Low incidence of late recurrence in patients with intermediate-risk prostate cancer treated by intensity-modulated radiation therapy plus short-term androgen deprivation therapy

Authors: Rihito Aizawa[1], Kenji Takayama[1], Kiyonao Nakamura[1], Takahiro Inoue[2], Toshinari Yamasaki[2], Takashi Kobayashi[2], Shusuke Akamatsu[2], Osamu Ogawa[2], Takashi Mizowaki[1]*

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

[2]: Department of Urology, Graduate School of Medicine, Kyoto University. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507 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: IMRT for prostate cancer

Abstract:

Objectives: This study evaluated the long-term outcomes of intensity-modulated radiation therapy (IMRT) combined with short-term neoadjuvant androgen deprivation therapy (ADT) in patients with intermediate-risk (IR) prostate cancer (PCa).

Materials and Methods: Patients with IR PCa treated with IMRT at our institution between September 2000 and November 2010 were analyzed retrospectively. The treatment consisted of IMRT (70–78 Gy in 35–39 fractions) combined with 6 months of neoadjuvant ADT. Salvage ADT was initiated when the prostate-specific antigen level was > 4.0 ng/mL

Results: In total, 106 consecutive patients with IR PCa (median age: 70 years old) were analyzed. The median follow-up period was 8.0 years. The overall survival, PCa-specific survival, biochemical failure, and clinical failure rates were 99.0%, 100.0%, 6.8%, and 1.9% at 5 years and 89.1%, 100.0%, 11.3%, and 2.9% at 10 years, respectively. Late recurrence (> 5 years) was observed in three cases (2.8%). The cumulative incidence rates of genitourinary (GU) and gastrointestinal (GI) toxicities (grade 2/3) were 10.5% and 5.8% at 5 years, and 14.7% and 5.8% at 10 years, respectively. No patient developed grade 4/5 GU toxicities or grade 3–5 GI toxicities.

Conclusion:

IMRT at a dose up to 78 Gy combined with short-term neoadjuvant ADT resulted in excellent long-term disease-free outcomes with acceptable morbidities among patients with IR PCa. In addition, the incidence

of late recurrence was very low. Further investigation is warranted to confirm our findings.

Key words: prostate cancer, intermediate risk, intensity-modulated radiation therapy, short-term androgen deprivation therapy, late recurrence

Introduction

External beam radiotherapy (EBRT) is a major treatment modality for nonmetastatic prostate cancer (PCa). Intensity-modulated radiation therapy (IMRT) achieves high-dose irradiation without increasing radiation-induced late toxicities, such as rectal bleeding, leading to its widespread clinical introduction [1]. High-dose EBRT via IMRT combined with short-term androgen deprivation therapy (ADT) has been recognized as the standard approach for intermediate-risk (IR) PCa, along with prostatectomy and brachytherapy [2].

Although favorable disease control via EBRT among patients with IR PCa has been well reported with regard to medium-term results (< 5 years) [3], late recurrence typically more than 5 years after EBRT continues to be an issue among physicians [4-8]. However, because most of those observations were based on studies using three-dimensional conformal radiotherapy which contained high-risk PCa patients in part, it remains unclear whether late recurrence will occur in a similar fashion when modern IMRT delivering a dose with higher conformity is applied to this risk group. Furthermore, although there are several long-term outcomes regarding high-dose IMRT, most studies evaluated outcomes as a failure-free "survival" rate [1,9,10]. Due to the considerable number of deaths from other causes without disease failure over long-term follow-up periods, it is difficult to determine whether the decreased rate is due to disease failure or death from other causes. Therefore, an investigation that can properly evaluate late recurrence following EBRT is required to obtain appropriate comparative data with

other treatment modalities, such as prostatectomy and brachytherapy.

We previously reported the 10-year outcomes of 50 patients with T1–2N0M0 PCa treated with IMRT [11]. However, these data were considered inappropriate for evaluating long-term disease control among patients with IR PCa, because that study included a considerable number of patients with a high Gleason score (GS) (≥ 8) or prostate-specific antigen (PSA) level (≥ 20 ng/mL) and subsequently less than half of the cohort was categorized as IR PCa (46%, n = 23). Therefore, in the current study, we retrospectively evaluated the clinical outcomes, including the rate of late recurrence, among patients who underwent IMRT combined with short-term neoadjuvant ADT (NA-ADT) for IR PCa, with a larger cohort (n = 106) and a long follow-up periods (8.0 years), which allowed us to properly evaluate the long-term efficacy of IMRT in this PCa risk group.

