Long-term clinical outcomes of external-beam radiation therapy for oligo-metastatic prostate cancer: A combination of prostate-targeted treatment and metastasis-directed therapy

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Short running title: PTT plus MDT for oligo-metastatic HSPCa

Abstract

Background:

Although promising outcomes of intensive treatment of the prostate (prostate-targeted treatment: PTT) and metastatic lesions (metastasis-directed therapy: MDT) have been reported for oligo-metastatic prostate cancer (OMPCa) patients, limited data are available regarding the efficacy of the combination of those two methods for synchronously diagnosed OMPCa.

Methods:

We retrospectively evaluated the clinical outcomes of synchronously diagnosed OMPCa patients treated with external-beam radiation therapy (EBRT) for the prostate and all metastatic lesions at our institution between January 2004 and April 2019. The prescribed dose was basically more than 70 Gy (1.8–2 Gy per fraction) for the prostate with or without whole pelvic irradiation, and more than 45 Gy (1.8–2 Gy per fraction) for the metastatic lesions. Long-term androgen-deprivation therapy was used as neoadjuvant and/or adjuvant therapy. Oligo-metastatic disease was defined as the presence of three or fewer metastatic lesions. Clinical outcomes were compared to evaluate the benefit of PTT plus MDT, using a cohort of 55 synchronous OMPCa patients treated with the standard of care (without PTT plus MDT) at our institution.

Results:

In total, 16 consecutive patients with synchronous OMPCa (median age: 66 years old) were analyzed. The median follow-up period was 7.4 years. The 8-year overall survival, prostate cancer-specific survival, biochemical failure-free, clinical failure-free, and castration-resistant prostate cancer (CRPC)-free rates were 64.8, 71.3, 38.5, 47.3, and 67.3%, respectively. No grade 3 or higher radiation-induced late toxicities occurred. As a result of the comparison, patients with PTT plus MDT had a significantly higher CRPC-free rate than those without PTT plus MDT ($p = 0.00741$).

Conclusions:

The combination of EBRT for the prostate and all metastatic lesions resulted in favorable long-term disease-free and survival outcomes with acceptable morbidities among synchronous OMPCa patients. Therefore, this approach may represent a promising treatment strategy for this population. Further investigation is needed.

Key words: prostate cancer, oligo-metastasis, external-beam radiation therapy, prostate-targeted treatment, metastasis-directed therapy

Introduction

Oligo-metastasis, characterized by the presence of a limited number of metastases (usually 1–5 lesions in most studies), is considered to be an oncological state that is intermediate between localized and widely disseminated disease. In patients with metastatic prostate cancer, however, lifelong androgen-deprivation therapy (ADT) monotherapy has been the mainstay of treatment, applied similarly to both patients with oligo-metastasis and those with multiple metastatic lesions in daily clinical practice.

Recently, two novel treatment approaches for oligo-metastatic prostate cancer (OMPCa) patients were investigated: radical treatment of the primary tumor, and high-intensity treatment of metastatic lesions.[1] The former method, referred to as prostate-targeted treatment (PTT), afforded survival benefits to newly diagnosed (synchronous) OMPCa patients,[2, 3] and is a promising alternative to conventional lifelong ADT. The latter method, referred to as metastasis-directed therapy (MDT), effectively controlled oligo-recurrent prostate cancer arising after initial curative treatments (metachronous OMPCa).[4-9] Considering that tumor cells may seed not only from the primary site but also from metastatic sites,[10] adding MDT for all metastatic lesions to PTT can, in theory, be an effective treatment strategy for synchronous OMPCa cases. However, in most studies of PTT, the details of treatments for metastatic

lesions are not available.[2, 3, 11] Moreover, in the majority of previous studies on the combination of PTT plus MDT, the study cohorts were heterogenous in terms of patient and prior treatment backgrounds with a relatively short follow-up term (≤ 5 years):[12-14] both patients with distant metastases and those with only pelvic lymph node metastases, or both patients whose PTT was performed with definitive external-beam radiation therapy (EBRT) and those with radical prostatectomy, were included together. To date, reports on the long-term clinical outcomes of adding MDT to PTT based on uniform treatment methods among patients with limited numbers of distant metastases have been sparse.

Herein, we conducted a retrospective study of EBRT for synchronous OMPCa patients based on a single institutional experience. To the best of our knowledge, this is the first study to evaluate the clinical outcomes of the combination of PTT plus MDT using EBRT in patients with limited numbers of synchronously detected distant metastases, with a long-term follow-up (median: 7.4 years).

Methods

This study followed the tenets of the Declaration of Helsinki, with approval from the Ethical Review Board of our institution (approval number: R1048 and R1049). Written informed consent was obtained from all patients.

Patients

We retrospectively analyzed the treatment outcomes of EBRT for patients with oligo-metastatic prostate cancer. The eligibility criteria for this study were as follows: (1) ~~castration-sensitive~~ prostate cancer with diagnosis of synchronous oligo-metastasis (~~N0–1~~M1a/b); (2) treated with EBRT for the prostate and all detected metastatic lesions at our institution between January 2004 and April 2019; (3) irradiation dose for metastatic lesions ≥ 45 Gy. In the current study, oligo-metastatic disease was defined as the presence of three or fewer distant metastatic lesions, in which lymph nodes located in same nodal region (e.g., para-aortic lymph nodes) were counted as a single metastatic lesion. ~~Patients with castration-resistant prostate cancer (CRPC) at the time of EBRT initiation were excluded.~~ To identify this subgroup, we retrospectively reviewed our institutional radiotherapy chart of consecutively treated during this period.

Initial evaluations included systematic needle biopsies, digital rectal

examinations, transrectal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy. For bone metastasis, in addition to accumulation on bone scintigraphy at the diagnosis, additional imaging examinations such as MRI of the site, bone scintigraphy after neoadjuvant ADT (NA-ADT) (decreased accumulation), or CT after NA-ADT (sclerotic change) were basically performed to exclude false metastasis. For lymph node metastasis, the shrinkage of enlarged nodes during ~~neoadjuvant ADT (~~NA-ADT~~)~~ was confirmed by CT for re-evaluation after NA-ADT, in order to eliminate false metastasis.

Neoadjuvant androgen deprivation therapy

The combination of long-term ADT was adopted in neoadjuvant and adjuvant settings, which was basically changed to intermittent ADT within several years (usually 2.5 years) in order to evaluate the effect of PTT plus MDT. NA-ADT basically consisted of combined androgen blockade (CAB) for 6 months, and adjuvant ADT (A-ADT) consisted of CAB or luteinizing hormone-releasing hormone ~~(LH-RH)~~ analogue alone. However, there were some variations in the duration. Longer NA-ADT was applied in some cases because our cohort included patients who were initially treated with ADT alone. In addition, lifelong A-ADT was applied in selected cases based on physicians'

judgement in consideration of the aggressiveness of the disease. Androgen receptor axis-targeted (ARAT) agents, such as abiraterone or enzalutamide, were not used during the NA-ADT or A-ADT course.

External-beam radiotherapy

EBRT consisted of irradiation of the pelvic lesion including the prostate plus seminal vesicles, metastatic lymph nodes, and pelvic nodal region, and irradiation of distant metastasis ~~(MDT)~~.

