# Retrospective Study of Salvage Dose-Escalated Intensity-Modulated Radiation Therapy in Radiotherapy-naïve, Non-metastatic, Castration-Resistant Prostate Cancer

# การศึกษาย้อนหลังบทบาทการรักษาด้วยรังสีปรับความเข้มในผู้ป่วยมะเร็งต่อมลูกหมากที่ยังไม่มีการแพร่กระจายแบบ castration-resistant prostate cancer

**Kanokphorn Thonglert[1], Pimpawee Ditjarern[1], Napapat Amornwichet[2], Petch Alisanant[1], Chonlakiet Khorprasert[2]**

*[1]Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital, Thai Red Cross Society*
*[2]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University*

**Corresponding author**
**Chonlakiet Khorprasert**
*Division of Radiation Oncology Department of Radiology Faculty of Medicine, Chulalongkorn University*
*1873 Rama IV road, Prathumwan, Bangkok, 10330*
*E-mail: Chonlakiet.k@chula.ac.th*

**กนกพร ทองเลิศ[1], พิมพ์ปวีณ์ ดิษเจริญ[1], ณปภัช อมรวิเชษฐ์[2], เพชร อลิสานันท์[1], ชลเกียรติ ขอประเสริฐ[2]**

[1]สาขารังสีรักษาและมะเร็งวิทยา ฝ่ายรังสีวิทยา โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย
[2]สาขารังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

**ผู้นิพนธ์ประสานงาน**
**ชลเกียรติ ขอประเสริฐ**
สาขารังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
1873 ถนนพระราม 4 เขตปทุมวัน แขวงปทุมวัน กรุงเทพฯ 10330
อีเมล: Chonlakiet.k@chula.ac.th

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## Abstract

**Backgrounds:** The role of salvage dose-escalated intensity-modulated radiation therapy (IMRT) for radiotherapy-naïve, non-metastatic, castration-resistant prostate cancer (nmCRPC) is controversial.

**Objectives:** This retrospective study reports the clinical outcomes of salvage dose-escalated IMRT in radiotherapy-naïve, nmCRPC.

**Materials and methods:** We retrospectively evaluated 22 patients with nmCRPC treated with salvage dose escalated IMRT between March 2009 and June 2019. The primary outcome was biochemical relapse-free survival (BRFS). The secondary outcomes were clinical progression-free survival (CPFS), metastasis-free survival (MFS), overall survival (OS), prognostic factors, and toxicities.

**Results:** The median follow-up was 43 months. The mean age at the time of salvage IMRT was 73.8 years. The median PSA prior to salvage IMRT was 6.68 ng/ml. All patients received dose-escalated IMRT 76-80 Gy to prostate and seminal vesicles. The median BRFS was 31 months, with a 5-year BRFS of 43.6%. The median CPFS was 37 months, with a 5-year CPFS of 47.4%. The median MFS was not-reach with a 5-year MFS of 50.6%. The 5-year OS was 62.4%, with a median OS of 73 months. In multivariate analysis, the PSA prior to EBRT was the only significant prognostic factor for better BRFS and CPFS. Grade 3-4 late gastrointestinal (GI) and genitourinary (GU) toxicities were 4.5% and 0%, respectively.

**Conclusion:** In radiotherapy-naïve patients with nmCRPC, salvage dose-escalated IMRT was a feasible treatment option with acceptable toxicity.



**Keywords:** Castration-resistant, Non-metastatic prostate cancer, Primary androgen deprivation therapy (ADT), Salvage radiotherapy



## บทคัดย่อ

**หลักการและเหตุผล:** บทบาทการรักษาด้วยรังสีปรับความเข้มในผู้ป่วยมะเร็งต่อมลูกหมากระยะที่ยังไม่มีการแพร่กระจายแบบ castration-resistant prostate cancer (Non-metastatic, castration-resistant prostate cancer: nmCRPC) ที่ไม่เคยได้รับการรักษาด้วยรังสีมาก่อนยังคงเป็นที่ถกเถียง

**วัตถุประสงค์:** เพื่อศึกษาผลทางคลินิกและผลข้างเคียงของการรักษาด้วยรังสีปรับความเข้มในผู้ป่วยมะเร็งต่อมลูกหมากแบบ nmCRPC ที่ไม่เคยได้รับการรักษาด้วยรังสีมาก่อน

