

# Long-term clinical outcomes of salvage pelvic radiation therapy for oligo-recurrent pelvic lymph nodes after definitive external-beam radiation therapy for non-metastatic prostate cancer

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## ABSTRACT

Although salvage external-beam radiation therapy (EBRT) is an attractive treatment option for pelvic lymph nodal recurrence (PeNR) in patients with prostate cancer (PCa), limited data are available regarding its long-term efficacy. This study examined the long-term clinical outcomes of patients who underwent salvage pelvic radiation therapy (sPRT) for oligo-recurrent pelvic lymph nodes after definitive EBRT for non-metastatic PCa. Patients who developed PeNR after definitive EBRT and were subsequently treated with sPRT at our institution between November 2007 and December 2015 were retrospectively analyzed. The prescribed dose was 45–50.4 Gy (1.8–2 Gy per fraction) to the upper pelvis, with up to 54–66 Gy (1.8–2 Gy per fraction) for recurrent nodes. Long-term hormonal therapy was used as neoadjuvant and/or adjuvant therapy. The study population consisted of 12 consecutive patients with PeNR after definitive EBRT (median age: 73 years). The median follow-up period was 58.9 months. The 5-year overall survival, PCa-specific survival, biochemical failure-free, clinical failure-free, and castration-resistant PCa-free rates were 82.5, 100.0, 62.3, 81.8, and 81.8%, respectively. No grade 2 or higher sPRT-related late toxicities occurred. In conclusion, more than half of the study patients treated with sPRT had a long-term disease-free status with acceptable morbidities. Moreover, most of the patients maintained hormonal sensitivity. Therefore, this approach may be a promising treatment method for oligo-recurrent pelvic lymph nodes.

**Keywords:** prostate cancer; oligo-metastasis; pelvic lymph nodal recurrence; salvage pelvic radiation therapy; metastasis-directed therapy

## INTRODUCTION

Definitive external-beam radiation therapy (EBRT) is one of the major treatment modalities for non-metastatic prostate cancer (PCa) [1]. Despite its favorable disease control, some patients develop clinical failure (CF) after definitive EBRT, especially among unfavorable risk PCa population. Lifelong hormonal therapy (HT) has been a mainstay of salvage treatment for patients with PCa recurrence, and similarly applied both to distant and regional recurrence in daily clinical practice. However, for patients with pelvic lymph nodal recurrence (PeNR),

curability through definitive salvage treatment may be expected in theory, because of the nature of regional locality. Nonetheless, a consensus regarding the use of salvage treatment for PeNR, based on current guidelines, has not yet been reached.

Recently, promising outcomes of salvage treatment with high-dose EBRT to metastatic lesions have been reported. A randomized phase 2 SABR-COMET trial suggested a survival benefit for patients with oligo-recurrent tumors whose metastatic lesions were treated by the addition of stereotactic body radiation therapy (SBRT) [2]. In patients

with PCa, salvage treatments for recurrent metastasis via high-dose EBRT or surgical resection, referred to as metastasis-directed therapy (MDT), have been used mainly in patients with oligo-recurrent or oligo-progressive PCa; these treatments are a promising alternative to conventional lifelong HT [3–6]. However, in most studies of MDT, the cohort included both patients with recurrent distant metastasis and those with PeNR alone. Moreover, the latter group typically included both patients who were treated with EBRT and those who underwent radical prostatectomy. Due to the heterogeneity of the patients and treatments in those studies, the true efficacy of definitive salvage treatment for PeNR after definitive EBRT remains unclear.

In this study, we retrospectively evaluated the long-term clinical outcomes of definitive salvage pelvic radiation therapy (sPRT) for PeNR after primary definitive EBRT. Our sPRT protocol consisted of prophylactic pelvic regional irradiation of the upper pelvis and an additional boost to recurrent nodes. To the best of our knowledge, our study is based on the longest reported follow-up period (median: 4.9 years) of definitive salvage EBRT for PeNR after definitive EBRT.