For irradiation of the pelvic region, the prostate plus seminal vesicles, metastatic pelvic lymph nodes, and pelvic nodal region were treated using intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiotherapy (3D-CRT) methods with conventional fractionated doses. The indication of prophylactic whole pelvic radiation therapy (WPRT) was basically based on the physician's judgement in consideration of the aggressiveness of the disease in each case. In the case of IMRT, the prostate plus seminal vesicles, metastatic lymph nodes, and pelvic nodal region were simultaneously treated using doses of 78, 66.3, and 58.5 Gy in 39 fractions, respectively. In the case of 3D-CRT, 70.4–74 Gy comprising 1.8–2 Gy per fraction (Gy/fr) were cumulatively prescribed for the prostate plus seminal vesicles,

with irradiation of metastatic lymph nodes and pelvic nodal region with a dose of 45–50.4 Gy comprising 1.8 Gy/fr.

For MDT, bone metastasis or metastatic lymph nodes were treated using 3D-CRT or IMRT methods with conventional fractionated doses. MDT was basically performed immediately after PTT (sequentially) or together with PTT (concurrently). In the case of 3D-CRT, more than 50 Gy comprising 1.8–2 Gy/fr were generally delivered to the metastatic sites. In the case of IMRT mainly for pelvic or lower lumbar bone metastasis, 66.3 Gy comprising 1.7 Gy/fr were delivered concurrently with the pelvic irradiation using the simultaneous-integrated boost method. However, there were some dose and field variations because treatment was basically determined by each physician in consideration of irradiation dose constraints of normal organs, such as the spinal cord or small bowel.

Follow-up

Patients were followed every 1–3 months during the first 2 years and every 3–6 months thereafter at our hospital or affiliated hospitals. No additional radiographic study after EBRT was required unless increasing prostate-specific antigen (PSA) levels, bone pain, or locoregional symptoms were observed. Salvage treatments after EBRT were

conducted at the physician's discretion, but were generally performed in accordance with the standard approaches for Japanese metastatic prostate cancer.

Statistical analysis

The time of occurrence of each event was calculated from the date of PTT initiation. The Kaplan–Meier estimate was used to calculate overall survival (OS), prostate cancer-specific survival (PCSS), biochemical failure (BF)-free, clinical failure (CF)-free, and castration-resistant prostate cancer (CRPC)-free rates. For evaluation of BF-free, CF-free, and CRPC-free rates, deaths without each event were censored at the time of last PSA evaluation or death. Patients who were lost-to-follow-up with best supportive care were categorized as 'died from prostate cancer' at the time of the last visit or the point when clinical data were available. BF was defined as follows: (1) PSA elevation > 2.0 ng/mL above the nadir (Phoenix definition), excluding cases due to acute prostatitis;[15] (2) a change in treatment due to disease progression. The CRPC status was defined as follows: (1) PSA elevation > 2.0 ng/mL above the nadir during ADT; (2) CF during ADT; (3) a change in treatment due to disease progression during ADT. PSA elevation during off-periods of intermittent ADT was not counted as CRPC. Late toxicities were assessed using Common Terminology Criteria for Adverse Events,

version 4.

The PCSS and CRPC-free rates for the presently reported PTT plus MDT series were compared with those of other treatment strategies: ADT alone with or without palliative therapies for local or metastatic sites. We searched for patients with synchronous OMPCa at the initiation of these treatments between September 2003 and September 2018, using our institutional database of prostate cancer. In the comparison, the timing of the occurrence of each event was calculated from the date of the initiation of primary ADT. Chi-square analysis, student's t-test, or Mann–Whitney U test were used to compare patient characteristics. The differences in PCSS and CRPC-free rates were estimated using the log-rank test, and a p-value <0.05 was considered significant.

All statistical analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

We identified 19 consecutive patients who met the eligibility criteria. Among them, 3 patients had CRPC at the initiation of PTT. They were excluded, and the remaining 16 patients were included in the analysis. The median patient age was 66 (range: 50–75) years at the initiation of EBRT. The median pretreatment PSA level was 30.4 (range: 5.7–547) ng/mL. Approximately 60% of the patients had ≥T3b disease (n = 10), half of the patients had a Gleason score (GS) sum ≥9 (n = 8), and approximately 40% of the patients had pelvic lymph nodes metastasis (n = 7). The median number of distant metastatic lesions was 1 (range: 1–3), and the metastatic lesions were as follows: bone metastasis, 13 cases (81.3%); para-aortic lymph nodes, 2 cases (12.5%); bone and para-aortic/inguinal lymph node metastasis, 1 case (6.3%). The patient characteristics are summarized in Table 1.

External-beam radiotherapy

All patients were treated via IMRT or 3D-CRT. A median dose of 74 (range: 67.5–78) Gy comprising 2 (range: 1.8–2.25) Gy/fr was administered to the prostate plus seminal vesicles. Prophylactic WPRT was performed in 14 patients (87.5%) and the median dose of WPRT was 52.2 (range: 45–58.5) Gy comprising 1.5–1.8 Gy/fr. Seven

patients (43.8%) with metastatic pelvic lymph nodes were treated with a median dose of 56 (range: 45–66.3) Gy comprising 1.7–2 Gy/fr. For MDT, a median dose of 57.25 Gy (range: 45–70.2) comprising 1.7–2 Gy/fr was prescribed for the metastatic lesions. The details of EBRT are summarized in Table 2.

Neoadjuvant and adjuvant androgen deprivation therapy

All patients received CAB prior to EBRT as NA-ADT. Fourteen patients (87.5%) received ADT in a planned neoadjuvant setting, with a median duration of 6.7 months (range: 5.1–12.2), whereas the remaining two patients (12.5%) were initially treated with ADT alone and subsequently underwent EBRT (duration: 15.7 and 23.2 months, respectively). Following the completion of EBRT, A-ADT was performed for 14 patients (87.5%). Among these 14 patients, two patients developed disease progression during A-ADT and treatment was changed to different agents (salvage ADT). Among the remaining 12 patients, 10 patients were treated with limited-term ADT (basically 2 years), whereas two patients were treated with lifelong ADT including one patient whose A-ADT was terminated 12.0 years after EBRT due to a stable clinical course. The median duration of A-ADT in all patients was 25.6 (range: 0–143.6) months. The details of NA-ADT and A-ADT are summarized in Table 2.