**วัสดุและวิธีการ:** ศึกษาย้อนหลังในผู้ป่วยมะเร็งต่อมลูกหมากแบบ nmCRPC ที่ได้รับการรักษาด้วยรังสีปรับความเข้มด้วยปริมาณรังสีที่สูงขึ้น ตั้งแต่เดือนมีนาคม 2552 ถึงเดือนมิถุนายน 2562 จำนวน 22 ราย โดยมีวัตถุประสงค์หลัก ได้แก่ เพื่อหาอัตราการอยู่รอดโดยปราศจากการกลับมาเพิ่มขึ้นของค่า Prostate-specific antigen (PSA) (Biochemical-relapse free survival: BRFS) และมีผลลัพธ์รองได้แก่ อัตราการอยู่รอดโดย

โรคสงบ (Clinical progression-free survival: CPFS) อัตราการอยู่รอดโดยปราศจากการแพร่กระจาย (Metastatic-free survival: MFS) อัตราการรอดชีพรวม (Overall survival: OS) ปัจจัยที่ส่งผลต่อผลการรักษาและผลข้างเคียงจากการรักษา

**ผลการศึกษา:** ค่ามัธยฐานการตรวจติดตาม 43 เดือนในผู้ป่วยมะเร็งต่อมลูกหมากมีอายุเฉลี่ย 73.8 ปี ค่ามัธยฐาน PSA ก่อนได้รับการรักษาด้วยรังสี 6.68 นาโนกรัม/มิลลิลิตร ผู้ป่วยทุกรายได้รับการรักษาด้วยรังสีปรับความเข้มปริมาณรังสี 76-80 เกรย์ พบว่าค่ามัธยฐานของ BRFS เท่ากับ 31 เดือน และมี BRFS 43.6% ที่ 5 ปี ค่ามัธยฐานของ CPFS เท่ากับ 37 เดือน และมี CPFS 47.4% ที่ 5 ปี ค่ามัธยฐานของ MFS ยังไม่ถึง และมี MFS 50.6% ที่ 5 ปี ค่ามัธยฐานของ OS เท่ากับ 73 เดือน และมี OS 62.4% ที่ 5 ปี ค่า PSA ก่อนการรักษาด้วยรังสีเป็นปัจจัยเดียวที่ส่งผลต่อ BRFS และ CPFS พบผลข้างเคียงระยะยาวเกรด 3-4 ต่อระบบทางเดินอาหาร 4.5% และไม่พบผลข้างเคียงระยะยาวเกรด 3-4 ต่อระบบทางเดินปัสสาวะ

**ข้อสรุป:** การรักษาด้วยรังสีปรับความเข้มเป็นทางเลือกหนึ่งที่สามารถนำไปใช้ได้ในผู้ป่วยมะเร็งต่อมลูกหมากแบบ nmCRPC

**คำสำคัญ:** การรักษาด้วยรังสีในผู้ป่วยที่โรคกลับเป็นซ้ำ, มะเร็งต่อมลูกหมากระยะที่ยังไม่มีการแพร่กระจาย, ยาต้านฮอร์โมนเพศชาย

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## Introduction

Prostate cancer is the third most commonly diagnosed cancer in the world and the fifth leading cause of death in men, accounting for 7.3% (1,414,259) of the new cancer cases and 6.8% (375,304) of the total cancer deaths in males worldwide.[1] Nowadays, the mainstay of treatment for localized prostate cancer is the combination of high-dose external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) or radical prostatectomy, which leads to excellent clinical results.[2] Nevertheless, some patients with localized prostate cancer are treated with ADT alone for various reasons. Although the initial response of ADT is usually excellent, the majority of patients eventually develop castration-resistant status. Among these CRPC patients, some remain with a localized disease without evidence of distant metastasis. Non-metastatic CRPC is an aggressive and lethal disease. Without treatment, most nmCRPC patients are associated with a high risk of distant metastases, declining quality of life, and prostate cancer death. Patients with nmCRPC have a metastatic-free survival of approximately 25 months, and 46% of these patients will develop metastasis within 2 years.[3] Recently, the phase III randomized controlled trials showed that the novel androgen receptor inhibitors – enzalutamide, apalutamide, and darolutamide –

improved metastasis-free survival (MFS) compared to placebo, making these drugs be the standard of care for nmCRPC.[4-6] However, accessibility of these new high-cost drugs is difficult for some patients. Although there is no prospective study to evaluate the efficacy of radiotherapy in nmCRPC, several retrospective studies have shown potential benefits.[7-14] However, the radiotherapy regimens were heterogeneous, and most radiation doses were relatively low (60-70 Gy).