## MATERIALS AND METHODS

This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethical Review Board of our institution (approval no.: R1048). Written informed consent was obtained from all patients.

### Eligibility criteria

Eligible patients were identified through a retrospective review of our prospectively maintained institutional PCa registry of patients who received EBRT. The eligibility criteria for this study were as follows: (1) clinical diagnosis of non-metastatic PCa with histological confirmation of prostate adenocarcinoma; (2) treatment consisting of definitive EBRT to the prostate and seminal vesicles alone as primary therapy, with subsequent development of PeNR without distant metastasis; (3) definitive treatment with sPRT at our institution between November 2007 and December 2015. Patients with castration-resistant PCa (CRPC) at the time of sPRT initiation were excluded, because the clinical course, prognosis, and role of salvage treatment of CRPC cases are totally different from those of hormone-sensitive cases.

Evaluation at the time of PeNR diagnosis after primary EBRT included chest-abdominal computed tomography (CT) and bone scan. The shrinkage of enlarged nodes during neoadjuvant-HT (NA-HT) was confirmed by CT for re-evaluation before sPRT, in order to eliminate false recurrence.

### Salvage pelvic radiation therapy

EBRT consisted of prophylactic pelvic regional irradiation of the upper pelvis, followed by boost irradiation of recurrent nodes via three-dimensional conformal radiation therapy, using pelvic bone registration in a supine position. A dose of 45–50.4 Gy (1.8–2 Gy per fraction) was delivered as prophylaxis to the pelvic region, with a total of 54–66 Gy (1.8–2 Gy per fraction) delivered to recurrent nodes. For prophylactic regional irradiation, the common, external, and internal iliac regions were included, whereas the obturator and presacral regions were excluded. The four-field box technique was basically used. The

superior border was set at L4/5 or at the level of the aortic bifurcation, which was extended to the L3/4 level for patients whose recurrent nodes were located near the L4/5 border. The inferior border was set immediately above the upper border of the primary EBRT field, in order to avoid overlap with the primary EBRT field. The lateral border was set 2–3 cm lateral to the common, external, or internal iliac vessels. For boost irradiation, the clinical target volume (CTV) was delineated based on CT during the simulation and before NA-HT (at the time of recurrence), which was expanded by 5–15 mm to define the planning target volume (PTV) to compensate for treatment set-up uncertainties. Multiple-field radiation therapy was used. The radiotherapy treatment plan was designed based on the disease condition before NA-HT. An example of the sPRT fields is presented in Fig. 1.

### Hormonal therapy

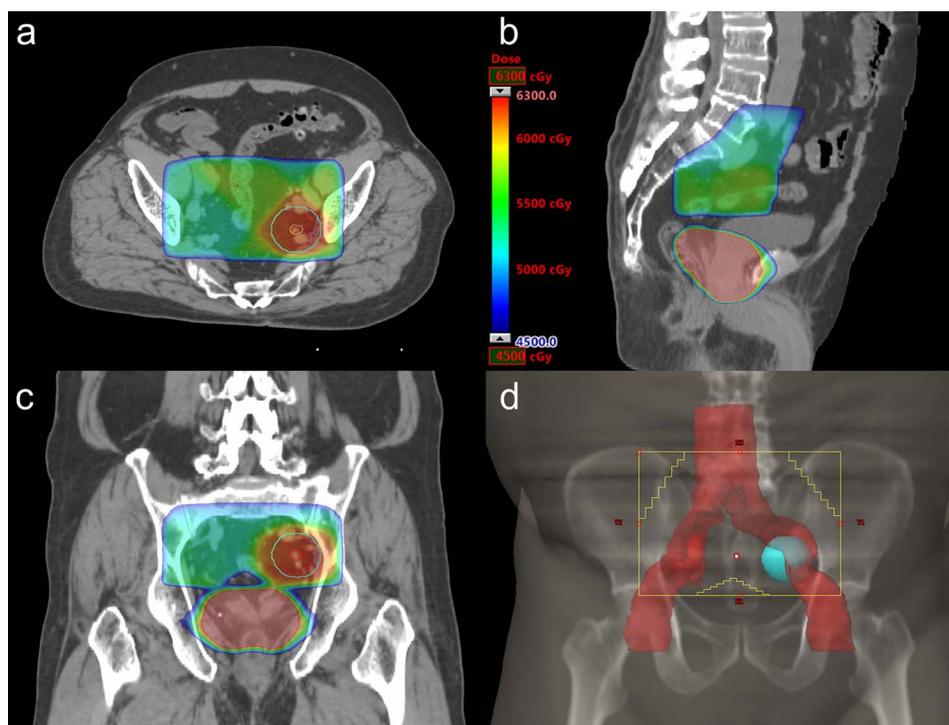
Long-term HT, consisting of 6-month NA-HT and 2-year adjuvant-HT (A-HT), was combined with sPRT. In general, combined androgen blockade was used for NA-HT, while luteinizing hormone-releasing hormone analogue monotherapy was used for A-HT. However, both the duration and contents of the HT varied depending on the patient's clinical condition, such as HT-related toxicities. Androgen receptor axis-targeted agents, such as abiraterone or enzalutamide, were not used during NA-HT or A-HT.

