Long-term safety of high dose whole pelvic IMRT for high risk localized prostate cancer through 10-year follow-up

Authors:

Authors: Rihito Aizawa, M.D.[1], Kiyonao Nakamura, M.D., Ph.D.[1], Yoshiki Norihisa, M.D.[1,2], Takashi Ogata, M.D.[1], Takahiro Inoue, M.D., Ph.D.[3,4], Toshinari Yamasaki, M.D., Ph.D.[3,5], Takashi Kobayashi, M.D., Ph.D.[3], Shusuke Akamatsu, M.D., Ph.D.[3], Osamu Ogawa, M.D., Ph.D.[3], Takashi Mizowaki, M.D., Ph.D.[1]

Affiliations:

[1]: Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto-shi, Kyoto, 606-8507, Japan

[2]: Department of Radiation Oncology, Bellland General Hospital, 500-3, Higashiyama, Naka-ku, Sakai-shi, Osaka, 599-8247, Japan.

[3]: Department of Urology, Graduate School of Medicine, Kyoto University. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto-shi, Kyoto, 606-8507, Japan.

[4]: Department of Nephro-Urologic Surgery and Andrology, Mie University Graduate

School of Medicine, 2-174 Edobashi, Tsu-shi, Mie, 514-8507, Japan

[5]: Department of Urology, Kobe City Medical Center General Hospital, 2-1-1 Minatojimaminami-cho, Chuo-ku, Kobe-shi, Hyogo, 650-0047, Japan.

Corresponding author: Takashi Mizowaki, M.D., Ph.D.

Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University.

54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

Phone: +81-75-751-3762; Fax: +81-75-771-9749; E-mail: mizo@kuhp.kyoto-u.ac.jp

Short running title: WP-IMRT for high risk PCa

Abstract

Background:

The aim of this study was to evaluate the long-term efficacy and safety of whole pelvic intensity-modulated radiation therapy with a simultaneous-integrated boost (WP-SIB-IMRT) for locally advanced prostate cancer (LAPCa).

Methods:

All patients with cT3–4N0M0 prostate cancer treated with WP-SIB-IMRT between February 2006 and September 2009 at our institution were analyzed retrospectively. The prescribed dose was 78 Gy to the prostate and 58.5 Gy to the prophylactic pelvic lymph nodal area in 39 fractions delivered using the simultaneous-integrated boost technique. All patients received short-term neoadjuvant androgen-deprivation therapy alone (median: 8.3 months). Propensity-score matching (PSM) analysis was performed to evaluate the additional benefit of prophylactic whole pelvic radiation therapy (WPRT), using the cohort of 203 LAPCa patients treated with prostate-only IMRT (PO-IMRT).

Results:

In total, 47 consecutive patients were analyzed. The median estimated risk of pelvic lymph node involvement was 57.5%. The median follow-up period was 10.5 years. The 10-year prostate cancer-specific survival and biochemical failure (BF) rates were 92.2

and 54.8%, respectively. The 10-year cumulative incidence rates of ≥ grade 2 late genitourinary and gastrointestinal toxicities were 21.6 and 17.2%, respectively. From a total of 250 patients, PSM analysis identified 76 patients with similar characteristics, and no significant difference in BF rates was observed between WP-SIB-IMRT and PO-IMRT cohorts (p=0.261).

Conclusions:

WP-SIB-IMRT for LAPCa was safe over long-term observation, although no clear benefit of WPRT was observed among our small and highly selected cohort. Regarding the additional efficacy of WPRT, further investigations are needed.

Key words

Prostate cancer, unfavorable risk, intensity-modulated radiation therapy, whole pelvic radiation therapy.

Introduction

Definitive external-beam radiation therapy (EBRT) is one of the major treatment modalities for locally advanced prostate cancer (PCa) [1]. In theory, prophylactic whole pelvic radiation therapy (WPRT) improves outcomes by sterilizing the pelvic lymph nodal area (PeLNA). However, three phase 3 randomized controlled trials comparing WPRT with prostate-only radiation therapy (PORT) demonstrated no survival benefits of prophylactic WPRT for nonmetastatic PCa (RTOG7704, GETUG-01, and NRG/RTOG9413) [2-4]. Therefore, the clinical significance of prophylactic WPRT for high-risk PCa remains controversial.

As most previous studies comparing WPRT and PORT used traditional three-dimensional radiotherapy (3D-CRT), the results may be influenced by lower doses to the prostate and inadequate coverage of PeLNA [5]. With the advent of intensity-modulated radiation therapy (IMRT), a higher radiation dose can be safely delivered both to the prostate and PeLNA by selectively sparing a significant volume of the rectum and bowels from high-dose radiation exposure. However, although favorable outcomes have been reported with regard to medium-term results [6-12], reports on 10-year clinical outcomes of prophylactic WPRT via IMRT are sparse; only one study reported long-term clinical outcomes, with a median follow-up of 7.5 years [13].

The principal objective of this study was to evaluate the long-term efficacy and safety of whole pelvic IMRT with simultaneous-integrated boost (WP-SIB-IMRT) for locally advanced PCa (LAPCa) with an increased risk of pelvic lymph node involvement (PLNI). We also performed propensity-score matching (PSM) analysis to compare clinical outcomes with those of prostate-only IMRT (PO-IMRT).

Materials and Methods:

This study followed the tenets of the Helsinki Declaration, with approval from the institutional ethics committee (approval number: R1048). Written informed consent was obtained from all patients.

Patients

To improve the clinical outcomes of LAPCa patients with a high risk of PLNI, we selectively applied WP-SIB-IMRT for such patients between February 2006 and September 2009. Initially, the treatment regimen was only applied to patients with a PSA level ≥ 30 ng/mL and Gleason score (GS) ≥ 7. After 2008, application of WP-SIB-IMRT was extended to all LAPCa patients without severe comorbidities. However, due to institutional limitations on IMRT capacity, we could not apply it to all patients, and the indication of WP-SIB-IMRT was generally determined by each physician's judgement in consideration of the aggressiveness of the disease in each case.

To assess the clinical outcomes of WP-SIB-IMRT for LAPCa, we retrospectively reviewed medical records of LAPCa patients who consecutively received WP-SIB-IMRT during this period at our institution. Patients were included if they had cT3–4N0M0 PCa with histological confirmation of adenocarcinoma of the prostate and received WP-SIB-

IMRT. Patients who irregularly received long-term neoadjuvant androgen-deprivation therapy (ADT) (cut-off: 1.5 years) were excluded. Initial evaluations included needle biopsies, digital rectal examinations, transrectal ultrasonography, computed tomography (CT), magnetic-resonance imaging (MRI), and bone scintigraphy. All pathological specimens were re-evaluated at our institution. The Roach equation was used to calculate the risk of PLNI [14].

Androgen-deprivation therapy

We previously reported the details of our institutional treatment protocol regarding combining ADT [15]. Neoadjuvant ADT (NA-ADT), in principle, comprised 6 months of combined androgen blockage (CAB), including minor variations regarding the duration. In the current study, patients who exceptionally received long-term NA-ADT were excluded (e.g., due to delayed introduction to our department), as described in the eligibility criteria (cut-off: 1.5 years). No adjuvant ADT (A-ADT) was applied. Instead, salvage ADT (S-ADT) was initiated in an early phase after recurrence (prostate-specific antigen [PSA] >4.0 ng/mL, or clinical failure [CF]), which basically consisted of continuous/intermittent CAB, luteinizing hormone-releasing hormone analogue

monotherapy, or antiandrogenic agent monotherapy. No androgen receptor axis targeted agent or chemotherapy were used in a castration-sensitive setting.