Oncological and survival outcomes and salvage treatments for disease failure

The median follow-up period after the initiation of PTT was 7.4 (range: 1.1–13.4) years. Eight patients (50.0%) died, five (31.3%) from PCa, during follow-up. The OS and PCSS rates were 83.3% (95% confidence interval [CI]: 48.2–95.6) and 91.7% (95% CI: 53.9–98.8) at 5 years, and 64.8% (95% CI: 31.0–85.2) and 71.3% (95% CI: 34.4–89.8) at 8 years, respectively (Fig. 1A–B). During follow-up, seven patients (43.8%) developed BF at a median of 3.0 years (range: 0.3–7.4) after EBRT: five developed BF after the completion of A-ADT and two developed BF during A-ADT (CRPC). All of those seven patients developed CF at a median of 5.6 years (range: 0.5–8.4) after EBRT. Their initial sites of CF were as follows: bone metastases, 5 cases; local failure, 1 case; liver metastasis, 1 case. During follow-up, two patients developed local failure: urinary obstruction, 1 case; radiographical relapse without clinical symptoms, 1 case. Therefore, the local control rate was estimated as 87.5%. During follow-up, seven patients (43.8%) developed CRPC at a median of 5.6 years (range: 1.1–8.7) after EBRT. The BF-free, CF-free, and CRPC-free rates were 57.7% (95% CI: 25.3–80.3), 85.2% (95% CI: 51.9–96.2), and 76.9% (95% CI: 43.0–92.2) at 5 years, and 38.5% (95% CI: 12.1–64.9), 47.3% (95% CI: 17.8–72.4), and 67.3% (95%

CI: 33.4–86.7) at 8 years, respectively (Fig. 2A–C). Recurrence at the MDT site was detected in one patient (6.3%), whereas no evidence suggestive of disease progression was observed at the MDT site in the remaining six patients with BF.

As a first-line salvage treatment for seven patients with disease progression, ADT was used in six patients, and an ARAT agent was used in one patient who developed failure during the A-ADT course (CRPC). No patients received ARAT agents or chemotherapy in a setting of castration-sensitive prostate cancer.

Radiation-induced late toxicity

Grade 2 late toxicities were observed in four patients (25.0%): rectal hemorrhage, 1 case; urinary tract obstruction requiring self-catheterization, 1 case; hematuria, 1 case; hematuria and pelvic insufficiency fracture, 1 case. No grade 3 or higher late toxicities were observed.

Comparison of survival and oncological outcomes

We identified 55 consecutive patients who met the same criteria for "oligo-metastatic disease", and received ADT alone with or without palliative therapy for the prostate or metastatic sites at our institution (control cohort). Their data were

compared with the presently reported results of the 16 patients who received PTT plus MDT (experimental cohort). The details of their treatment strategy were previously reported.[16] Comparisons of patient characteristics are summarized in Table 3. The median follow-up periods after the initiation of primary ADT were 8.7 (range: 1.6–14.5) years for the 16 patients who received PTT plus MDT, and 6.9 (range: 1.5–14.9) years for the 55 patients without PTT plus MDT. The PCSS rate was superior in the PTT plus MDT cohort compared with that in the control cohort, although no significant differences were observed (91.7 vs. 82.0% at 5 years, 91.7 vs. 72.3% at 8 years; $p = 0.667$). The CRPC-free rate was significantly better in the PTT plus MDT cohort than in the control cohort (75.8 vs. 38.7% at 5 years, 66.3 vs. 19.4% at 8 years; $p = 0.00741$). The results of comparison of PCSS and CRPC-free rates are presented in Figure 3A–B.

Discussion

Oligo-metastatic disease is generally categorized into synchronous and metachronous OMPCa according to the timing of metastasis development. Synchronous OMPCa is characterized by the simultaneous presence of an untreated primary tumor and oligo-metastatic lesions. For this state, radical treatment for the primary tumor, referred to as PTT, is recommended in the current treatment guideline from the National Comprehensive Cancer Network (version 1, 2020).[17] On the other hand, metachronous OMPCa is generally characterized by recurrence with oligo-metastatic lesions after radical treatment of the primary tumor. For this state, a promising outcome of high-intensity treatment for metastatic lesions, referred to as MDT, has been reported, which may help to avoid or delay the initiation of systemic therapies.

In the current study, we retrospectively evaluated the long-term clinical outcomes of the combination therapy of PTT plus MDT for all metastatic lesions using EBRT in synchronous OMPCa patients. As no clear definition of “oligo-metastasis” has been formally proposed,[18] the current study included patients with three or fewer distant metastatic lesions (lymph nodes located in same nodal region were counted as a single metastatic lesion) (M1a/b). Our treatment protocol consisted of high-dose EBRT (up to 78 Gy) for the prostate (with or without WPRT) and all metastatic lesions (conventional

fractionated EBRT), in combination with long-term ADT ~~(basically 2.5 years)~~. As a result, we observed a certain number of patients who maintained a long-term disease-free status (BF-free rate at 8 years: 38.5%). In addition, long-term survival outcomes were favorable, and no severe EBRT-related toxicities were observed. Compared with patients treated without PTT plus MDT, those who received PTT plus MDT had better outcomes regarding the CRPC-free rate ($p = 0.00741$), although these were the results of direct comparison. These results suggested the effectiveness of our treatment strategy for synchronous OMPCa.

Survival benefits of PTT for synchronous OMPCa have been reported based on the medium-term results of prospective studies.[2, 3, 19] The STAMPEDE trial randomized 2,061 patients with synchronous metastatic prostate cancer to the standard of care (lifelong ADT with or without docetaxel) or that standard plus EBRT for the prostate (55 Gy in 20 fractions over 4 weeks or 36 Gy in 6 fractions over 6 weeks).[3] In the prespecified subgroup analysis, EBRT for the prostate improved the overall survival (OS) of patients with low metastatic burdens at a median follow-up duration of 37 months (OS rates at 3 years: 81 vs. 73%, respectively, hazard ratio: 0.68 [95% CI: 0.52–0.90], $p = 0.007$). Similarly, a meta-analysis of two randomized controlled trials (STAMPEDE and HORRAD) [3, 11] showed that the addition of EBRT for the prostate

improved the 3-year OS by 7% in patients with fewer than five bone metastases (hazard ratio: 0.73 [95% CI: 0.58–0.92], p = 0.0071).[2] In the current study, we observed favorable long-term survival outcomes among patients with up to three distant metastases (PCSS rate at 8 years: 71.3%), although no significant differences regarding PCSS were observed between our experimental cohort and control cohort (p = 0.667). Our findings regarding benefits for both disease control and survival outcomes are not conclusive due to our small sample size and retrospective nature of the analysis. However, these results suggest that PTT is an effective treatment method for synchronous OMPCa, which has the potential to improve survival outcomes.

Although the clinical benefits of MDT mainly using stereotactic body radiation therapy or surgical resection have been reported, most studies were performed in settings of oligo-recurrent metastatic prostate cancer (metachronous OMPCa).[1, 4-7] The clinical benefit of adding MDT to PTT for synchronous OMPCa patients has been controversial. Tsumura et al. retrospectively evaluated the clinical outcomes of PTT (high-dose-rate brachytherapy) with or without MDT (EBRT) in OMPCa patients with regional and/or distant (45% of the cohort) metastases.[13] Patients treated with MDT exhibited better CRPC-free survival than those without MDT (hazard ratio: 0.319 [95% CI: 0.116–0.877], p = 0.0269). In the current study, the combination of PTT plus MDT

using EBRT was associated with 38.5% BF-free and 67.3% CRPC-free rates at 8 years. These results would support the potential benefit of adding MDT to PTT for this population. Currently, an ongoing phase 2 study (NCT02716974) is recruiting patients to evaluate the outcomes of radical prostatectomy (± adjuvant EBRT) combined with consolidative SBRT for metastatic lesions, and chemohormonal therapy, for prostate cancer with up to five metastatic lesions. The validity of our approach will likely be verified by this prospective study.