### Follow-up

Prostate-specific antigen (PSA) levels were assessed every 3–6 months after sPRT completion. No additional radiographic studies were performed after sPRT unless the PSA level was elevated or clinical symptoms suggestive of CF had occurred. Salvage treatment for disease failure after sPRT was administered at the physician's discretion, but was generally performed in accordance with the standard of care in Japan for recurrent PCa.

### Statistical analysis

The time to the occurrence of each event was calculated from the initiation of sPRT. The Kaplan–Meier method was used to evaluate overall survival, PCa-specific survival, biochemical failure (BF)-free, CF-free, and CRPC-free rates. For the latter four items, death from other causes without each event was censored at the last visit. BF was evaluated based on the Phoenix definition (nadir +2 ng/mL) [7]. A change in treatment due to disease progression before the PSA level reached to nadir +2 ng/mL was also regarded as BF. CRPC status was defined as continuous PSA elevation (nadir +2 ng/mL), CF, or a change in treatment due to disease progression during HT. PSA elevation occurring during the off-period of intermittent HT was not regarded as a CRPC event. Acute and late toxicities were assessed using Common Terminology Criteria for Adverse Events, version 3. We did not perform univariate and multivariable analyses that would typically enable the identification of predictive factors affecting disease control, due to the small sample size. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.5-1) (The R Foundation for Statistical Computing, Vienna, Austria) [8].



**Fig. 1.** Total dose distributions of primary and salvage external-beam radiation therapy are superimposed on a planning computed tomography in (a) axial, (b) sagittal, (c) coronal plane, and (d) beam's eye view (dose color wash legend: blue 45 Gy to red 63 Gy; Yellow contouring: clinical target volume; Sky blue contouring: planning target volume; Red contouring: vessels).

## RESULTS

### Patient characteristics

We identified 17 patients who developed and treated PeNR without distant metastasis during the study period. The recurrent nodes were located cranially to the previously irradiated field in all cases. The details of recurrence patterns following the primary definitive EBRT were reported previously [9–11]. Of these 17 patients, four had received HT alone due to severe concomitant illnesses or patient's request, and one had developed CRPC during NA-HT. The remaining 12 patients met the eligibility criteria, and therefore were included in the analysis.

The median age of the 12 patients at primary EBRT was 68 years (range, 50–73 years). Seven patients had high-risk disease and five patients had very-high-risk disease, based on the National Comprehensive Cancer Network risk classification (version 4.2019) [1]. Our institutional treatment protocol for primary EBRT in combination with HT has been previously described [9–11]. In brief, a median dose of 78 Gy (range, 70–78 Gy) was used to treat the prostate and seminal vesicle alone via intensity-modulated radiation therapy ( $n = 11$ ) or three-dimensional conformal radiation therapy ( $n = 1$ ), which was combined with short-term HT before EBRT (median, 6.7 months). The characteristics of the 12 patients at the time of primary EBRT are summarized in Table 1.