Intensity-modulated radiation therapy

The clinical target volume (CTV) comprised two parts: the prostate and seminal vesicles (CTV_PSV) and PeLNA (CTV_LN). CTV_PSV included the prostate and proximal two-thirds of seminal vesicles for non-T3b cases and whole structures for T3b cases. CTV_LN was set distal to the aortic bifurcation, and delineated using a vascular expansion technique (+7 mm), to include the common/external/internal iliac and obturator lymph nodal regions. The planning target volume (PTV) for CTV_PSV (PTV_PSV; universal 8–9-mm margins, except for a 6-mm margin to the rectum side) and CTV_LN (PTV_LN; a universal 5-mm margin) were created to account for organ motion and set-up uncertainties. The prescribed doses were 78 Gy at 2 Gy per fraction (Gy/fr) for PTV_PSV and 58.5 Gy at 1.5 Gy/fr for PTV_LN (equal to 50.1 Gy at 2 Gy/fr with α/β =1.5 Gy), delivered using the simultaneous integrated boost technique. The prescribed doses were defined as the mean dose of the PTV_PSV (D mean) and the dose covering 90% volume of PTV_LN (D90), respectively. The total dose was reduced by 2 fractions in patients with risk factors for rectal bleeding, such as an advanced age (≥80

years), receiving anticoagulant/antiplatelet therapy, and severe diabetes mellitus. Set-up error correction was performed based on the pelvic bone structure.

Patient follow-up

Details of the follow-up schedule was previously described [15]. Patients were followed every 1–3 months during the first 2 years and every 3–6 months thereafter. No additional radiographic study after IMRT was required, unless an increase in the PSA level or symptoms suggesting CF were observed.

Statistical analyses and propensity matching

Time zero was defined as the date of IMRT initiation. The Kaplan–Meier method was used to assess overall survival (OS) and PCa-specific survival (PCSS), and the cumulative incidence method accounting for death without each event being a competing risk was used to assess biochemical failure (BF), CF, castration-resistant PCa (CRPC), and S-ADT induction rates. Patients lost to follow-up receiving best supportive care due to disease progression were categorized as “death from PCa” at the time of the last visit. BF was evaluated based on the Phoenix definition [16]. A PSA increase > 2.0 ng/mL above the nadir, including the testosterone recovery phase, was judged as a BF event. CF

was defined as a recurrent disease confirmed via radiographic studies with or without symptoms. CRPC was defined as the earliest timing of the following: *(1)* PSA increase of 25% from the nadir and a minimum 2.0 ng/mL under castration levels of testosterone (<50 ng/dL) tested at a minimum of 1-week intervals, or during ADT (if testosterone levels were not assessed with appropriate timing); *(2)* change in the contents of salvage ADT due to disease progression; or *(3)* CF during salvage therapy.

Acute (within the first 90 days after initiating IMRT) and late genitourinary (GU) and gastrointestinal (GI) toxicities were evaluated based on the Common Terminology Criteria for Adverse Events version 4.0. Cumulative incidence rates of late GU and GI toxicities were calculated accounting for death without each event being a competing risk. Urinary frequency, incontinence, and urgency were excluded from the calculation of cumulative incidence rates of late GU toxicities because these symptoms also occur due to aging, and so may confound the evaluation of true radiation-induced GU toxicities.

In addition, we performed PSM analysis to compare oncological outcomes of WP-SIB-IMRT with PO-IMRT. As a comparative control, we selected 203 patients who consecutively received high-dose PO-IMRT (≥74 Gy) for cT3–4N0M0 PCa combined with short-term NA-ADT alone between September 2000 and May 2011 at our institution. The details of patient and treatment characteristics are summarized in Table 1, and

treatment details were also previously reported [15]. Chi-square analysis, the Mann-Whitney U test, or Student's t-test was used to compare patient and treatment characteristics, and the incidence of pelvic lymph node recurrence. PSM was performed to create balanced comparable cohorts of patients receiving WP-SIB-IMRT and PO-IMRT, whose propensity score was calculated based on the following reported predictive factors for disease progression: pretreatment PSA (iPSA), clinical T stage (T3b–4 vs. T3a), Gleason score (GS) sum (≥9 vs. ≤8), number of cores with a GS sum of 8–10 (≥5 vs. ≤4), duration of NA-ADT, and age at the initiation of IMRT (≤70 vs. ≥71 years old) [17]. A one-to-one nearest-neighbor matching method was used, with a caliper width of 0.2 [18]. The univariate analysis (UVA) (Log rank or Gray test) was performed to assess differences, and a p-value <0.05 denoted significance.

All statistical analyses were performed using EZR version 1.41 [19], which is a graphical user interface for R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results:

Patient and treatment characteristics

Fifty-one patients met the eligibility criteria. Among them, three patients had developed CRPC during NA-ADT, and one patient had irregularly received A-ADT following the completion of WP-SIB-IMRT. These patients were excluded, and the remaining 47 patients were included in the analysis.

The median patient age was 67 (interquartile range [IQR]: 62–71) years at the initiation of WP-SIB-IMRT. The median iPSA level was 57.9 (IQR: 34.6–87.6) ng/mL. More than half of the patients (n=24) had ≥T3b disease, and approximately 40% of the patients (n=18) had a GS sum ≥9. Therefore, approximately one-third (n=16) and two-thirds (n=31) of the patients were categorized into high-risk and very high-risk groups according to the National Comprehensive Cancer Network risk classification (version 2, 2019) [1], respectively. Their risk of PLNI was estimated as 57.5 (IQR: 45.6–77.5) %.

All patients received NA-ADT consisting of CAB with a median duration of 8.3 (IQR: 7.6–10.2) months. For WP-SIB-IMRT, the full dose was prescribed to 87.2% (n=41), whereas the reduced dose was prescribed to 12.8% (n=6).

The details of patient and treatment characteristics are summarized in Table 1.

Survival and oncological outcomes

The median follow-up period was 10.5 (IQR: 9.4–11.3) years. During follow-up, there were seven deaths: four due to PCa, and three from other causes. PCSS rates at 5 and 10 years were 100% (95% confidence interval [CI]: not available [N/A]–N/A) and 92.2% (95% CI:77.6–97.4), respectively (Figure 1A). During follow-up, 51.1% (n=24), 25.5% (n=12), and 19.1% (n=9) developed BF, CF, and CRPC, with a median period of 4.2 (IQR: 2.4–6.3), 5.1 (IQR: 4.5–6.7), and 6.1 (IQR: 3.9–8.4) years after WP-SIB-IMRT, respectively. Of the 24 patients who developed BF, 25% (n=6) developed BF within 2 years after WP-SIB-IMRT (early recurrence). S-ADT was initiated in all 24 patients with BF, with a median period of 4.9 (IQR: 2.8–8.1) years after WP-SIB-IMRT. The cumulative incidence rates of BF at 5 and 10 years were 32.6% (95% CI: 19.5–46.4) and 54.8% (95% CI: 38.4–68.6), respectively (Figure 1B). The initial sites of CF were the pelvic bones in 25% (n=3), other bones in 58.3% (n=7), the prostate and bone (fifth lumbar vertebra) in 8.3% (n=1), and mediastinal lymph nodes in 8.3% (n=1). Only one patient developed pelvic lymph node recurrence during follow-up (pelvic regional control rate: 97.9%). The rates of survival and oncological outcomes are summarized in Table 2.

Toxicities

Details of acute and late toxicities (≥ grade 2) are summarized in Table 3.

Acute toxicities mostly comprised grade 1–2 urinary frequency or retention for GU toxicities, and grade 1–2 anal pain or rectal hemorrhage for GI toxicities, resolved spontaneously or with medication. No grade 3–4 acute GU or GI toxicities were observed.

During follow-up, grade 2–3 late GU toxicities were noted in 42.6% (n=20): grade 2 urinary frequency in 12.8% (n=6), both urgency and incontinence in 2.1% (n=1), grade 2 urinary retention in 21.3% (n=10), and grade 2–3 hematuria in 6.4% (n=2 for grade 2, n=1 for grade 3). The cumulative incidence rates of grade ≥ 2 late GU toxicities (except for urinary frequency, urgency, and incontinence) were 17.0% (95% CI: 7.9–29.1) at 5 years and 21.6% (95% CI: 11.0–34.4) at 10 years, respectively (Figure 1C). No grade ≥4 late GU toxicities were observed. During follow-up, grade ≥2 late GI toxicities were noted in 21.3% (n=10): grade 2 rectal hemorrhage in 17.0% (n=8), proctitis in 2.1% (n=1), and grade 4 ileus (sigmoid volvulus requiring surgery) in 2.1% (n=1). The cumulative incidence rate of grade ≥ 2 late GI toxicities was 17.2% (95% CI: 8.0–29.4) at 5 years and it remained unchanged at 10 years (Figure 1C). No grade 5 late GI toxicities were observed.

