinetics to predict prognosis.⁵⁹ However, owing to the discordance between risk classification and positivity of PSMA PET/CT,⁶⁰ integrating novel predictors is needed for subsequent treatment options.

Third, PSMA PET cannot detect all recurrences. The prevalence of non-PSMA-expressed prostate cancer is 4–10%.⁶¹ PSMA expression

and ADT initiation may explain some variable detection sensitivities observed in PSMA ligand imaging.⁶² PSMA expression in low- and high-grade tumors is inadequate.^{63,64} In addition, PSMA PET scans at BCR resulted in approximately 8% false positive interpretations in benign lesions.⁶⁵ Disease severity did not correspond to cancer detection on PSMA PET scans. Therefore, salvage treatment should be considered after reviewing PET scan results, treatment history, and tumor status.

This study has few limitations. First, our meta-analysis may have been compromised by the lack of random assignment, low methodological quality, and heterogeneity. Cost and availability could be thresholds for accepting the clinical use of imaging tools.⁶⁶ General use remains limited, and few studies have reported the outcomes of salvage treatment in BCR.⁶⁷ Second, the pooled rates of oncological outcomes between LND and RT could not be directly compared. In two retrospective comparisons, RT showed better PSA progression-free survival than LND.^{18,28} However, prospective randomized trials are necessary for more evidence. Third, some studies had incomplete data and insufficient follow-up periods. We did not strictly exclude these studies because focal salvage treatment using PET scans in BCR was pioneered only in some institutions. The reported subgroups were included in a single study if they met the inclusion criteria. Fourth, it is important to acknowledge that definitions of

key outcomes, such as PSA response and disease progression, varied across the included studies. This variability in outcome definitions may have introduced heterogeneity into the pooled results and limits the direct comparability of studies. The strength of this meta-analysis was the few studies included. To the best of our knowledge, our study is the first to focus on the pooled rates of the oncological outcomes of salvage LND and RT in the forthcoming PET scan era. Our study results suggest that clinicians consider treatment failure when planning salvage treatment, especially for LND.

5. Conclusion

Despite salvage LND or RT, about half of BCR patients with PET-positive nodal recurrence showed disease progression, suggesting the limited effectiveness of focal therapies alone. RT appeared to provide better short-term disease control than LND, highlighting the importance of treatment selection. However, focal salvage treatment may be insufficient because patients with PET-positive lymph nodes show significant disease progression. Therefore, proper timing of the PSMA PET scan, concomitant systemic therapy, and salvage therapy type should be evaluated for future trial designs in BCR. Furthermore, the optimal sequence of salvage management should be determined at BCR using PET emission tomography.

Authors' contributions

Se Young Choi contributed to conception and design.

Se Young Choi, Yun-Jung Yang, Eun-Jung Yang, Kyungchan Min, Jong Hyun Tae, Chung Un Lee, Joongwon Choi, and Jung Hoon Kim contributed to data acquisition.

Se Young Choi and Yun-Jung Yang contributed to analysis and interpretation of data.

Se Young Choi and Yun-Jung Yang contributed to drafting of the manuscript.

Jong Hyun Tae, Joongwon Choi, Jung Hoon Kim and Tuan Thanh Nguyen contributed to critical revision of the manuscript.

Se Young Choi contributed to obtaining funding.

Se Young Choi contributed to supervision.

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Conflict of interest

The authors declare no conflicts of interest.

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Data availability statements

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnrl.2025.05.002>.

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