The median age of patients at the sPRT was 73 years (range, 55–80 years). The median time to PeNR from primary EBRT was 53.6 months (range, 22.1–123.9 months). No patient received HT at the time of PeNR. The recurrent nodes were limited to the common,

external, and internal iliac regions, with a median of 1 (range, 1–2) recurrent node per patient. The median diameter of the recurrent nodes before and after NA-HT was 10 mm (range, 7–18 mm) and 3 mm (range, 0–8 mm), respectively. The median PSA level at the time of PeNR was 4.7 ng/mL (range, 2.6–6.6 ng/mL). The characteristics of the patients at the time of sPRT are summarized in Table 2.

### Treatment

The median dose of prophylactic pelvic regional irradiation was 50.4 Gy (range, 45–50.4 Gy) at 1.8–2 Gy per fraction; the median total dose of irradiation was 63 Gy (range, 54–66 Gy) at 1.8–2 Gy per fraction. All patients received HT as neoadjuvant and/or adjuvant treatment, along with sPRT. The median duration of HT in combination with sPRT was 30.5 months (range, 6.2–42.6 months); the median durations of NA-HT and A-HT were 6.3 months (range, 4.1–18.5 months) and 23.0 months (range, 0–26.1 months), respectively. Two patients received prolonged NA-HT (17.4 and 18.5 months) because sPRT was postponed due to treatment for concomitant illnesses. In three patients, A-HT was terminated prematurely (0, 1.2, and 11.5 months) due to HT-related toxicities. The details of sPRT and combined HT are summarized in Table 2.

### Oncological outcomes

The median follow-up period was 58.9 months (range, 8.4–96.5 months). Three patients died during follow-up, all from causes unrelated to PCa. The 5-year overall survival and PCa-specific

**Table 1. Patient and treatment characteristics at primary treatment**

Age (years)	
Median	68
Range	50–73
Clinical T stage at diagnosis, n (%)	
T1c	1 (8)
T2	5 (42)
T3	6 (50)
iPSA (ng/mL)	
Median	22.6
Range	10.1–103.6
Gleason score, n (%)	
7	2 (17)
8	7 (58)
9	2 (17)
10	1 (8)
NCCN risk classification, n (%)	
High risk	7 (58)
Very high risk	5 (42)
Primary treatment, n (%)	
EBRT	12 (100)
IMRT	11 (92)
3D-CRT	1 (8)
Prescription dose and dose per fraction	
Prescription dose (Gy)	70–78 (median, 78)
Dose per fraction (Gy)	2
Radiation field, n (%)	
Prostate and seminal vesicle	12 (100)
Duration of combining HT to primary EBRT (months)	
Median	6.7
Range	3.7–14.6

*Abbreviations:* iPSA: initial prostate-specific antigen; NCCN risk classification: the National Comprehensive Cancer Network risk classification version 4, 2019; EBRT: external-beam radiation therapy; IMRT: intensity-modulated radiation therapy; 3D-CRT: three-dimensional conformal radiation therapy; HT: hormonal therapy.

survival rates were 82.5% (95% confidence interval [CI] 46.1–95.3%) and 100.0% (95% CI not available [NA] –NA), respectively (Fig. 2). During follow-up, five patients developed BF at a median of 35.6 months (range, 8.9–66.7 months) after sPRT; four developed BF after the completion of A-HT and one developed BF during A-HT (CRPC). The initial pattern was BF in all patients with disease failure. Two of these patients developed CF (lung metastasis, n = 1; intraprostatic relapse, n = 1), but none developed further PeNR (in-field recurrence). At the most recent follow-up visit, five patients were receiving treatment with HT, whereas the remaining seven patients were followed up without HT (58.3%). During follow-up, two patients developed CRPC (8.9 and 44.9 months after sPRT), but no patient received androgen receptor axis-targeted agents or chemotherapy. The 5-year BF-free, CF-free, and CRPC-free rates were 62.3% (95% CI 27.7–84.0%), 81.8% (95% CI 44.7–95.1%), and 81.8% (95% CI 44.7–95.1%), respectively (Fig. 3).