A higher dose of EBRT with curative intent resulted in better biochemical control.[15-18] With the application of dose-escalated advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) with image-guided radiotherapy (IGRT), the toxicity is not increased.[19] Therefore, this study aimed to evaluate the clinical outcomes and toxicities of salvage dose-escalated IMRT for radiotherapy-naïve nmCRPC.

## Materials and Methods

### Patient selection

We retrospectively reviewed 22 radiotherapy-naïve nmCRPC treated with salvage dose-escalated IMRT between March 2009 and June 2019. All patients were clinically localized at the time of diagnosis and were initially treated with ADT alone, then developed nmCRPC. Castration-resistant was defined as continuously increasing serum PSA despite ongoing ADT. When the PSA level increased with or without local progression, all patients underwent radiological evaluation, which included abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), and bone scan, to exclude regional (nodal) and distant metastatic disease. Patients have not been diagnosed with any other malignancy, have not previously been treated with pelvic radiotherapy or radical prostatectomy, and follow-up time after EBRT was longer than 6 months. All patients were initially treated with ADT until progression before salvage radiotherapy. Primary ADT consisted of a luteinizing hormone-releasing hormone (LHRH) agonist with/without non-steroidal antiandrogen or bilateral orchidectomy.

### Radiotherapy

Before radiotherapy, all patients underwent CT simulation with a slice thickness of 3 mm in a supine position. Patients were required to have an empty rectum and a comfortably full bladder before the CT scan.

A clinical target volume (CTV) encompassed the prostate and the seminal vesicles. The pelvic node irradiation was determined by the physician's judgment. A planning target volume was generated by adding a 8-mm margin in all directions, except in the posterior, where a 5-mm margin was added. Image fusion with MRI was performed to improve the accuracy of CTV delineation. The rectum, bladder, small bowel, and femoral heads were outlined as organs at risk (OARs). Before every fraction, image-guided radiotherapy (IGRT) was performed using cone-beam computed tomography (CBCT).

The prescribed radiation dose was 76-80Gy, 1.8-2.23Gy per fractions, 5 fractions per week, using a 6-10 MV x-ray from the linear accelerator (Varian Medical Systems®, Palo Alto, Ca, USA) with IMRT/VMAT and IGRT technique. Additional antiandrogen treatment may be given according to the physician's decision; however, enzalutamide, apalutamide, and darolutamide were unavailable during the study period.

**Follow-up**

After salvage radiotherapy, all patients were followed every 3 to 4 months in the first 2 years, then every 6 months after that. In addition to DRE, PSA measurement was performed every visit. No further imaging was required unless there was an increase in PSA or a new onset of symptoms. In this situation, MRI or CT pelvic and bone scans would be performed.

**Objectives**

The primary objective of this analysis was to explore the biochemical relapse-free survival (BRFS), defined from the first day of the EBRT to the time of PSA rising above the nadir of ≥ 2 ng/ml. This corresponds with the 2006 RTOG-ASTRO Phoenix Consensus definition.[20]

We evaluated the secondary endpoints of clinical progression-free survival (CPFS), metastatic-free survival (MFS), overall survival (OS), the pattern of failure, prognostic factors of BRFS, CPFS, MFS, and toxicity. CPFS was defined as the time from the first day of RT to clinical progression or death from any causes. MFS was defined as the time from the first day of RT to distant metastasis or death from any causes. OS was calculated from the first day of RT to the time of death from any causes. The toxicity criteria were based on the criteria of Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE terms for genitourinary (GU) toxicities included urinary obstruction, cystitis (noninfective), and urinary incontinence. The gastrointestinal (GI) toxicities included diarrhea and proctitis.