Our study had several limitations, including the retrospective nature of the analysis and the small sample size. Novel diagnostic modalities with high sensitivity, such as prostate-specific membrane antigen-positron emission tomography, were not used because most of our patients were treated before these diagnostic modalities became covered by national insurance. Thus, we may have included cases with undetected metastases, which could lead to underestimation of the clinical outcomes. Furthermore, we performed PTT plus MDT for selected patients among synchronous OMPCa cases. As mentioned above, our evaluation of the efficacy of PTT plus MDT was solely based on the results of direct comparison, because we were not able to use methods to adjust the patient background between the experimental and control cohorts, such as propensity-score matching analysis, due to the small sample size. Therefore, the

clinical results and efficacy of the combination therapy of PTT plus MDT in our study were highly subject to selection bias. Due to these limitations, our findings are not conclusive but merely hypothesis-generating. Nevertheless, we believe that our study provides baseline data on this novel treatment strategy for synchronous OMPCa, because, to the best of our knowledge, our results represent the longest follow-up of patients receiving PTT in combination with MDT. The validity of our approach should be further investigated, especially in terms of patient selection for this type of treatment, given the lack of a standard definition of oligo-metastasis.

In conclusion, the combination of PTT plus MDT using EBRT resulted in favorable disease control and survival outcomes, with acceptable morbidities. This approach would therefore be a promising novel treatment strategy for synchronous OMPCa patients. Prospective studies are warranted to confirm these findings.

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Conflict of Interest:

The authors declare that they have no competing interests.

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Figure legends:

Figure 1. Kaplan–Meier curves showing overall survival (A) and prostate cancer-specific survival (B) rates after external-beam radiation therapy. EBRT, external-beam radiation therapy.

Figure 2. Kaplan–Meier curves showing biochemical failure-free (A), clinical failure-free (B), and castration-resistant prostate cancer-free (C) rates after external-beam radiation therapy. CRPC castration-resistant prostate cancer; EBRT, external-beam radiation therapy.

Figure 3. Kaplan–Meier curves of prostate cancer-specific survival (A) and castration-resistant prostate cancer-free (B) rates after the initiation of primary androgen-deprivation therapy for patients treated with PTT plus MDT versus those without PTT plus MDT. PTT, prostate-targeted treatment; MDT, metastasis-directed therapy; CRPC castration-resistant prostate cancer; ADT, androgen-deprivation therapy.

This document has been checked by a professional medical editor, who is a native speaker of English.

Tables

Table 1. Patient characteristics.

Age (years)	
Median (range)	66 (50–75)
Clinical stage, n (%) *	
T2bN0M1b	1 (6.25)
T3aN0M1b	3 (18.75)
T3aN1M1b	2 (12.5)
T3bN0M1a	1 (6.25)
T3bN0M1b	2 (12.5)
T3bN1M1a	1 (6.25)
T3bN1M1b	4 (25.0)
T4N0M1a	2 (12.5)
iPSA (ng/mL)	
Median (range)	30.4 (5.7–547)
Gleason score, n (%)	
3+4	2 (12.5)
4+3	1 (6.25)
4+4	4 (25)
4+5	5 (31.25)
5+4	1 (6.25)
5+5	2 (12.5)
Not available	1 (6.25)
Histology, n (%)	
Adenocarcinoma	16 (100.0)
Number of distant metastasis, n (%)	
1	14 (87.5)
2	1 (6.25)
3	1 (6.25)
Median number of metastasis (range)	1 (1–3)
Follow-up period (from initiation of PTT), year	
Median (range)	7.4 (1.1–13.4)

Footnote: iPSA, pretreatment prostate-specific antigen; PTT, prostate-targeted

treatment.

*; Clinical T stage was evaluated based on the findings of digital rectal examination or magnetic resonance imaging.

Table 2. Treatment characteristics.

NA-ADT, n (%)	
CAB	16 (100.0)
Duration of NA-ADT	
Planned neoadjuvant setting, n (%)	14 (87.5)
Median duration (range) (months)	6.7 (5.1–12.2)
Initially treated with ADT alone, n (%)	2 (12.5)
Duration (range) (months)	15.7–23.2
A-ADT, n (%)	
CAB	9 (56.25)
LH-RH	5 (31.25)
none	2 (12.5)
Duration of A-ADT	
Limited-term, n (%)	10 (62.5)
Lifelong, n (%)	2(12.5)
Terminated/changed duo to disease progression, n (%)	2(12.5)
None, n (%)	2 (12.5)
Median duration (range) (months)	25.6 (0–143.6)
EBRT technique, n (%)	
IMRT	8 (50.0)
3D-CRT	7 (43.75)
IMRT+3D-CRT	1 (6.25)
EBRT to the prostate	
n (%)	16 (100.0)
Dose (median, range) (Gy)	74 (67.5–78)
Dose per fraction (range) (Gy)	1.8–2.25
EBRT to pelvic nodal region	
n (%)	14 (87.5)
Dose (median, range) (Gy)	52.2 (45–58.5)
Dose per fraction (range) (Gy)	1.5–1.8
EBRT to metastatic pelvic lymph nodes	
n (%)	7 (43.75)
Dose (median, range) (Gy)	56 (45–66.3)

Dose per fraction (range)	1.7–2
EBRT to distant metastasis	
n (%)	16 (100.0)
Dose (median, range) (Gy)	58 (45–70.2)
Dose per fraction (range) (Gy)	1.7–2

Footnote: NA-ADT, neoadjuvant androgen deprivation therapy; CAB, combined androgen blockade; A-ADT, adjuvant androgen deprivation therapy; LH-RH, luteinizing hormone-releasing hormone analogue; EBRT, external-beam radiation therapy; IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy.