On comparison of WP-SIB-IMRT with PO-IMRT, no significant differences

were observed regarding late GU (p=0.398) and GI (p=0.296) toxicities (Figure 2A–B).

Propensity-score matching analysis

From the total of 250 patients (WP-SIB-IMRT: 47, PO-IMRT; 203), PSM identified 76 patients (38 patients from each cohorts) with similar baseline characteristics (Table 1). No significant differences in pretreatment characteristics were observed between the two cohorts. The median follow-up periods for the whole matched cohort, WP-SIB-IMRT matched cohort, and PO-IMRT matched cohort were 10.4 (IQR: 8.8–11.6), 10.6 (IQR: 9.3–11.5), and 10.0 (IQR: 7.3–11.5) years, respectively. The 10-year cumulative incidence rates of BF were 53.7% (95% CI: 35.3–68.9) in the matched WP-SIB-IMRT cohort and 68.6% (95% CI: 46.2–83.2) in the matched PO-IMRT cohort (p=0.872) (Figure 3A–B). No significant differences were observed between the two cohorts. During the follow-up, CF was observed in 26.3% (n=10) in the matched WP-SIB-IMRT cohort and 23.7% (n=9) in the matched PO-IMRT cohort. The initial sites of CF of the matched WP-SIB-MRT cohort were the pelvic bones in 20% (n=2), other bones in 60% (n=6), prostate and bone (fifth lumbar vertebra) in 10% (n=1), and mediastinal lymph nodes in 10% (n=1). The initial sites of CF of the matched PO-IMRT cohort were the pelvic bones in 11.1% (n=1), other bones in 22.2% (n=2), prostate in 11.1% (n=1),

prostate and bones in 11.1% (n=1), para-aortic lymph nodes in 11.1% (n=1), lung metastasis in 11.1% (n=1), and pelvic lymph nodes in 22.2% (n=2). During the follow-up, pelvic lymph node recurrence occurred in 2.6% (n=1) in the matched WP-SIB-IMRT cohort, and 7.9% (n=3) in the matched PO-IMRT cohort. No significant difference was observed in the incidence of pelvic lymph node recurrence (p= 0.607). ~~Comparisons of the cumulative incidence of BF are provided in Figure 3A, B, and~~ Comparisons of survival and oncological outcomes are summarized in Table 2.

Discussion:

Herein, we present the 10-year clinical outcomes of WP-SIB-IMRT for LAPCa based on a single institutional experience. WP-SIB-IMRT was safe and well-tolerated, leading to excellent survival outcomes despite the highly unfavorable risk profile of PCa (PCSS rate at 10 years: 92.2%). To the best of our knowledge, the current study involved the longest reported follow-up period of WPRT via IMRT (median: 10.5 years).

Regarding the dose fractionation scheme of WP-SIB-IMRT, two strategies have been applied: hypofractionation versus conventional fractionation to the prostate. In the former strategy, the prostate is irradiated via moderate hypofractionation with a fraction size generally between 2.55 and 2.72 Gy/fr, in combination with WPRT via conventional fractionation (e.g., 1.8–2Gy/fr) [6-9,20]. This fractionation has been commonly used in contemporary investigational studies. In contrast, in the latter strategy, the prostate is irradiated with a conventional fraction (e.g., 2–2.25 Gy/fr) in combination with WPRT with a smaller fraction size (e.g., 1.5–1.62 Gy/fr), which has been less commonly investigated [12,10]. We adopted the latter strategy in order to compare the clinical outcomes with those of our PO-IMRT approach using a conventional fraction [15]. As the results of comparison, no significant increase of late GI and intractable GU toxicities was observed (Fig. 2A–B). In addition, pelvic regional

control was considered excellent (97.9%), despite the use of the smaller fractional dose (1.5 Gy/fr to 58.5 Gy in total, equal to 50.1 Gy at 2 Gy/fr with α/β =1.5 Gy). It was thus considered that the escalated total dose may compensate for the smaller fractional dose in terms of pelvic regional control.

In our PSM analysis, no significant differences in disease control, including regional control, were observed between the two matched cohorts (Table 2). However, these results should be interpreted with caution given the small sample size for PSM analysis (n=76/250), and our findings, therefore, cannot be used to draw a definitive conclusion regarding the additional effect of prophylactic WPRT on disease control. In addition to this limitation, we propose two hypotheses to explain our negative results.

One hypothesis is that the existence of undetectable metastases outside the pelvis reduced the effect of prophylactic WPRT, given the highly advanced nature of disease in our cohort (median PLNI: 57.5%). Approximately one-eighth of our cohort (n=6/47) had developed disease progression in a very early phase (< 2 years). In addition, two-thirds of initial CF sites were located outside the irradiation field (n=8/12). These results suggest the possibility that a certain number of our patients already had undetected metastases outside the pelvis at the initial diagnosis, for whom the benefit of prophylactic WPRT may be modest. For populations at high risk of harboring distant metastases, current

advances in imaging modalities, such as prostate-specific membrane antigen positron emission tomography/CT (PSMA-PET/CT), may be of use to detect truly regionally localized cases [21,22]. According to the POP-RT trial comparing WPRT (n=110) and PORT (n=114) for high-risk and very high-risk PCa (median PLNI: 37.8%) in which PSMA-PET/CT was used in approximately 80% of the patients for staging, WPRT significantly improved the BF-free survival rate (95.0 vs. 81.2% at 5 years, respectively, hazard ratio [HR] 0.23, 95% CI 0.1–0.52, $p<0.0001$) [11]. On the other hand, for a population with a relatively lower risk of harboring distant metastases, optimizing regional control via WPRT may lead to improved disease control. Currently, the NRG/RTOG 0924 trial (NCT01368588) is on-going to assess the benefit of prophylactic WPRT mainly among intermediate- to high-risk nonmetastatic PCa patients. The optimal candidates for prophylactic WPRT need to be further explored.

The other hypothesis was that the cumulative dose of 78Gy at 2 Gy/fr to the prostate was insufficient to achieve optimal control of the primary site. Suboptimal local control may have masked potential benefits of prophylactic WPRT. In this regard, it has been attempted to increase the local dose using brachytherapy boost to the prostate, in order to evaluate the effect of prophylactic WPRT without being interrupted by local relapse [23,24]. According to a prospective cohort trial comparing WPRT (n=401) and

PORT (n=411) for non-metastatic PCa (intermediate-risk: 21%, high-risk; 79%) in combination with high-dose-rate brachytherapy (HDR-BT) boost to the prostate, WPRT significantly improved the BF-free survival rate (89 vs. 81% at 5 years, respectively, HR 1.714, 95% CI 1.156–2.542, p=0.007) [23]. Similarly, on subgroup analysis of a multi-institutional retrospective study of 1,170 patients with biopsy-proven GS 9–10 PCa, WPRT was correlated with significantly improved BF-free survival among patients who received EBRT+ brachytherapy (HR 0.5, 95% CI 0.2–0.9, p=0.02), but not among patients receiving EBRT alone (HR 0.8, 95% CI 0.6–1.2, p=0.4) [24]. These results suggest that prophylactic WPRT would be effective if a highly escalated dose is delivered to the prostate. In our study, we could not rule out the possibility that undetected local relapse may have masked the effect of prophylactic WPRT, because evaluation of local sites via MRI or re-biopsy at the time of BF was not routinely performed. Currently, the PIVOTALboost trial (ISRCTN80146950) is on-going to assess the additional effect of WPRT over PORT in combination with or without boost to intraprostatic dominant lesions via HDR-BT or IMRT. Our hypothesis will be examined based on the results of that study.