**Statistical analysis**

The survival rates were calculated using the Kaplan-Meier method. The risk factors associated with survival rates were evaluated with Cox's proportional hazard model, where significant variables in univariate analysis (P-value < 0.2) were included in a multivariable analysis. The pattern of failure and toxicity were summarized using descriptive statistics. All calculations were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and Stata version 14.0 (StataCorp. College Station, Texas, USA). The value of $P < 0.05$ was considered to indicate statistical significance.

**Results**

**Patient characteristic**

The patient characteristics are summarized in **Table 1**. At the time of diagnosis, the median age was 69.4 years (95% CI, 66.4-72.4 years), with a mean initial PSA of 73.56 ng/ml (95% CI, 43.6-103.76 ng/ml). The median interval between the start of ADT and the start of salvage IMRT was 54 months (95%CI, 41.5-66.6 months).

**Table 1.** Patients and treatment characteristics at the time of radiation therapy

| Characteristic | n(%) |
|---|---|
| Number of patients | 22 |
| Age at time of diagnosis (years) | |
| Mean (95% CI) | 69.4 (66.4-72.4) |
| Age at time of EBRT start (years) | |
| Mean (95% CI) | 73.8 (70.6-77.1) |
| ECOG | |
| 0 | 1 (4.5%) |
| 1 | 20 (90.9%) |
| 2 | 1 (4.5%) |
| T stage | |
| T1-T2b | 0 (0%) |
| T2c | 3 (13.6%) |
| T3a | 4 (18.2%) |
| T3b | 7 (31.8%) |
| T4a | 7 (31.8%) |
| Missing | 1 (4.5%) |
| N stage | |
| N0 | 20 (90.9%) |
| N1 | 2 (9.1%) |
| Pathology | |
| Adenocarcinoma | 22 (100%) |
| Histologic Grade Group | |
| 1 | 2 (9.1%) |
| 2 | 3 (13.6%) |
| 3 | 4 (18.2%) |
| 4 | 4 (18.2%) |
| 5 | 6 (27.3%) |
| Missing | 3 (13.6%) |
| PSA at time of diagnosis (ng/ml) | |
| Mean (95% CI) | 73.56 (43.46-103.76) |
| Pretreatment PSA (ng/ml) | |
| Median (IQR) | 6.68 (3.00-16.76) |
| Hormonal therapy prior to EBRT | |
| ADT | 11 (50.0%) |
| Bilateral orchiectomy | 4 (18.2%) |
| ADT and bilateral orchiectomy | 7 (31.8%) |
| The interval between HT and EBRT (months) | |
| Mean (95% CI) | 54.1 (41.5-66.6) |
| Radiotherapy technique | |
| IMRT | 22 (100%) |
| Pelvic node irradiation | |
| Yes | 8 (36.4%) |
| No | 14 (63.6%) |
| Prescribed radiation dose (Gy) | |
| Median (IQR) | 77.94 (76.81-79.62) |

EBRT external beam radiotherapy, PSA prostate-specific antigen, HT hormonal treatment, IMRT intensity-modulated radiation therapy, CI confidential interval, IQR interquartile range

The mean age at the time of EBRT was 73.8 years (95% CI, 70.6-77.1 years), with a median PSA prior to EBRT was 6.68 ng/ml (IQR, 3.00-16.67 ng/ml). Ten patients (45.5%) had Grade Group 4-5, while only two patients (9.1%) had Grade Group 1. Eighteen of the patients (81.8%) had T stage ≥ 3. Most patients had N0, only two of them (9.1%) had N1.

All patients were treated with IMRT or VMAT techniques. The dose per fraction was 1.8-2.23 Gy with a total dose of 76-80 Gy. The median prescribed dose to the primary tumor was 77.94 Gy (IQR, 76.81-79.62 Gy). The median biological effective dose was 130 Gy (IQR, 126.72-133.33 Gy), assuming an $\alpha/\beta$ ratio of 3; the median equivalent dose with a fraction of 2 Gy was 78 Gy (IQR, 76-80 Gy). Eight patients (36.4%) received irradiation of the pelvic nodes, two of which had positive nodes (9.1%).