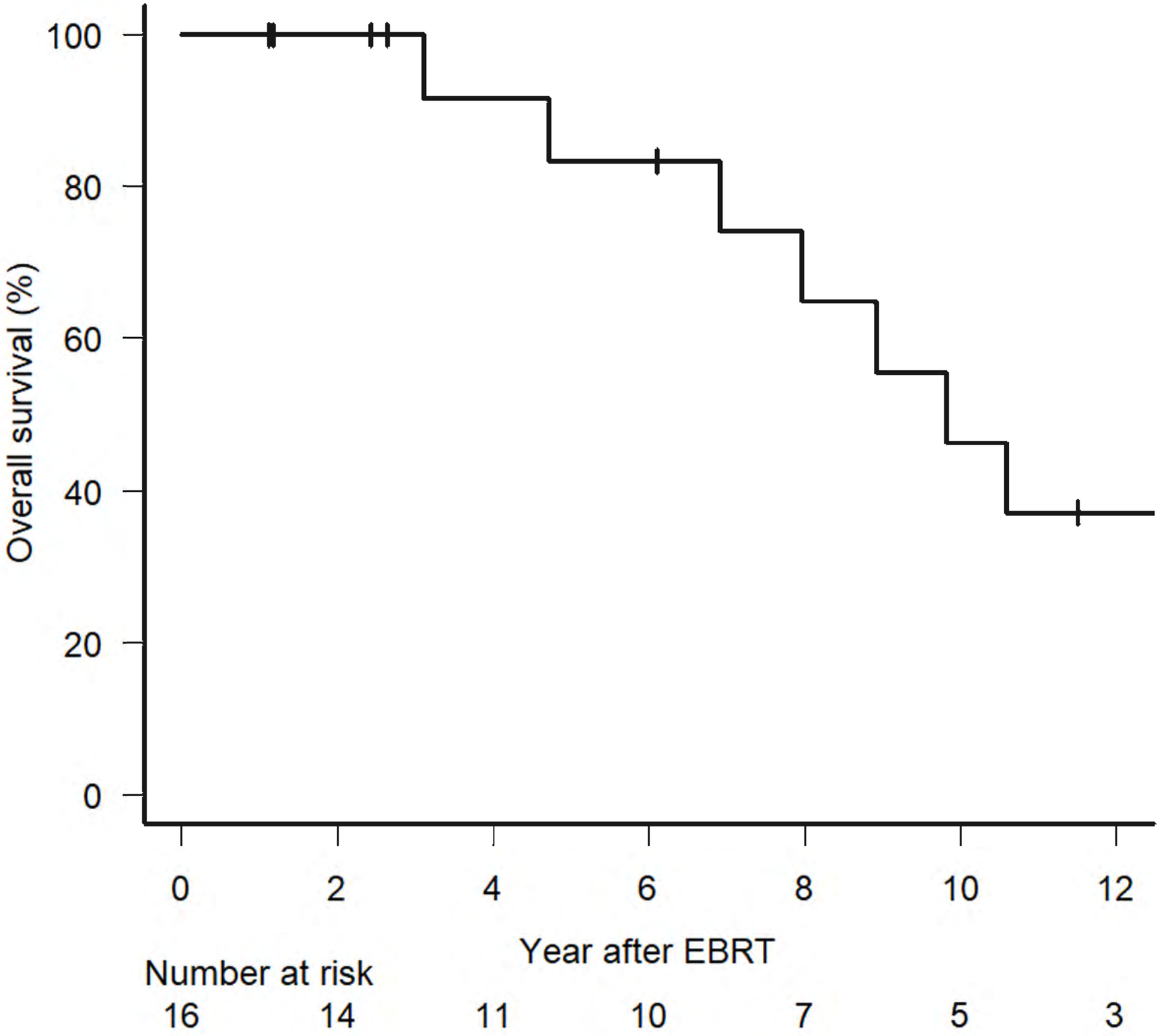
Table 3. Comparison of patient characteristics between the experimental cohort and the control cohort.

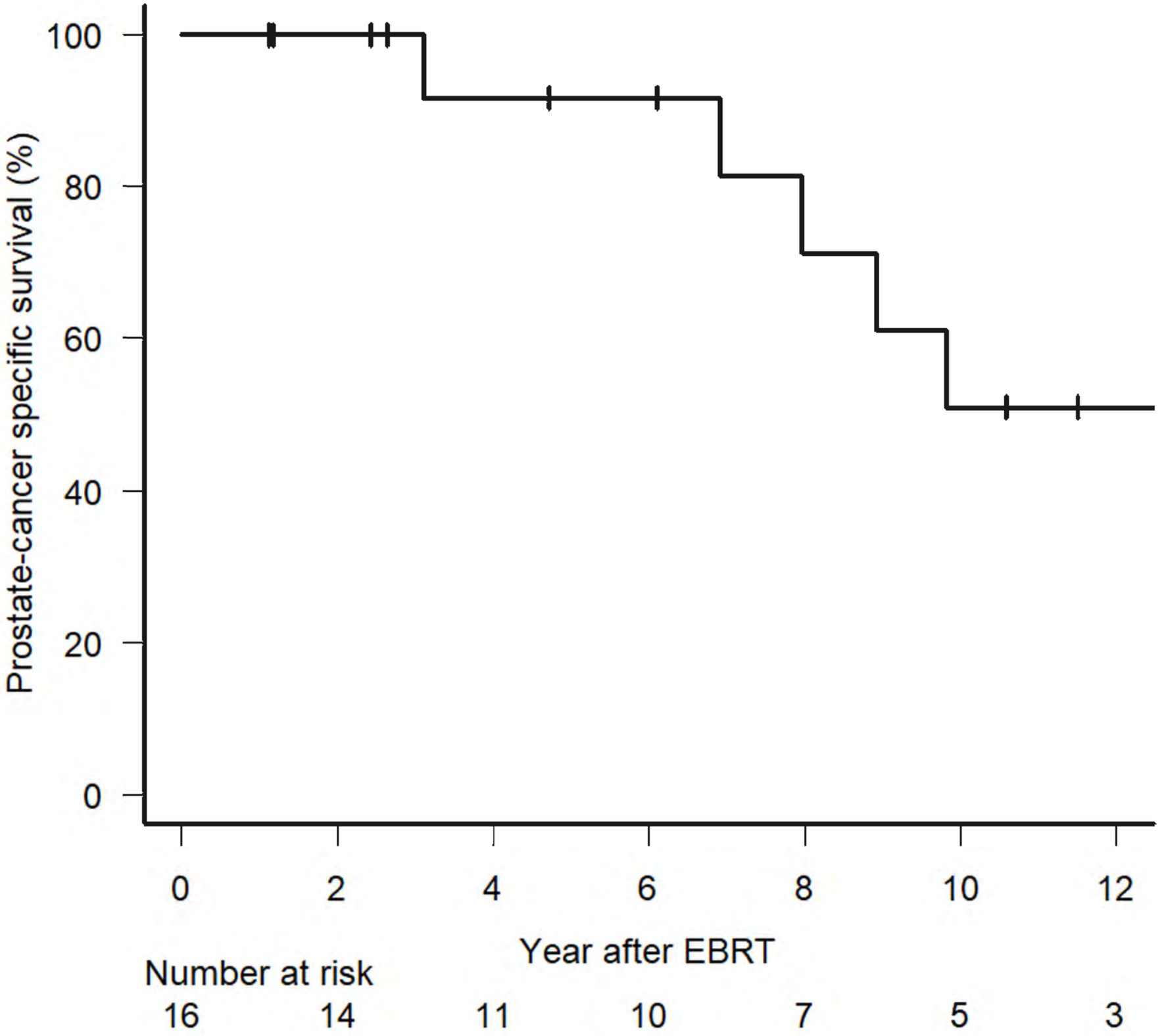
	Experimental cohort (n = 16)	Control cohort (n = 55)	*p* value
Age at initiation of primary ADT (years)			
Median (range)	63 (49–74)	71 (52–90)	0.00103
T stage, n (%)			0.932*
T1c–3a	6 (37.5)	21 (38.2)	
T3b–4	10 (62.5)	28 (50.9)	
not available	0 (0)	6 (10.9)	
N stage, n (%)			0.441*
N0	9 (56.2)	21 (38.2)	
N1	7 (43.8)	30 (54.5)	
not available	0 (0)	4 (7.3)	
M stage, n (%)			0.877
M1a	2 (12.5)	10 (18.2)	
M1b	14 (87.5)	45 (81.8)	
iPSA (ng/mL)			
Median (range)	30.4 (5.7–547)	90.5 (6–2120)	0.125
Gleason score, n (%)			
6–8	7 (43.8)	27 (49.1)	1*
9–10	8 (50.0)	28 (50.9)	
not available	1 (6.2)	0 (0)	