Our study has several limitations. Firstly, this was a retrospective study utilizing a small cohort. Secondly, WP-SIB-IMRT was applied to selected patients

among our LAPCa cases, because we could not apply WP-SIB-IMRT to all LAPCa patients due to limitations of the institutional capacity. The indication of WP-SIB-IMRT was basically determined by the physician's judgement in consideration of the aggressiveness of the disease in each case. Therefore, the presence of a selection bias should be considered. In the current study, PSM analysis was employed to reduce the effect of this selection bias in the comparison of oncological outcomes. Thirdly, the high incidence of BF due to the absence of A-ADT may hamper evaluation of the true benefit of prophylactic WPRT in a biochemical control. Therefore, our findings regarding the clinical value of prophylactic WPRT are merely hypothetical. Nevertheless, we believe our data would serve as benchmark data of WPRT via IMRT for locally advanced prostate cancer with multiple unfavorable risks, which would merit further investigation in prospective trials, because the present study described long-term outcomes treated under a predetermined uniform treatment policy.

In conclusion, WP-SIB-IMRT was safe and well-tolerated over the periods of long-term observation. However, in the current study, the oncological benefits of prophylactic WPRT among LAPCa patients with an unfavorable risk profile remained unclear. Therefore, it should be further investigated, especially in terms of the optimal candidates and local dose.

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Tables:

Table 1. Patients and treatment characteristics of the entire and matched cohorts.

Table 2. Oncological and survival outcomes of the entire and matched cohorts.

Table 3. Summary of grade ≥ 2 acute/late genitourinary and gastrointestinal toxicities, graded based on the Common Terminology Criteria for Adverse Events version 4.0.

Figure legends:

Figure 1. Kaplan–Meier curves of overall and prostate-cancer-specific survival (A), and cumulative incidence curves of biochemical failure, clinical failure, and castration-resistant prostate cancer (B). Cumulative incidence curves of grade ≥ 2 late genitourinary and gastrointestinal toxicities (C). OS, overall survival; PCSS, prostate cancer-specific survival; BF, biochemical failure; CF, clinical failure; CRPC, castration-resistant prostate cancer; GU, genitourinary; GI, gastrointestinal.

Figure 2. Cumulative incidence curves of grade ≥ 2 late genitourinary toxicities (except urinary frequency, incontinence, and urgency) (A) and gastrointestinal toxicities (B) among the entire cohort. WP-SIB-IMRT, whole pelvic intensity-modulated radiation therapy with simultaneous-integrated boost; PO-IMRT, prostate-only intensity-modulated radiation therapy.

Figure 3. Cumulative incidence curves of biochemical failure among the entire (A) and matched (B) cohort. WP-SIB-IMRT, whole pelvic intensity-modulated radiation therapy with simultaneous-integrated boost; PO-IMRT, prostate-only intensity-modulated radiation therapy.

Table 1. Patients and treatment characteristics of the entire and matched cohorts.

	Entire cohort				Propensity score matched cohort			
	WP-SIB-IMRT (n=47)	PO-IMRT (n=203)	total (n=250)	*p* value	WP-SIB-IMRT (n=38)	PO-IMRT (n=38)	total (n=76)	*p* value
Clinical characteristic								
Age								
Median (IQR), year-old	67 (62–71)	70 (65–75)	70 (64–74)	0.002	67 (61–71)	67 (63–70)	67 (62–71)	0.925
≤70, n (%)	32 (68.1)	102 (50.2)	134 (53.6)	0.041	12 (31.6)	9 (23.7)	21 (27.6)	0.608
≥71, n (%)	15 (31.9)	101 (49.8)	116 (46.4)		26 (68.4)	29 (76.3)	55 (72.4)	
T stage, n (%)				0.003				0.818
T3a	23 (48.9)	148 (72.9)	171 (68.4)		22 (57.9)	20 (52.6)	42 (55.3)	
T3b–4	24 (51.1)	55 (27.1)	79 (31.6)		16 (42.1)	18 (47.4)	34 (44.7)	
T3a:T3b:T4, n	23:21:3	148:49:6	171:70:9		22:13:3	20:15:3	42:28:6	
Combined GS, n (%)				0.015				0.805
6–8	29 (61.7)	162 (79.8)	191 (76.4)		25 (65.8)	27 (71.1)	52 (68.4)	
9–10	18 (38.3)	41 (20.2)	59 (23.6)		13 (34.2)	11 (28.9)	24 (31.6)	
6:7:8:9:10, n	0:12:17:18:0	10:96:56:38:3	10:108:73:56:3		0:10:15:13:0	0:15:12:11:0	0:25:27:24:0	
iPSA, ng/mL				<0.001				0.119
Median (IQR)	57.9 (34.6–87.6)	22.9 (14.3–45.2)	27.1 (15.8–57.5)		44.5 (32.0–71.3)	30.9 (17.6–79.9)	36.7 (21.7–72.9)	
cores with GS 8–10, n (%)				0.722				0.767
≤4	37 (78.7)	167 (82.3)	204 (81.6)		32 (84.2)	30 (78.9)	62 (81.6)	
≥5	10 (21.3)	36 (17.7)	46 (18.4)		6 (15.8)	8 (21.1)	14 (18.4)	

NCCN classification, n (%)				0.001				0.818
High-risk	16 (34.0)	125 (61.6)	141 (56.4)		16 (42.1)	18 (47.4)	34 (44.7)	
Very high-risk	31 (66.0)	78 (38.4)	109 (43.6)		22 (57.9)	20 (52.6)	42 (55.3)	
PLNI proportion				<0.001				0.128
Median (IQR)	57.5 (45.6–77.5)	36.5 (22.6–49.3)	40.1 (24.4–55.2)		54.1 (43.2–70.2)	42.6 (30.7–73.2)	46.9 (34.5–70.9)	
Duration of NA-ADT, month				<0.001				0.547
Median (IQR)	8.3 (7.6–10.2)	6.2 (4.9–8.1)	6.9 (5.0–8.5)		8.0 (7.2–9.9)	7.6 (6.5–11.0)	7.9 (6.8–10.4)	
A-ADT	Not applied	Not applied	Not applied		–	–	–	
PSA at S-ADT, ng/mL				0.148				0.429
Median (IQR)	4.5 (3.9–5.2)	5.2 (4.2–6.4)	5.0 (4.1–6.4)		4.5 (3.7–5.3)	4.9 (3.9–6.2)	4.6 (3.8–6.2)	
IMRT dose, n (%)								
To the prostate				0.546				0.375
78Gy	41 (87.2)	167 (82.3)	208 (83.2)		33 (86.8)	29 (76.3)	62 (81.6)	
74Gy	6 (12.8)	36 (17.7)	42 (16.8)		5 (13.2)	9 (23.7)	14 (18.4)	
To the pelvic nodal region				–				–
58.5Gy	41 (87.2)	–			33 (86.8)	–		
55.5Gy	6 (12.8)	–			5 (13.2)	–		
Follow-up periods, year				0.411				0.201
Median (IQR)	10.5 (9.4–11.3)	10.3 (8.8–12.6)	10.4 (9.0–12.2)		10.6 (9.3–11.5)	10.0 (7.3–11.5)	10.4 (8.8–11.6)	

Foot note: WP-SIB-IMRT, whole pelvic intensity-modulated radiation therapy with simultaneous-integrated boost; PO-IMRT, prostate-only intensity-modulated radiation therapy; IQR, interquartile range; GS, Gleason score; iPSA, pre-treatment prostate-specific antigen; NCCN risk classification, the National Comprehensive Cancer Network risk classification version 2, 2019; PLNI, pelvic node involvement; NA-ADT, neoadjuvant androgen-deprivation therapy; A-ADT, adjuvant

androgen-deprivation therapy; PSA, prostate-specific antigen; S-ADT, salvage androgen-deprivation therapy; IMRT, intensity-modulated radiation therapy.