**Biochemical relapse-free survival (BRFS)**

The median follow-up time after EBRT was 43 months (range, 20-105 months). The median BRFS was 31 months (range, 3-78 months), with a BRFS of 43.6% in 3-year and 5-year **(Figure 1)**. At the last follow-up, 12 patients (54.5%) experienced biochemical failure after EBRT.

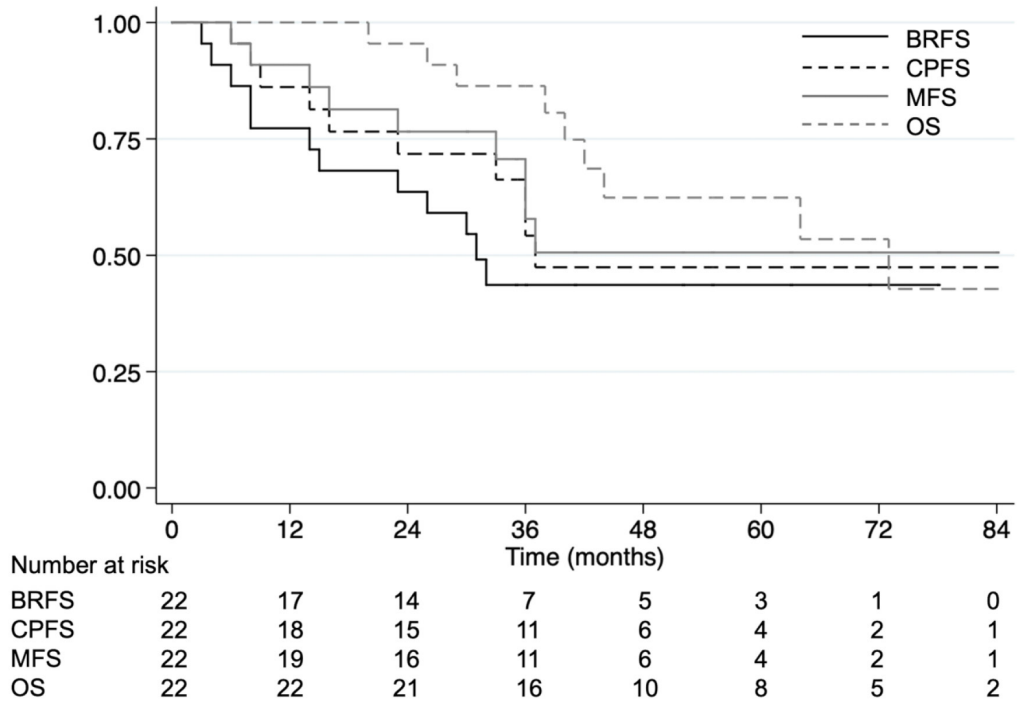


**Figure 1** Biochemical relapse-free survival (BRFS), clinical progression-free survival (CPFS), metastasis-free survival (MFS), and overall survival (OS) of patients with non-metastatic, castration-resistant prostate cancer (nmCRPC) treated with external beam radiotherapy (EBRT)

On the univariate analysis, PSA prior to EBRT ≥ 13 ng/ml and pelvic node involvement were unfavorable prognostic factors of BRFS. Multivariate analysis showed that only PSA prior to EBRT was the independent prognostic factor associated with BRFS (HR 13.60 (95% CI, 2.62-70.88)) **(Table 2)**. The median BRFS in patients with PSA before EBRT ≥ 13 ng/ml was 14 months, compared with the non-reach in patients with PSA before EBRT < 13 ng/ml.

**Table 2.** Univariate and multivariate analyses of prognostic factors of biochemical relapse-free survival (BRFS)

| Prognostic factors | Biochemical relapse-free survival (BPFS) | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (< 70 vs ≥ 70 y) | 1.89 (0.57-6.31) | 0.30 | | |
| Pre-RT PSA (≥ 13 vs < 13 ng/ml) | 15.03 (2.98-75.75) | 0.001 | 13.6 (2.62-70.88) | 0.002 |
| T stage (T4 vs T2-3) | 2.03 (0.64-6.41) | 0.23 | | |
| N stage (N1 vs N0) | 4.95 (0.90-27.22) | 0.07 | 2.29 (0.41-12.84) | 0.35 |
| Grade group (4-5 vs 1-3) | 2.25 (0.65-7.78) | 0.21 | | |
| Total dose (< 78 vs ≥ 78 Gy) | 0.64 (0.20-2.02) | 0.44 | | |