**Table 2. Patient and treatment characteristics at sPRT**

Age (years)	
Median	73
Range	55–80
Time to PeNR after primary EBRT (months)	
Median	53.6
Range	22.1–123.9
Number of PeNR, n (%)	
One	11 (92)
Two	1 (8)
Diameter of PeNR before NA-HT (mm)	
Median	10
Range	7–18
Diameter of PeNR after NA-HT (mm)	
Median	3
Range	0–8
PSA at PeNR (ng/mL)	
Median	4.7
Range	2.6–6.6
Prescription dose and dose per fraction of prophylactic pelvic regional irradiation	
Prescription dose (Gy)	45–50.4 (median, 50.4)
Dose per fraction (Gy)	1.8–2 (median, 1.8)
Prescription dose and dose per fraction of total irradiation	
Prescription dose (Gy)	54–66 (median, 63)
Dose per fraction (Gy)	1.8–2 (median, 1.8)
Radiation technique, n (%)	
3D-CRT	12 (100)
Duration of NA-HT plus A-HT (months)	
Median	30.5
Range	6.2–42.6
Duration of NA-HT (months)	
Median	6.3
Range	4.1–18.5
Duration of A-HT (months)	
Median	23.0
Range	0–26.1

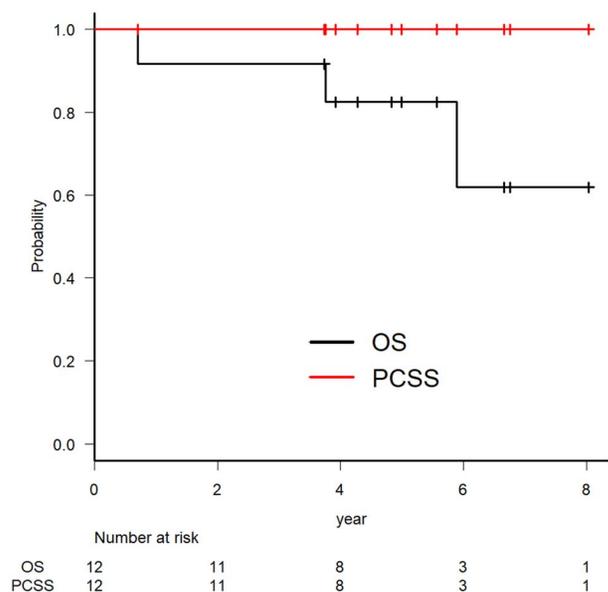
*Abbreviations:* sPRT: salvage pelvic radiation therapy; PeNR: pelvic lymph nodal recurrence; EBRT: external-beam radiation therapy; NA-HT: neoadjuvant-hormonal therapy; PSA: prostate-specific antigen; 3D-CRT: three-dimensional conformal radiation therapy; A-HT: adjuvant-hormonal therapy.

### sPRT-related toxicity

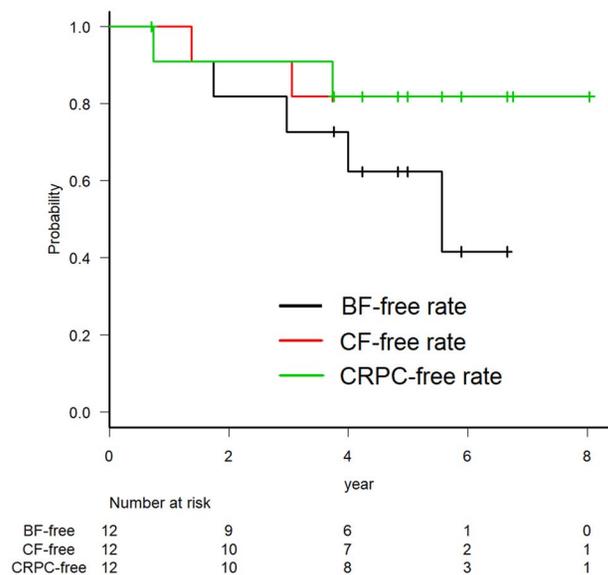
No grade 3 or higher acute sPRT-related toxicities were observed; two patients developed acute diarrhea (grade 2) and fatigue (grade 2), respectively. Furthermore, no grade 2 or higher sPRT-related late toxicities were observed.