Table 2. Oncological and survival outcomes of the entire and matched cohorts.

	Entire cohort			Propensity score matched cohort		
	WP-SIB-IMRT (n=47)	PO-IMRT (n=203)	*p* value	WP-SIB-IMRT (n=38)	PO-IMRT (n=38)	*p* value
Overall survival, % (95% CI)			0.571			0.487
5-year	100.0 (N/A–N/A)	94.0 (89.7–96.5)		100.0 (N/A–N/A)	97.1 (81.4–99.6)	
10-year	85.5 (70.5–93.2)	82.2 (75.9–87.1)		84.9 (67.4–93.4)	90.8 (74.1–97.0)	
PCa-specific survival, % (95% CI)			0.573			0.585
5-year	100.0 (N/A–N/A)	97.9 (94.6–99.2)		100.0 (N/A–N/A)	97.1 (81.4–99.6)	
10-year	92.2 (77.6–97.4)	94.0 (89.0–96.8)		90.4 (73.0–96.8)	93.7 (76.8–98.4)	
Biochemical failure, % (95% CI)			0.222			0.261
5-year	32.6 (19.5–46.4)	28.3 (22.3–34.7)		32.4 (17.9–47.7)	29.7 (15.9–44.9)	
10-year	54.8 (38.4–68.6)	40.9 (33.9–47.8)		53.7 (35.3–68.9)	68.6 (46.2–83.2)	
Clinical failure, % (95% CI)			0.27			0.872
5-year	13.6 (5.4–25.4)	9.4 (5.9–14.0)		11.4 (3.5–24.4)	10.8 (3.3–23.2)	
10-year	27.9 (15.4–41.9)	18.8 (13.6–24.7)		29.0 (14.9–44.8)	24.1 (11.0–40.0)	
CRPC-progression, % (95% CI)			0.724			0.87
5-year	8.8 (2.8–19.3)	7.5 (4.4–11.6)		8.1 (2.0–19.8)	10.8 (3.4–23.3)	
10-year	18.4 (8.5–31.2)	16.5 (11.6–22.1)		19.9 (8.6–34.6)	20.1 (8.6–35.0)	
ADT-induction, % (95% CI)			0.0941			0.781
5-year	26.0 (14.3–39.4)	23.9 (18.2–30.0)		24.2 (11.8–39.0)	27.1 (13.9–42.1)	
10-year	47.6 (31.9–61.7)	36.5 (29.7–43.4)		44.5 (27.6–60.1)	51.8 (31.9–68.5)	

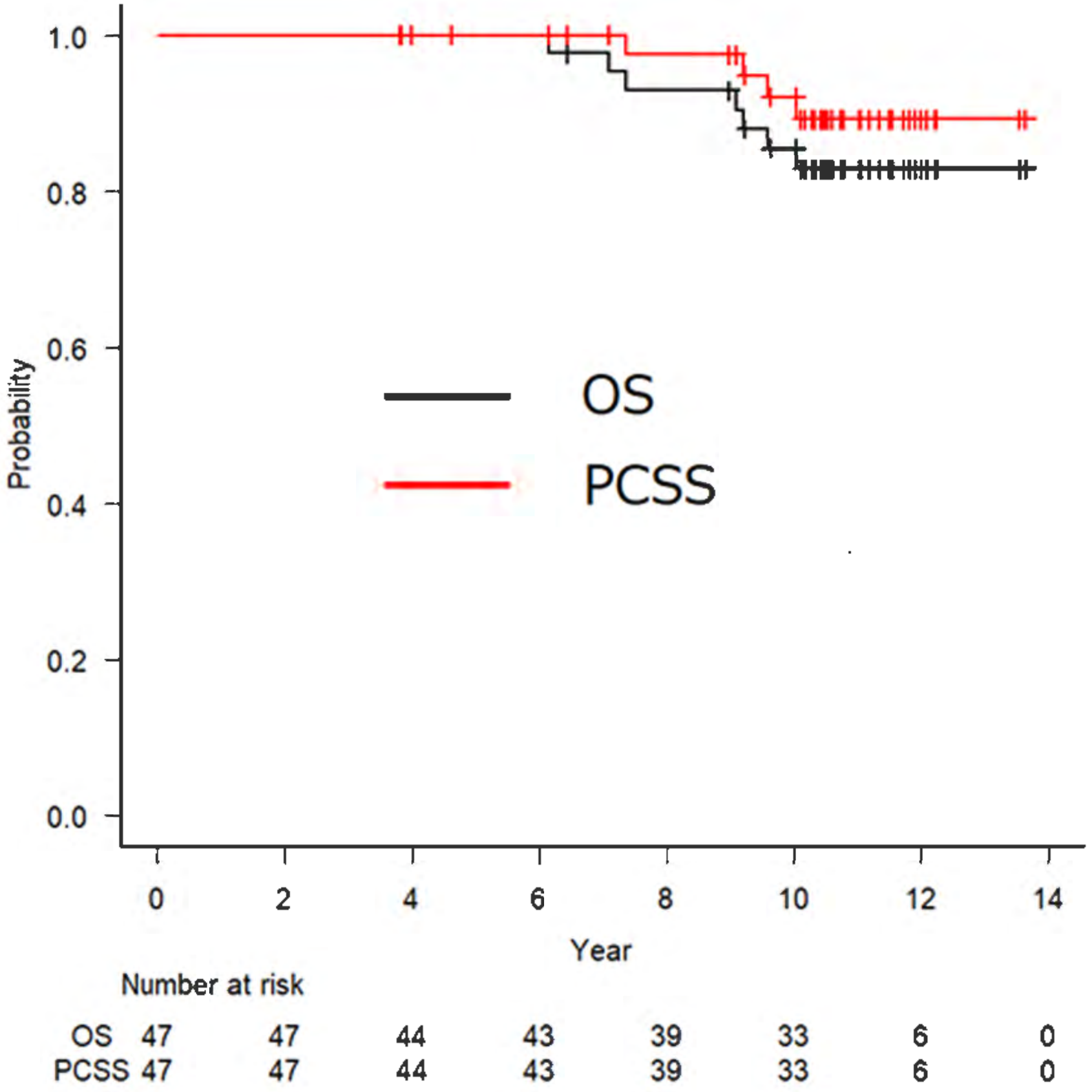
Late GU toxicities			0.398			–
5-year	17.0 (7.9–29.1)	10.4 (6.7–15.1)		–	–	
10-year	21.6 (11.0–34.4)	20.8 (15.4–26.8)		–	–	
Late GI toxicities			0.296			–
5-year	17.2 (8.0–29.4)	20.8 (15.5–26.6)		–	–	
10-year	17.2 (8.0–29.4)	23.5 (17.8–29.6)		–	–	

Foot note: WP-SIB-IMRT, whole pelvic intensity-modulated radiation therapy with simultaneous-integrated boost; PO-IMRT, prostate-only intensity-modulated radiation therapy; 95% CI, 95% confidence interval; N/A, not available; PCa, prostate cancer; CRPC, castration-resistant prostate cancer; ADT, androgen-deprivation therapy; GU, genitourinary; GI. gastrointestinal.

Table 3. Summary of grade ≥ 2 acute/late genitourinary and gastrointestinal toxicities, graded based on the Common Terminology Criteria for Adverse Events version 4.0.