**Clinical progression free-survival (CPFS) and metastasis-free survival (MFS)**

The 3-year and 5-year CPFS was 54.2% and 47.4%, with the median CPFS of 37 months (range, 6-84 months). The 3-year and 5-year MFS were 57.8% and 50.6%, respectively. The median MFS was not-reach (range, 6-84 months) (Fig.1). Of 12 patients with biochemical failure, 10 and 9 developed clinical failure and distant metastases, respectively. Only 1 (4.5%) patient had local recurrence. The pattern of failure is summarized in **Table 3**.

On the multivariate analysis, the PSA prior to EBRT was the only independent predictor for CPFS (HR 7.12 (95% CI, 1.58-32.08)). The median CPFS in patients with PSA before EBRT ≥ 13 ng/ml was 23 months, compared with the non-reach in patients with PSA before EBRT < 13 ng/ml. For MFS, the PSA prior to EBRT (HR 19.14 (95% CI, 2.69-136.02)), T stage (HR 6.77 (95% CI, 1.18-38.95)) and N stage (HR 13.04 (95% CI, 1.33-127.76)) were significant predictive factors on the multivariate analysis

**Table 3.** Pattern of recurrence

| Pattern of failure | N |
|---|---|
| Local | 1 |
| Regional | 0 |
| Local and regional | 0 |
| Local and distant | 0 |
| Regional and distant | 1 |
| Distant | 8 |

**Overall survival (OS)**

The median survival was 73 months (range, 20-105 months) with a 3-year OS of 86.4% and a 5-year OS of 62.4% (Fig. 1). Among 22 patients, 10 (43.5%) died during the period of this analysis. Of these 10 patients, 6 died of prostate cancer, 3 died of other diseases, and 1 died of an unknown cause.

**Toxicity**

All patients completed the treatment without interruption. The most frequent acute GU toxicity was cystitis. Acute GU toxicity was as follows: grade 2 cystitis in 5 patients (22.7%), grade 2 urinary obstruction in 1 patient (4.5%). There was no acute GU toxicity grade ≥ 3. For acute GI toxicity, grade 3 diarrhea occurred in 1 patient (4.5%). No grade 4 GI toxicity occurred.

No late grade 2 or higher GU toxicity occurred. There were 2 patients (9.1%) with late grade 2 proctitis and only 1 patient (4.5%) with late grade 4 proctitis. Acute and late complications were summarized in **Table 4**.

**Table 4.** Acute and late complication

| Complication | Acute toxicity grade n(%) | | | Late toxicity grade n(%) | | |
|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 2 | 3 | 4 |
| Rectal | | | | | | |
| Diarrhea | 0 (0%) | 1 (4.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Proctitis | 0 (0%) | 0 (0%) | 0 (0%) | 2 (9.1%) | 0 (0%) | 1 (4.5%) |
| Urinary | | | | | | |
| Obstruction | 1 (4.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Cystitis, noninfective | 5 (22.7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Incontinent | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

## Discussion

We investigated the clinical outcomes of prostate cancer patients who underwent salvage dose-escalated IMRT for radiotherapy-naïve nmCRPC patients treated with ADT alone at diagnosis. Our findings for patients at 5 years were as follows: biochemical control in 43.6%, clinical control in 47.4%, and metastatic control in 50.6%. The 5-year OS was 62.4%. The predictor of worse clinical outcomes was PSA before EBRT ≥ 13 ng/ml. Salvage dose-escalated IMRT was well tolerated, with grade ≥ 3 toxicity in only 4.5% of patients.