### DISCUSSION

This study evaluated the long-term clinical outcomes of patients who underwent sPRT for PeNR after definitive EBRT for non-metastatic PCa. Our treatment protocol consisted of the administration of



**Fig. 2.** Kaplan–Meier curves for overall survival and prostate cancer-specific survival rates after salvage pelvic radiation therapy. OS, overall survival; PCSS, prostate cancer-specific survival.



**Fig. 3.** Kaplan–Meier curves for biochemical failure-free, clinical failure-free, and castration-resistant prostate cancer-free rates after salvage pelvic radiation therapy. BF, biochemical failure; CF, clinical failure; CRPC, castration-resistant prostate cancer.

45–50.4 Gy to the upper pelvis, followed by a boost irradiation for recurrent nodes, with a median total dose of 63 Gy (both 1.8–2 Gy per fraction), in combination with long-term HT (generally 2.5 years).

More than half of our patients maintained disease-free status during long-term follow-up, and were free from HT at the most recent visit. In addition, no severe EBRT-related toxicities were observed. These results support the validity of our treatment approach for PeNR after definitive EBRT.

Lifelong HT, commonly used in daily clinical practice for PeNR, is unsatisfactory for achieving a curative outcome. Despite the excellent initial response to HT and its medium-term effectiveness [12], most patients treated with HT alone eventually show progression to CRPC, which is one of the most refractory forms of disease failure; it also places patients at high risk of PCa-specific mortality. Additionally, long-term HT can be associated with numerous toxicities, including cardiovascular disease and dementia, which are of particular concern given the long life expectancy among this population [13, 14]. Therefore, an alternative to HT monotherapy has long been sought. Among the alternative treatment methods, both MDT via SBRT and the surgical dissection of metastatic nodes have been tested for efficacy and feasibility in many prospective studies and retrospective series [3–5, 15]. In the current study, treatment with sPRT combined with long-term HT resulted in a 5-year BF-free rate of 62.3%. Tran et al. studied 53 patients with pelvic and/or lumbo-aortic nodal failure after curative treatment for PCa who underwent elective nodal radiation therapy (pelvic regional irradiation with a dose of 45 or 50.4 Gy, plus boost irradiation for positive nodes, with a median total dose of 64.4 Gy). They similarly reported a 43% biochemical disease-free survival rate at 5 years after a median follow-up duration of 44 months [5]. In addition, in our study, most patients maintained hormonal sensitivity during the long follow-up period (CRPC-free rate at 5 years: 81.8%). Considering that the time to CRPC is regarded as a reasonable surrogate for survival outcome [16], the favorable CRPC-free rate determined in our study suggests a survival benefit associated with the use of sPRT, although we could not compare the efficacy of our treatment approach with that achieved using conventional lifelong HT due to absence of comparative clinical data regarding HT monotherapy in this subgroup.

Regarding MDT for PeNR, two strategies have been practiced: focusing only to recurrent sites, or including prophylactic pelvic region. SBRT is most commonly used as a treatment modality of the former approach. Although SBRT for PeNR provides excellent local control, some patients subsequently develop further PeNR, which remains a cause for concern [6]. In the report regarding MDT for oligo-recurrent PCa, Decaestecker et al. observed that, among patients treated with SBRT for PeNR, 41.7% developed further PeNR after SBRT [17]. Bleser et al. conducted a retrospective analysis of failure patterns following MDT (SBRT for recurrent nodes alone or elective nodal radiation therapy) in patients with nodal oligo-recurrent hormone-sensitive PCa (N1 and/or M1a). They reported that further lymph nodal progression occurred less frequently in the group treated with elective nodal radiation therapy than in the group treated with SBRT for recurrent nodes alone ( $P < 0.001$ ), especially in the pelvic region (4% vs 31%, respectively,  $P < 0.001$ ) [3]. In our patients, treatment with sPRT resulted in 100% regional control, which was consistent with the findings in previous reports regarding regional irradiation [3, 5]. These results indicate a potential benefit for using prophylactic pelvic regional irradiation to achieve regional control, which may avoid the need to perform additional salvage treatments such as