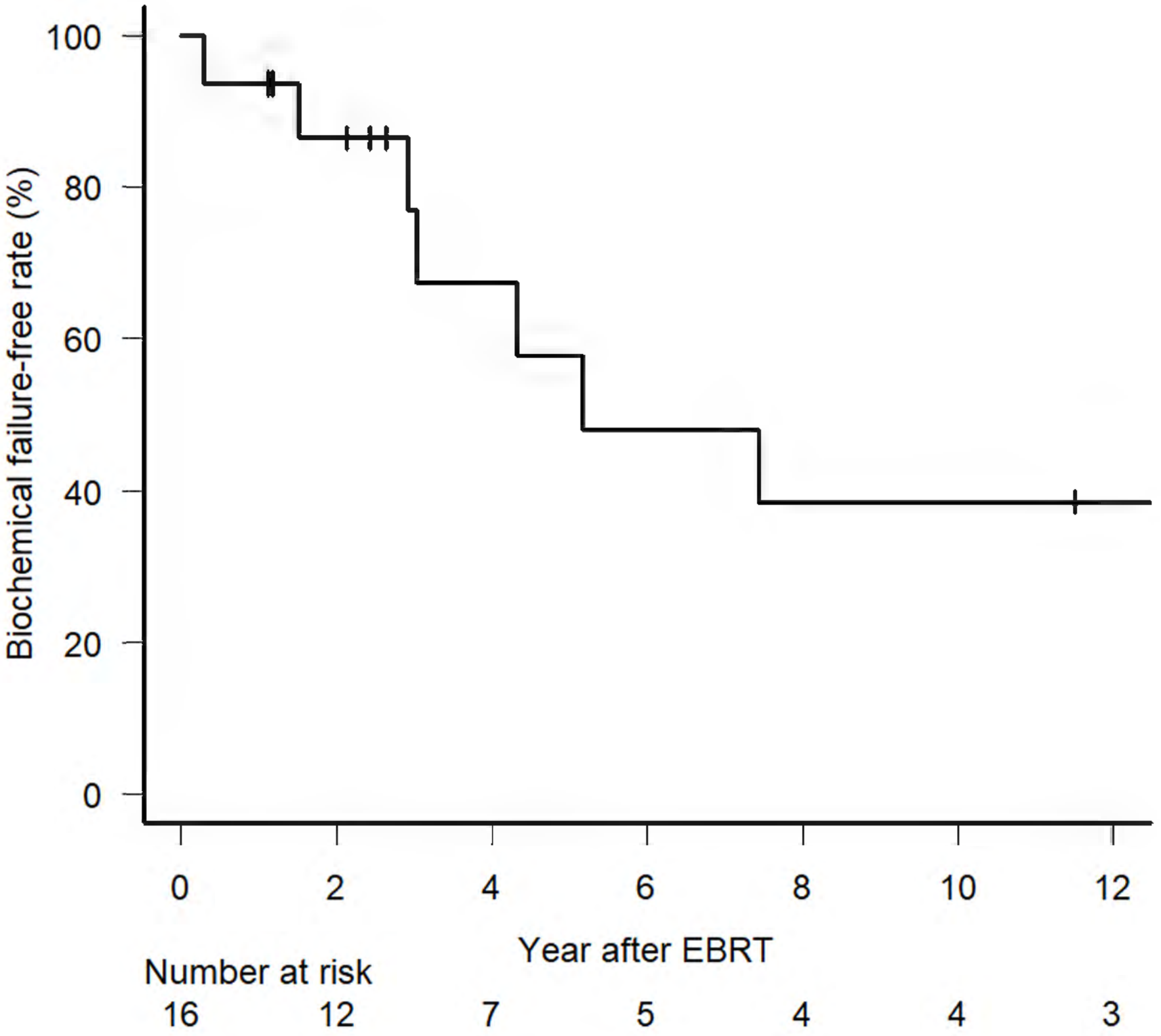
Number of distant metastasis, n (%)			
1	14 (87.5)	35 (63.6)	
2	1 (6.25)	10 (18.2)	
3	1 (6.25)	10 (18.2)	
Median (range)	1 (1–3)	1 (1–3)	0.0776
Follow-up period (from initiation of primary ADT), year			
Median (range)	8.7 (1.6–14.5)	6.9 (1.5–14.9)	0.549

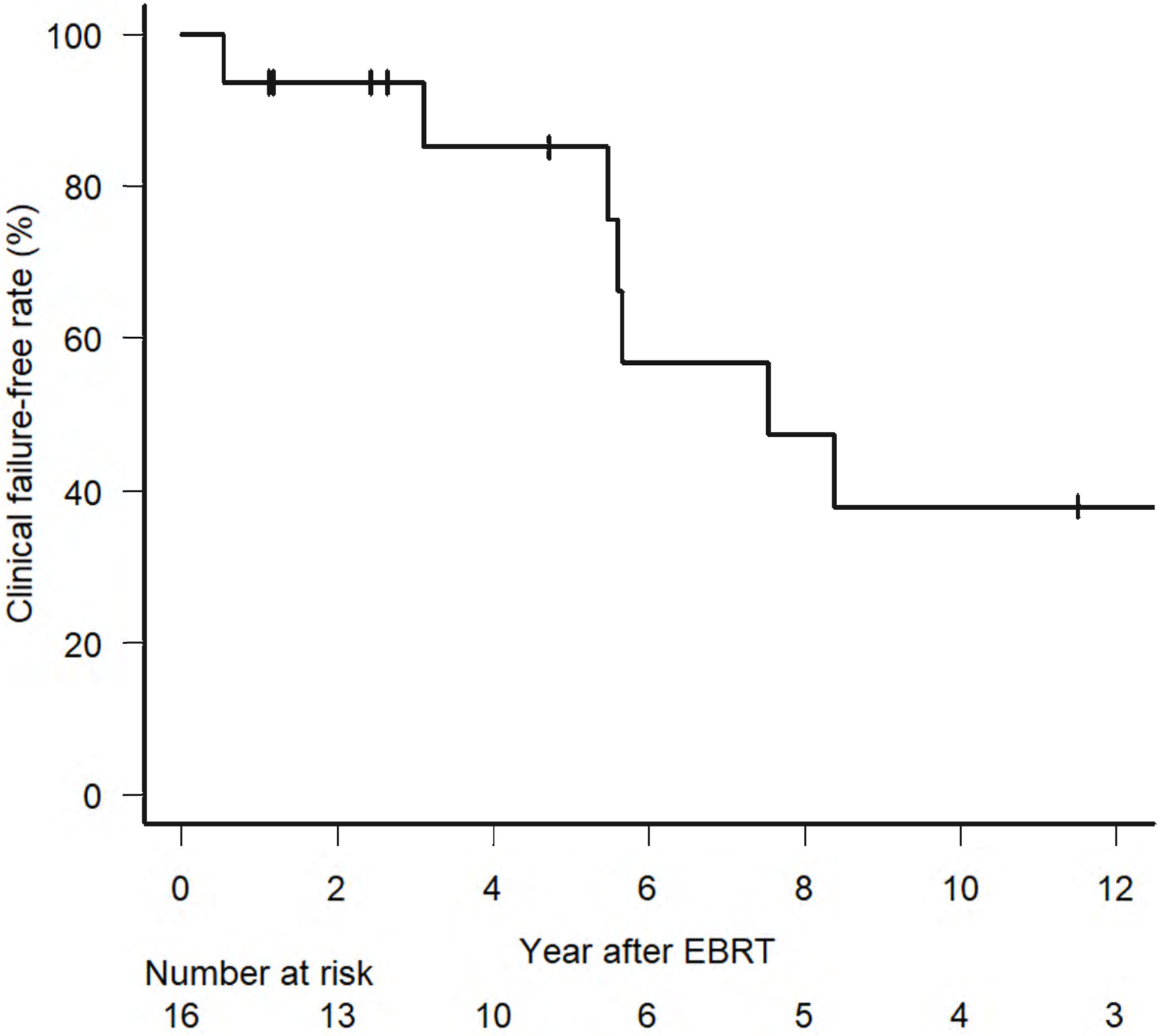
Footnote: ADT, androgen-deprivation therapy; iPSA, pretreatment prostate-specific antigen.