Similar results **(Table 5)** were observed in studies reported by Botticella et al.[13] and Aizawa et al.[14]. Botticella et al.[13] had studied 42 patients with nmCRPC who were treated with EBRT to a total dose of 78 Gy, reported that the 5-year BRFS and MFS were 39.4% and 60%, respectively. A retrospective study by Aizawa et al.[14] also reported the 5-year BRFS of 32.3% and the 5-year CPFS of 56%. Although the patients in the study reported by Aizawa et al. were more favorable, the dose of EBRT was lower (median dose of 70.4Gy in 38 fractions) compared to our study. However, the results from some studies appear less favorable than our studies. A large retrospective study of 140 nmCRPC patients treated with EBRT by Sasaki et al. found that 5-year CPFS was 36.7% and 5-year OS was 48.1%.[10] Pascoe et al.[12], a cohort study of 13 nmCRPC who underwent EBRT, observed the median BRFS of 15 months and the median MFS of 18.5 months, while our study found that the median BRFS was 31 months and the median MFS was NR.

**Table 5.** Literature overview of studies evaluating the role of salvage EBRT in non-metastatic, castration-resistant prostate cancer

| First author | No of patients | EBRT dose (Median) | Median follow-up (months) | Median BRFS<br>5-yr BRFS | Median CPFS<br>5-yr CPFS | Median MFS<br>5-yr MFS | Median OS<br>5-yr OS |
|---|---|---|---|---|---|---|---|
| Sasaki et al.[10] | 140 | 66 Gy | 20.7 | -<br>- | -<br>36.7% | -<br>- | -<br>48.1% |
| Pascoe et al.[12] | 13 | 64 Gy | - | 15 months<br>- | -<br>- | 18.5 months<br>- | 42 months<br>- |
| Botticella et al.[13] | 42 | 78 Gy | 53 | 27.4 months<br>39.4% | -<br>- | 27.4 months<br>60.0% | NR<br>65.0% |
| Aizawa et al.[14] | 31 | 70.4 Gy | 66.6 | 19.3 months<br>32.3% | 16 months<br>56.0% | -<br>- | -<br>74.6% |
| Present study | 22 | 77.94 Gy | 43 | 31 months<br>43.6% | 37 months<br>47.4% | NR<br>50.6% | 73 months<br>62.4% |

EBRT external beam radiotherapy, BRFS biochemical-relapse free survival, CPFS clinical progression-free survival, MFS metastatic-free survival, OS overall survival, NR not reach

Although a dose-escalated EBRT in the definitive setting has better biochemical control, the role of salvage dose-escalated EBRT in the nmCRPC setting remains controversial. Ogawa et al.[11] discovered that local control after irradiation of ≥ 66 Gy was 98%, compared with 83% for those receiving < 66 Gy (p = 0.024). In the Botticella et al. study[13], all patients were treated with EBRT to a total dose of 78 Gy in conventional fractionation. No patient developed local failure, and a systemic control was up to 60%. In the Sasaki et al. study[10], a total dose of ≥ 60 Gy was a significant prognostic factor for overall survival in the univariate analysis (HR 0.63, p = 0.001). Besides, Nakamura et al.[7] also found that a total dose of ≥ 60 Gy was one of the prognostic factors in a multivariate analysis associated with better survival (HR 0.24, p = 0.026). In our study, we used the relatively uniform and high dose EBRT regimen (76-80 Gy) with advanced techniques (IMRT/VMAT with IGRT). The local control was excellent, and the toxicity was relatively low. Local recurrence occurred only in 1 patient (4.5%). Our clinical results were comparable to the Botticella et al. study, which had similar baseline patient characteristics and EBRT dose.

In our study, multivariate analysis revealed PSA before EBRT ≥ 13 ng/ml was a significant prognostic factor that resulted in lower BRFS (HR 13.6, p = 0.002), CPFS (HR 7.12, p = 0.01), and MFS (HR 19.14, p = 0.003) than patients with PSA before EBRT < 13 ng/ml. The PSA prior to the EBRT level was also reported as a prognostic factor in previous studies. Smith et al.[3] studied the natural history of nmCRPC and found that baseline PSA ≥ 13.1 ng/ml was associated with shorter OS (HR 2.34, p < 0.0001), time to first bone metastasis (HR 1.98, p < 0.0001), and bone metastasis-free survival (HR 1.98, p < 0.0001). Botticella et al.[13] reported that the pre-EBRT PSA ≥ 5 ng/ml was associated with BRFS (HR 0.9, p = 0.05). Sanguineti et al.[8] found that higher PSA at RT was likely to develop the distant disease in univariate analysis (p = 0.07), especially patients with pre-EBRT PSA higher than 20 ng/ml. Ogawa et al.[11] reported that patients with pre-EBRT PSA > 20 ng/ml had worse PFS in univariate analysis (p = 0.026). Pascoe et al.[12] found that pre-EBRT PSA was correlated time to progression (p = 0.017) and time to metastasis (p = 0.025). To conclude, nmCRPC patients with lower PSA before EBRT tend to have better outcomes.