repeated MDT or HT re-initiation. Therefore, prophylactic irradiation of the pelvic region may be a promising method for the treatment of PeNR.

Currently, the OLIGOPELVIS phase 2 study is investigating the role of pelvic irradiation (54 Gy in 30 fractions to the pelvic region and 66 Gy in 30 fractions to positive sites) for PeNR following curative treatment for non-metastatic PCa [18]. Approximately half of the enrolled patients had previously been treated with definitive EBRT or salvage EBRT for failure following radical prostatectomy. Similar to the strategy in our study, the treatment fields in pelvic irradiation were limited to the upper pelvis in order to avoid overlap with previous radiation therapy fields. According to their early study report, treatment termination due to acute toxicities was not necessary for any of the patients, and the early toxicities were acceptable: grade 2 and 3 urinary toxicities at 1 year of 6 and 4.4%, and digestive toxicities of 6 and 0%, respectively. Therefore, the authors of the study report stated that pelvic irradiation for PeNR was acceptable, even in patients with a history of prostatic irradiation. The validity of our treatment approach for PeNR will likely be verified by this prospective study, when the full results become available.

There were several limitations of our study, including the retrospective nature of analysis. First, patient selection bias should be mentioned. Because the recurrent nodes of our patients were located cranial to the previously irradiated fields in all cases, as referred to in Results, our radiation methods of sPRT may not be applicable to patients with recurrent nodes located in or peripheral to previously irradiated fields due to expected increases in radiation therapy-related toxicities. Second, the evaluation of intraprostatic relapse via re-biopsy or magnetic resonance imaging, or the elimination of distant metastasis using novel imaging modalities with a higher sensitivity, such as prostate-specific membrane antigen-positron emission tomography, were not performed at the time of PeNR diagnosis. Therefore, the clinical outcomes may have been underestimated due to the potential migration of such cases. Third, the number of patients included in this study was relatively small, rendering it difficult to provide definitive conclusions regarding its efficacy. Nevertheless, we believe that our results provide baseline data supporting the merits of definitive salvage EBRT for PeNR patients after definitive EBRT, because our study was based on the longest-term clinical outcomes in a group of patients with relatively homogenous backgrounds. Further investigations are needed to confirm the validity of our treatment strategy.

In conclusion, treatment with sPRT resulted in long-term disease-free status in more than half of the patients with PeNR, with acceptable morbidities. In addition, in most patients who developed disease failure despite sPRT, hormonal sensitivity was maintained during the long-term follow-up period. Our approach would therefore be a promising treatment for PeNR, although further investigations are needed to confirm our findings.

#### PRESENTATION AT A CONFERENCE

This work was presented in part at the 319th meeting of Kansai Branch of Japan Radiological Society and the 31st annual meeting of the Japanese Society for Radiation Oncology.

#### CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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#### ABBREVIATIONS

EBRT	external-beam radiation therapy
PeNR	pelvic lymph nodal recurrence
PCa	prostate cancer
sPRT	salvage pelvic radiation therapy
CF	clinical failure
HT	hormonal therapy
SBRT	stereotactic body radiation therapy
MDT	metastasis-directed therapy
CRPC	castration-resistant PCa
CT	computed tomography
NA-HT	neoadjuvant-HT
CTV	clinical target volume
PTV	planning target volume
A-HT	adjuvant-HT
PSA	prostate-specific antigen
BF	biochemical failure

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