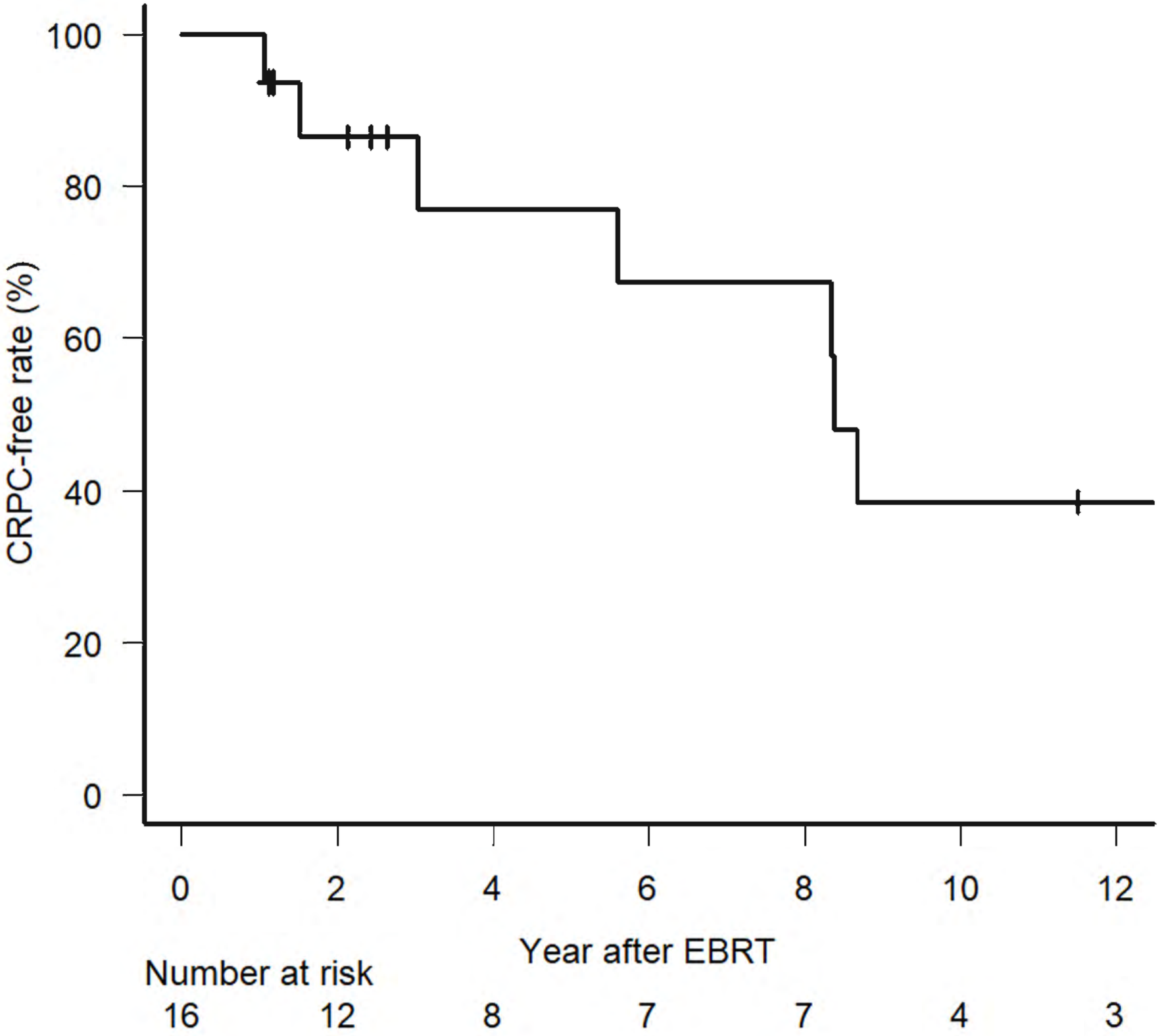
*: assessed among patients whose data was available.