	Grade 2	Grade 3	Grade 4	Grade 5
Acute toxicities, % (n)				
Genitourinary				
urinary frequency	29.8 (14)	–	–	–
urinary tract pain	4.3 (2)	0 (0)	–	–
urinary retention	36.2 (17)	0 (0)	0 (0)	0 (0)
Gastrointestinal				
nausea	4.3 (2)	0 (0)	–	–
anal pain	12.8 (6)	0 (0)	–	–
proctitis	2.1 (1)	0 (0)	0 (0)	0 (0)
rectal hemorrhage	19.1 (9)	0 (0)	0 (0)	0 (0)
Late toxicities, % (n)				
Genitourinary				
urinary frequency	12.8 (6)	–	–	–
urinary urgency	2.1 (1)	–	–	–
urinary incontinence	2.1 (1)	0 (0)	–	–
urinary retention	21.3 (10)	0 (0)	0 (0)	0 (0)
hematuria	4.3 (2)	2.1 (1)	0 (0)	0 (0)
Gastrointestinal				
rectal hemorrhage	17.0 (8)	0 (0)	0 (0)	0 (0)

proctitis	2.1 (1)	0 (0)	0 (0)	0 (0)
ileus	0 (0)	0 (0)	2.1 (1)	0 (0)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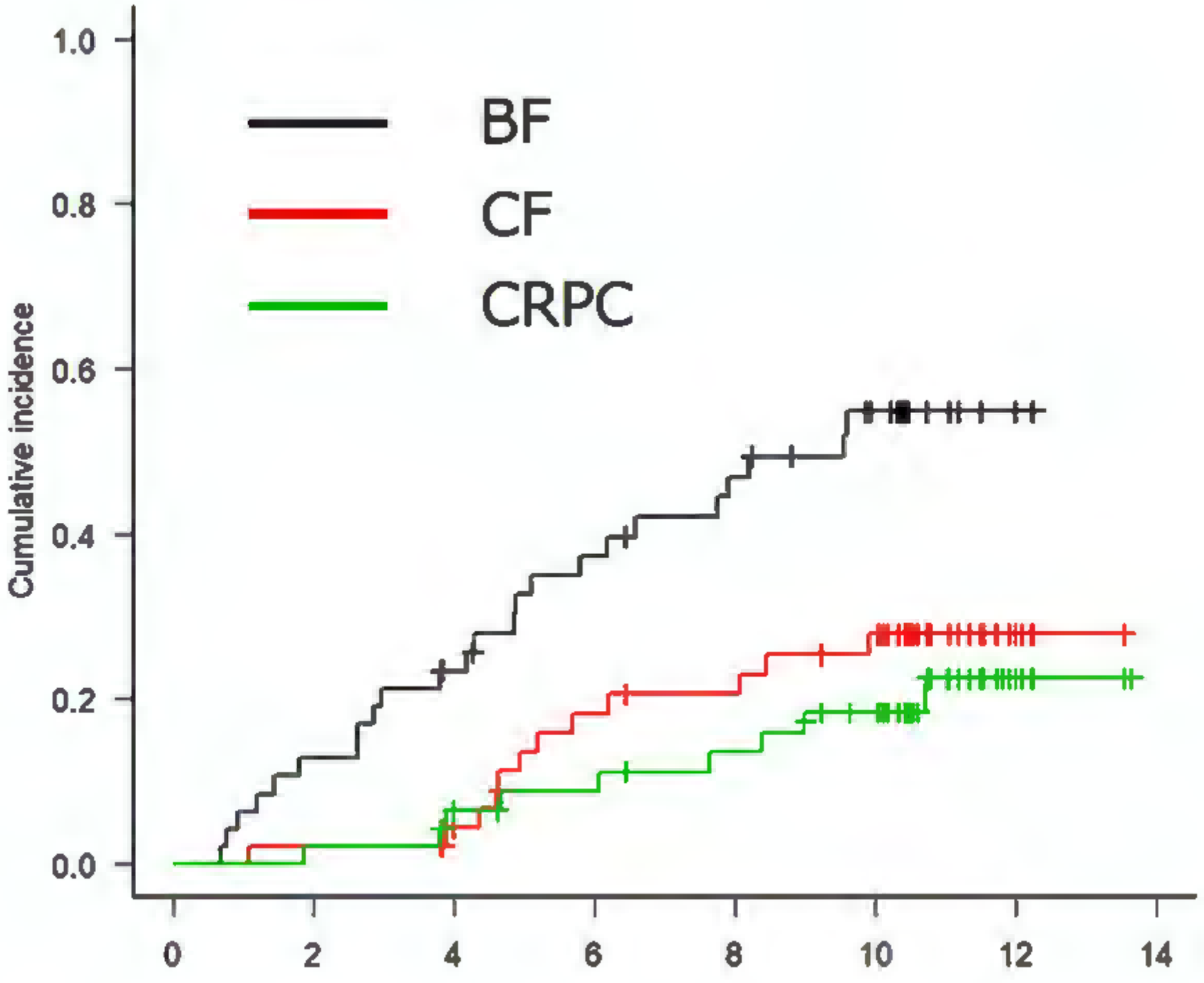
PCSS 47 47 44 43 39 33 6 0