In the present study, the rate of GI and GU toxicity was acceptable and comparable with other previous studies.[8, 9, 11, 13, 14, 16] However, we detected late grade 4 radiation proctitis in 1 patient (4.5%), which was higher than in RTOG 0126 (<1%).[16] After reviewing the treatment planning, we discovered that the rectal volumes in this patient that exceeded 70 and 75 Gy were 25% and 22%, respectively, exceeding the rectal dose constraint. Dose and volume criteria that are associated with GI toxic effects have been previously published. The large (> 15%) volume of the rectum > 70 Gy was associated with late rectal toxicity.[21] These findings indicate that it is critical to maintain the dose constraint of the rectum in order to avoid severe toxicity.

The standard treatments in patients with nmCRPC are enzalutamide, apalutamide, and darolutamide. In patients with high-risk nmCRPC, phase III RCTs including the PROSPER, SPARTAN, and ARAMIS trials recently revealed that enzalutamide, apalutamide, or darolutamide improved MFS compared to placebo. In the PROSPER trial, the median MFS improved from 14.7 months in the placebo group to 36.6 months in the enzalutamide group (HR 0.29, p <0.001).[5] In the SPARTAN trial, the median MFS was 40.5 months in the apalutamide group compared to 16.2 months in the placebo group (HR 0.28, p < 0.001).[6] The ARAMIS trial also demonstrated a significantly better MFS in the darolutamide group than the placebo group, with a median survival of 40.4 months vs. 18.4 months (HR 0.41, p < 0.001).[4] The role of salvage EBRT in patients with radiotherapy-naïve nmCRPC is controversial. Although the STAMPEDE trial demonstrated the benefit of EBRT to the primary tumor in patients with a low disease burden[22], there is no strong evidence to support the primary tumor treatment in this setting. A post hoc analysis of the SPARTAN trials assessed the impact of initial radical local treatment on the OS. The HR for OS was better in the apalutamide group. However, the benefit of apalutamide is clearer in patients who previously underwent definitive local therapy.[23] There is an assumption that EBRT could eradicate the local tumor and prevent subsequent metastasis. Therefore, we hypothesized that the combination of salvage EBRT and novel antiandrogens in radiotherapy-naïve nmCRPC might improve local control, extend metastasis-free survival and increase patient lifespan. However, the combination of dose-escalated IMRT with novel antiandrogens should be further investigated.

There are a few limitations to our study. First, the definition of CRPC status in our study was defined as a continuous rising PSA despite ongoing ADT. The Prostate Cancer Working Group 2 (PCWG2) described CRPC as an increasing PSA greater than 2 ng/ml higher than the nadir despite castration levels of testosterone (less than 50 ng/ml).[24] We used this definition because we included patients who were treated before this concept was introduced, and serum testosterone levels were not routinely measured in our institution at the time. Secondly, this cohort is a retrospective study. The retrospective nature of this study required a review of individual patient data, which may have been subject to incomplete data collection. Because most patients' primary ADT was performed in other hospitals, radiographic imaging was unavailable during the initial staging. Finally, the sample size is relatively small. Nevertheless, our result provides favorable results of salvage dose-escalated IMRT for radiotherapy-naïve nmCRPC. Further prospective studies are needed to evaluate the impact of salvage dose-escalated IMRT with radiotherapy-naïve nmCRPC.

## Conclusion

In conclusion, for a patient with radiotherapy-naïve nmCRPC, high-dose salvage EBRT was a feasible treatment option with acceptable toxicity. This approach was associated with ex-

cellent local control. The biochemical, clinical, and metastatic controls were acceptable. The combination of high-dose salvage EBRT and novel antiandrogen should be investigated in future prospective studies.

**Competing Interests**

All authors declare no competing financial interests.

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