Patients and Methods

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

Patients

We retrospectively analyzed the treatment outcomes of patients with nonmetastatic IR PCa according to the National Comprehensive Cancer Network (NCCN) risk classification (version 2, 2019) [2] who were treated with IMRT between September 2000 and November 2010 at our institution. Specifically, IR PCa was defined as follows: one or more features of clinical T2b–T2c, GS of 7, or pretreatment PSA level of 10–20 ng/mL. To identify this subgroup, we reviewed our prospectively maintained institutional PCa registry.

Initial evaluations included systematic needle biopsies, digital rectal examinations, transrectal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy (BS). All pathological specimens obtained at other hospitals were re-evaluated at our institution.

Neoadjuvant androgen deprivation therapy

NA-ADT, consisting of combined androgen blockage for 6 months, was planned before

initiating IMRT. However, this approach contained some variations in the duration of NA-ADT because a number of patients were introduced to our hospital after ADT had been initiated at another hospital. In addition, patients with liver dysfunction or special requests were administered luteinizing hormone-releasing hormone analogue alone.

Intensity-modulated radiation therapy

The details of our CT simulation and IMRT treatment planning procedures have been described previously [12]. Briefly, patients were immobilized in a prone position using a thermoplastic shell, which extended from the mid-thigh to the upper one-third of the leg, in combination with a vacuum pillow and leg support. Patients were instructed to empty their urinary bladder and rectum approximately 1–1.5 hours before CT and before each treatment. For IMRT, 15-MV photon beams from the Clinac 2100C, Clinac 2300 C/D, or Clinac-iX linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) or 6-MV photon beams from the Novalis linear accelerator (BrainLAB, Feldkirchen, Germany) were used. The clinical target volume (CTV) was risk-adoptedly set based on the prostate and base of the seminal vesicles for T1–2b cases and the proximal two-thirds of seminal vesicles for T2c cases, with reference to MRI. The planning target volume (PTV) was established by adding 9-mm margins to the CTV, except for a 6-mm margin to the rectal side and a 10-mm margin in the cranio-caudal direction, to account for organ motion or set-up uncertainties. A set-up error correction was performed based on the pelvic bony structure.

The prescribed doses were 74 Gy in 37 fractions for the T1–2b cases and 78 Gy in 39 fractions for the T2c cases. The prescribed dose was defined as the average dose of the PTV (D mean). In each group, the total dose was reduced by 4 or 8 Gy in patients with risk factors for rectal bleeding due to high-dose irradiation, such as an advanced age (≥ 80 years), anticoagulant/antiplatelet therapy, and severe diabetes mellitus (glycosylated hemoglobin ≥ 8.0%).

Patient follow-up and salvage androgen deprivation therapy

No adjuvant ADT was administered to any patient after completing IMRT. Patients were followed every 1–3 months during the first 2 years and every 3–6 months thereafter. The interval was extended to once a year in select patients with a stable clinical course. No additional radiographic study after IMRT was required unless the PSA level increased or symptoms suggesting recurrence, such as bone pain or locoregional symptoms, were observed. We waited to initiate salvage ADT (S-ADT) until the PSA level increased above 4.0 ng/mL in a monotonically increasing manner to eliminate false failure cases (biochemical failure [BF] without continuous PSA elevation). Before initiating S-ADT, CT and BS were conducted to determine whether clinical failure (CF) had occurred.

Clinical data was collected using the prospectively maintained institutional database and a follow-up data sheet at every visit.

Outcome evaluation and statistical analyses

The time of occurrence of each event was calculated from the date of IMRT initiation. Overall survival and PCa-specific survival rates were calculated using the Kaplan–Meier estimate. To account for death without each event being a competing risk, the cumulative incidence method was used to estimate the rates of BF, CF, and late radiation toxicities, in which death was not count as the event. BF was evaluated using the Phoenix definition (nadir plus 2.0 ng/mL) [13]. CF was defined as recurrent disease confirmed via radiographic studies. Gray's test was used to compare BF and CF rates between the favorable intermediate-risk (FIR) and unfavorable intermediate-risk (UFIR) groups [2]. Due to the small number of events, we did not perform univariate or multivariable analyses of prognostic factors affecting disease control.