Number at risk

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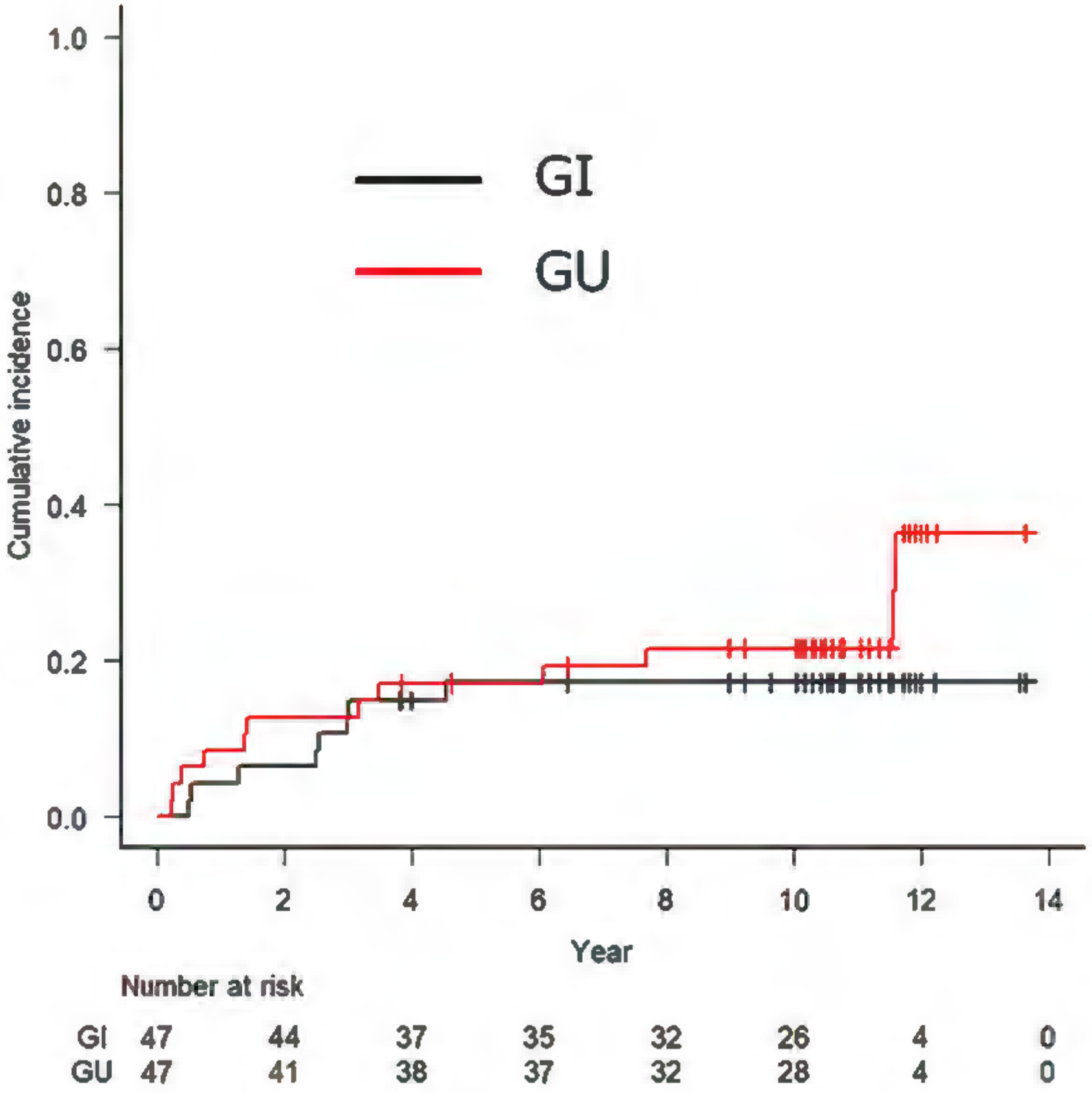
CF	47	46	42	35	31	26	5	0
CRPC	47	46	41	39	34	28	6	0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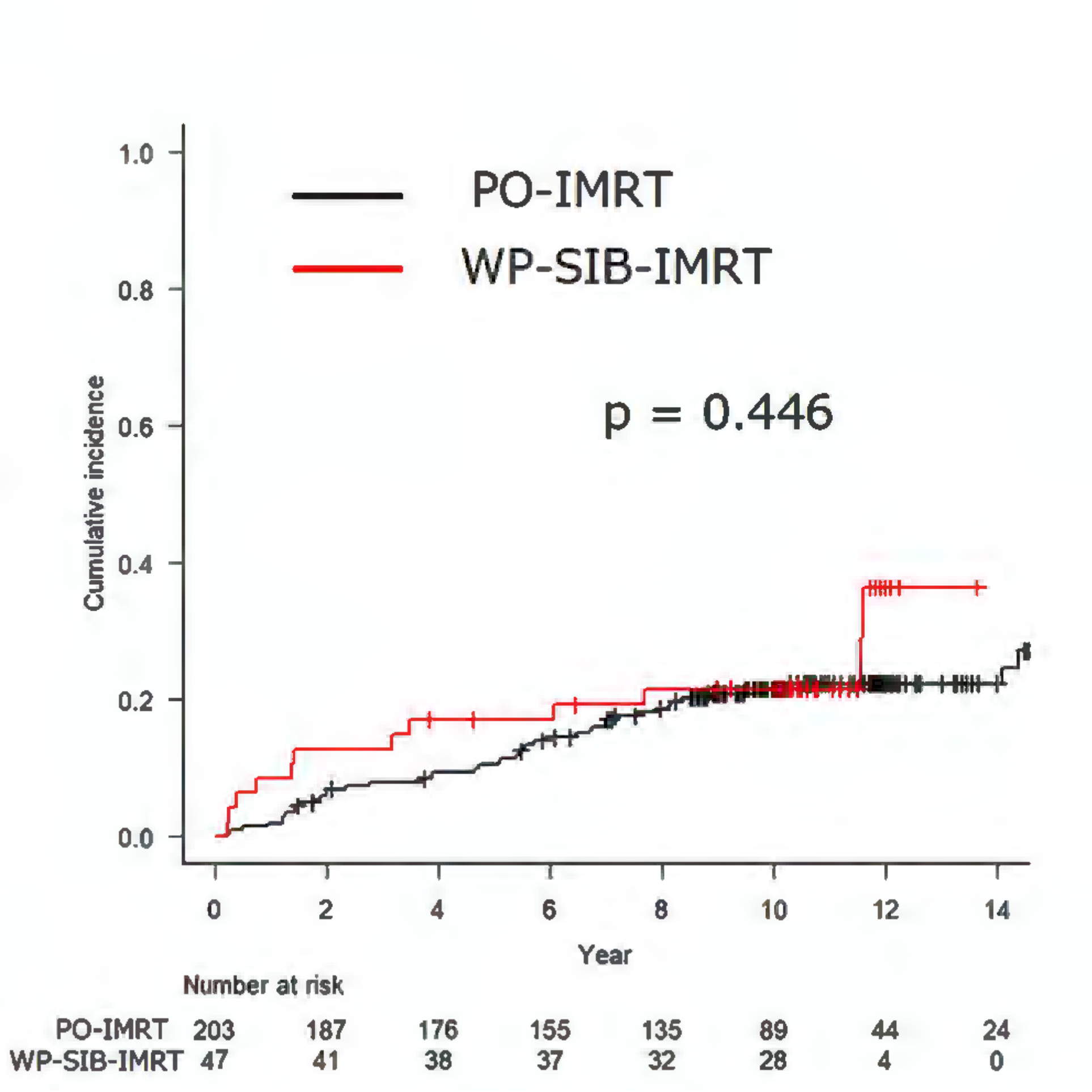
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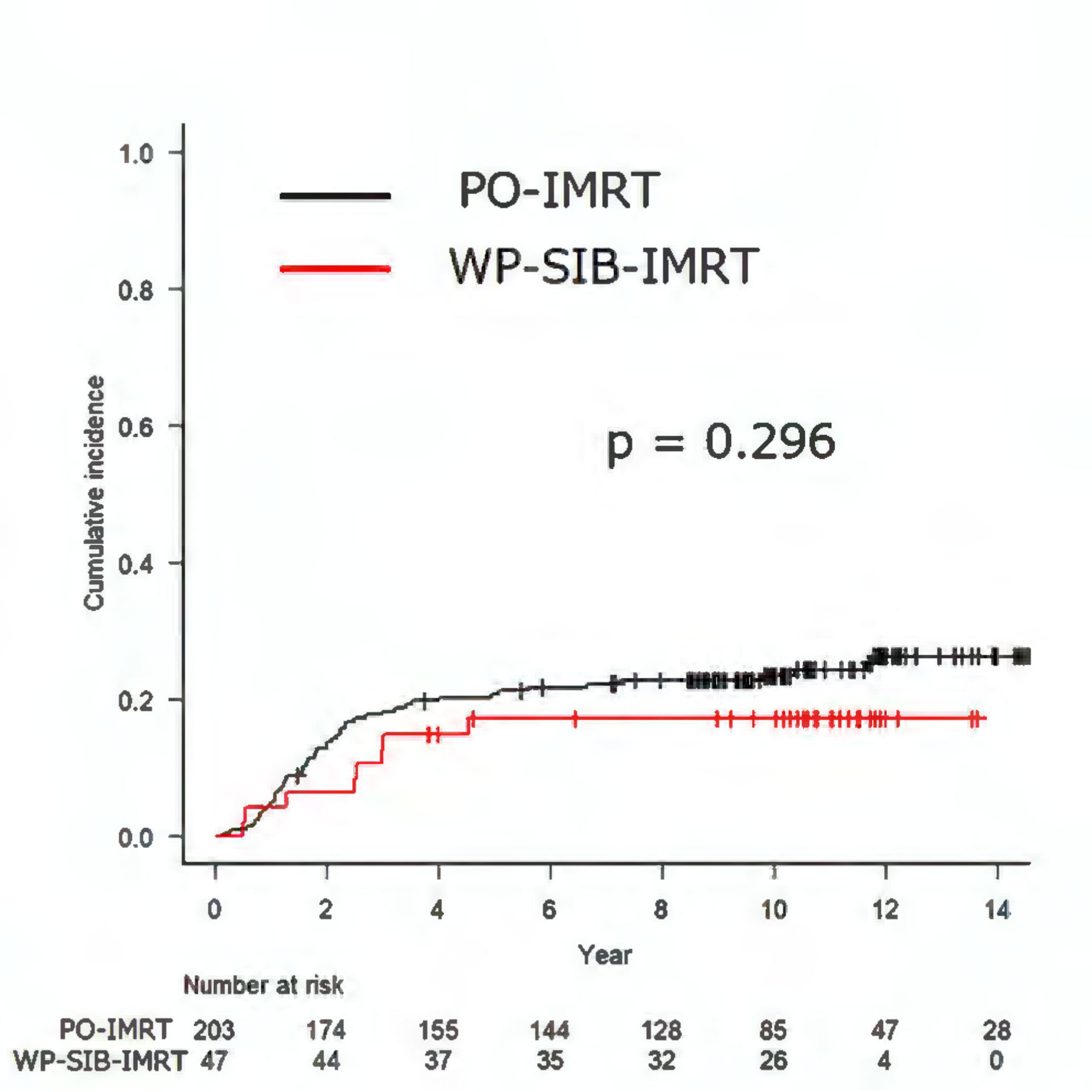
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WP-SIB-IMRT
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Cumulative incidence