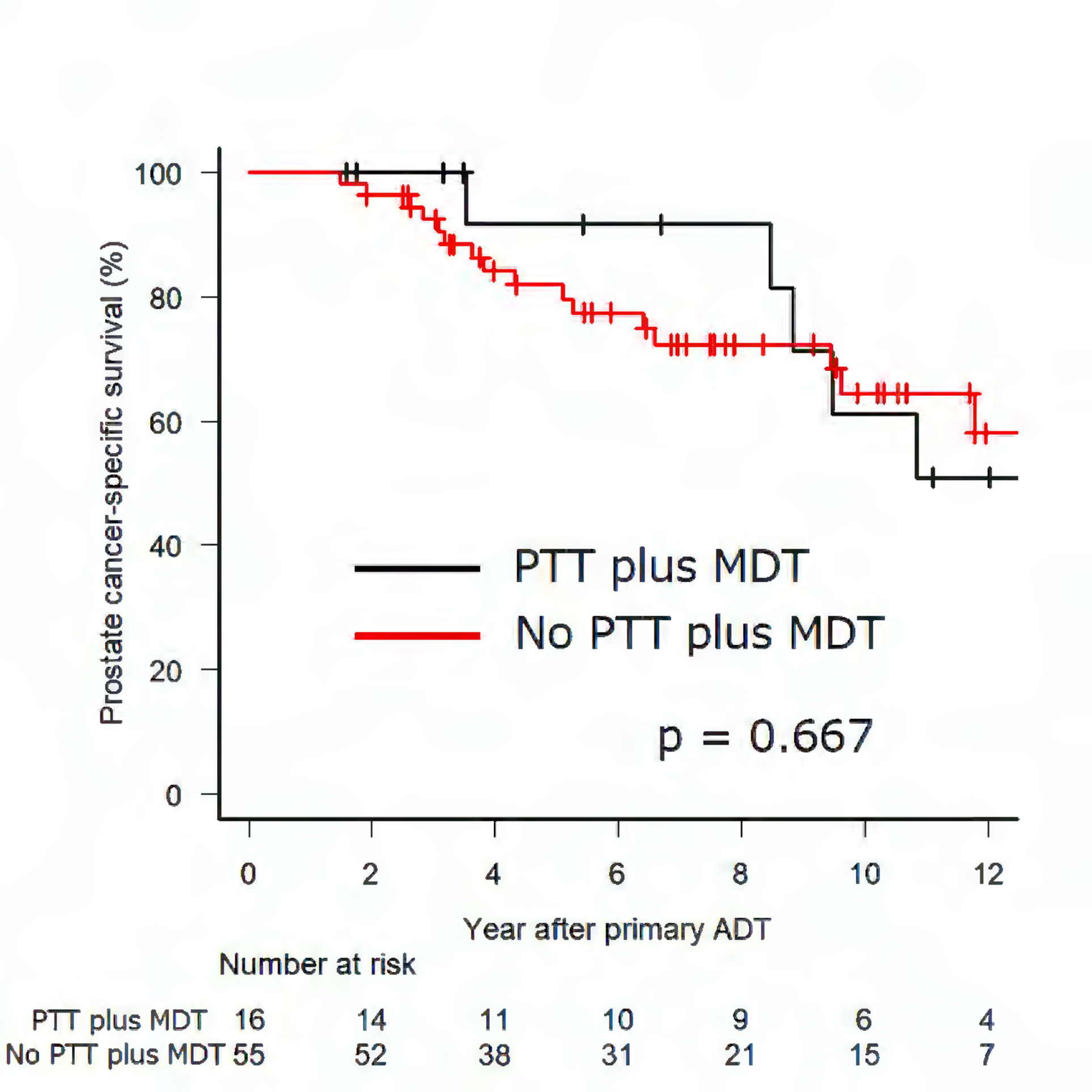

100
80
60
40
20
0
Overall survival (%)
0
2
4
6
8
10
12
Year after EBRT
Number at risk
16
14
11
10
7
5
3


Prostate-cancer specific survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Year after EBRT
Number at risk
16
14
11
10
7
5
3


Biochemical failure-free rate (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Year after EBRT
Number at risk
16
12
7
5
4
4
3

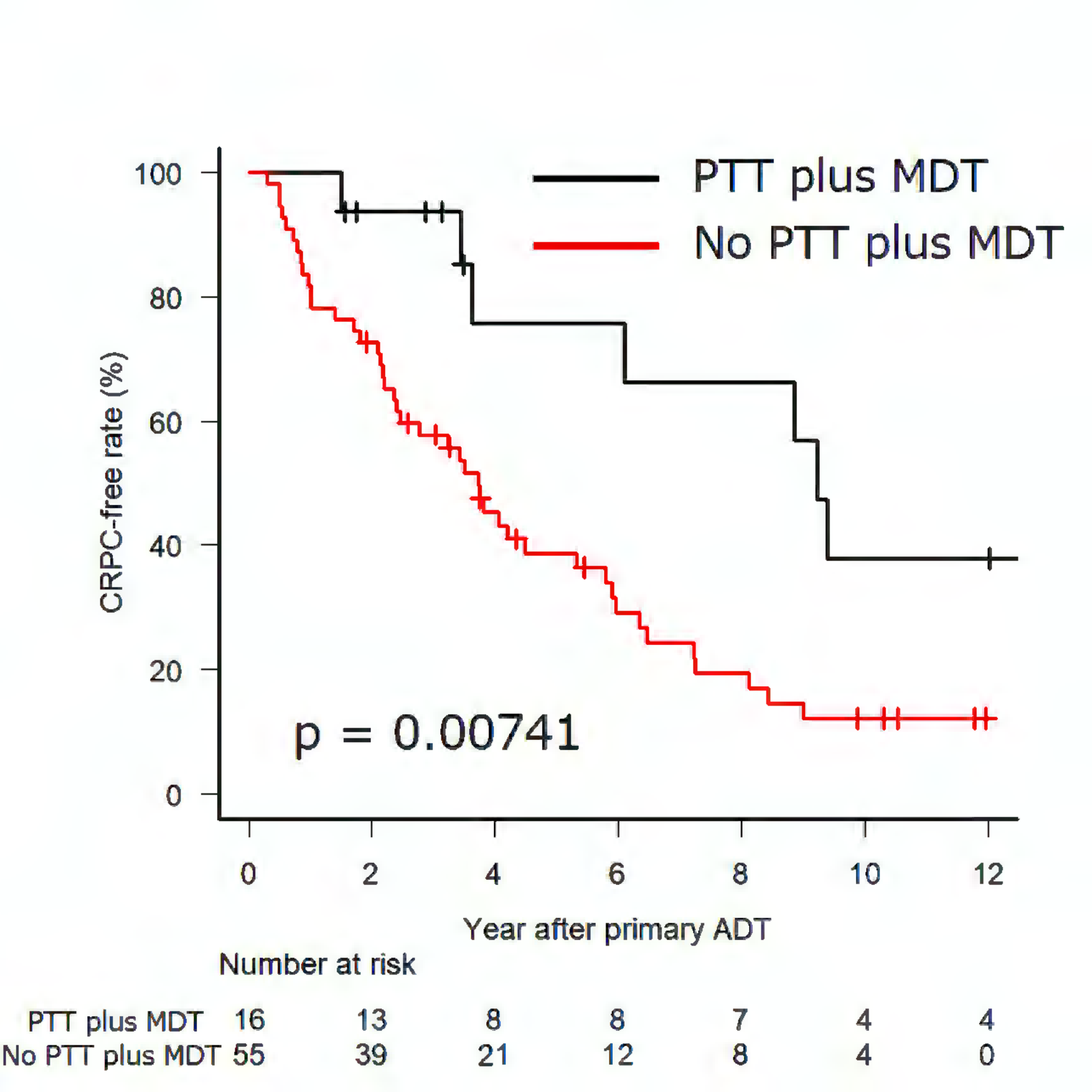

100
80
60
40
20
0
Clinical failure-free rate (%)
0
2
4
6
8
10
12
Year after EBRT
Number at risk
16
13
10
6
5
4
3


100
80
60
40
20
0
CRPC-free rate (%)
0
2
4
6
8
10
12
Year after EBRT
Number at risk
16
12
8
7
7
4
3



Number at risk

PTT plus MDT	16	14	11	10	9	6	4
No PTT plus MDT	55	52	38	31	21	15	7


PTT plus MDT
No PTT plus MDT
CRPC-free rate (%)
100
80
60
40
20
0
p = 0.00741
0
2
4
6
8
10
12
Year after primary ADT
Number at risk
PTT plus MDT 16 13 8 8 7 4 4
No PTT plus MDT 55 39 21 12 8 4 0