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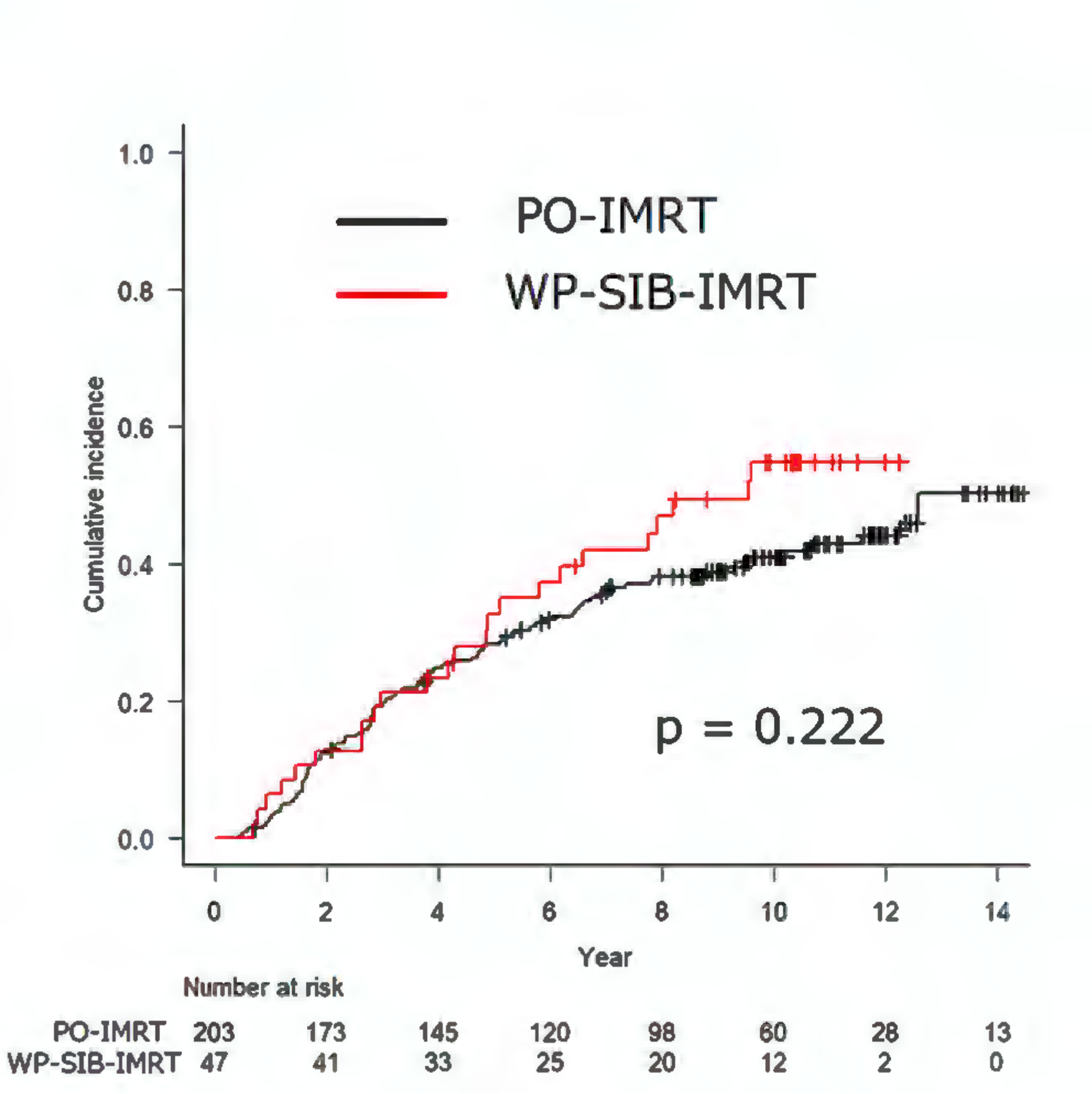
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WP-SIB-IMRT
Cumulative incidence
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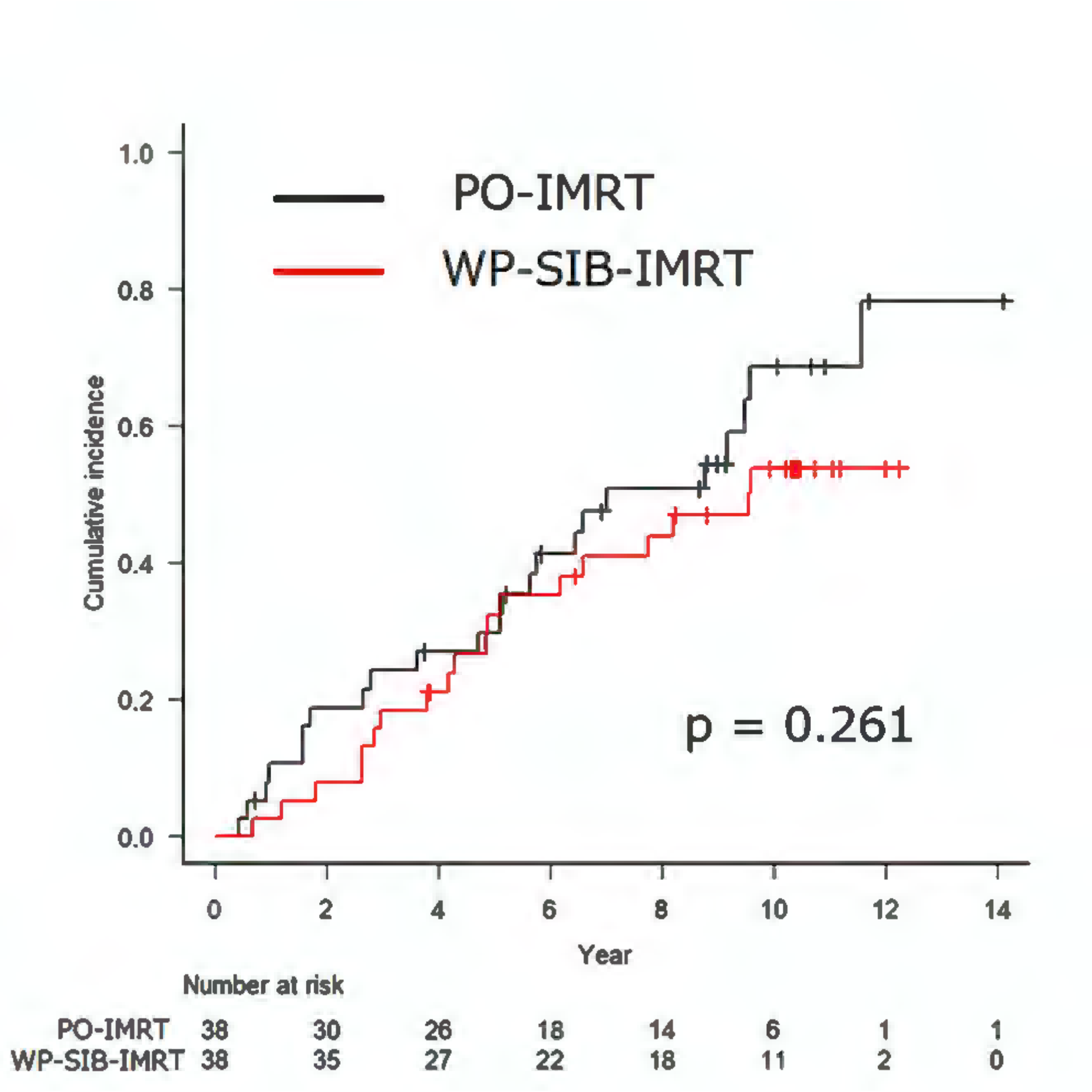
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WP-SIB-IMRT
Cumulative incidence
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Year
Number at risk
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