Acute (within the first 90 days after initiating IMRT) and late genitourinary (GU) and gastrointestinal (GI) toxicities related to IMRT were evaluated based on the National Cancer Institute Common Toxicity Criteria version 2. The time to development of the worst-grade toxicity was documented for late toxicities. Rectal bleeding caused by hemorrhoids was excluded as a toxicity.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) [14].

Results

Patient characteristics

We identified 114 patients with IR PCa treated with IMRT between September 2000 and November 2010. Of them, one patient was treated with low-dose radiation (66 Gy) due to severe concomitant illnesses, and seven patients exceptionally underwent long-term NA-ADT (> 1 year). Therefore, these eight patients were excluded from the evaluation, and the remaining 106 patients were analyzed.

The median patient age was 70 (interquartile range [IQR]: 65–75) years at the initiation of IMRT. The distribution of the clinical T stage was as follows: T1c, 35 cases; T2a, 33 cases; T2b, 24 cases; and T2c, 14 cases. The median pretreatment PSA level was 10.3 (IQR: 6.5–12.7) ng/mL. Approximately 80% of the patients (n = 87) had a GS of 7. Subsequently, 26 and 80 patients were categorized into the FIR and UFIR groups, respectively [2].

The patient characteristics are summarized in Table 1.

Treatments

All but one patients received NA-ADT for a median duration of 6.4 (IQR: 5.5–7.7) months. The one patient with FIR PCa did not receive NA-ADT. The median dose of IMRT was 74 (IQR: 70–74) Gy delivered in 37 (IQR: 35–37) fractions. The details of the treatments are summarized in Table 1.

Oncological and survival outcomes

The median follow-up period was 8.0 (IQR: 7.0–9.4) years. During follow-up, six patients died, but none from PCa. The overall survival and PCa-specific survival rates were 99.0% (95% confidence interval [CI]: 93.2–99.9) and 100.0% (95% CI: 100.0–100.0) at 5 years and 89.1% (95% CI: 73.9–95.7) and 100.0% (95% CI: 100.0–100.0) at 10 years, respectively (Fig. 1A).

During follow-up, 10 patients (all in the UFIR group) developed BF at a median of 3.1 (IQR: 1.9–5.3) years after IMRT. The initial pattern of disease failure was BF in all patients who developed disease failure. Of these 10 patients, 3 (2.8%) developed BF more than 5 years after IMRT (late recurrence), whereas the remaining 7 developed BF within 5 years after IMRT. S-ADT was initiated in 7 (70.0%) of these patients due to continuous PSA elevation over a median of 5.1 (IQR: 2.6–6.2) years after IMRT; the median PSA level at initiation of S-ADT was 6.9 (IQR: 5.2–8.1) ng/mL. The remaining three patients maintained a stable disease course after BF without adding salvage treatment. During follow-up, three PCa patients developed CF (all in the UFIR group) at 2.8 (bone metastasis), 2.3 and 5.7 years (pelvic lymph node metastasis) after IMRT, respectively. No patient developed symptoms suggestive of local failure. The BF and CF rates were 6.8% (95% CI: 3.0–12.8) and 1.9% (95% CI: 0.4–6.2) at 5 years and 11.3% (95% CI: 5.5–19.2) and 2.9% (95% CI: 0.8–7.6) at 10 years (Fig. 1B). The 5- and 10-year BF rates were 0.0% (95% CI: 0.0–0.0) and 0.0% (95% CI: 0.0–0.0) in the FIR group and 9.0% (95% CI:

3.9–16.7) and 14.9% (95% CI: 7.3–25.0) in the UFIR group, respectively (p = 0.0601) (Fig. 2a). The 5- and 10-year CF rates were 0.0% (95% CI: 0.0–0.0) and 0.0% (95% CI: 0.0–0.0) in the FIR group and 2.5% (95% CI: 0.5–8.0) and 3.8% (95% CI: 1.0–9.9) in the UFIR group, respectively (p = 0.318) (Fig. 2b).

Toxicities

Acute GU toxicities consisted mostly of urinary frequency, urgency, or dysuria. The total dose was reduced to 70 Gy in one patient due to a grade 3 urinary obstruction requiring self-catheterization that developed during IMRT course. No grade 4 or higher acute GU toxicities were observed. Acute GI toxicities consisted mostly of pain or bleeding with defecation. No grade 3 or higher acute GI toxicities were observed.

During the follow-up, grade ≥ 2 late GU toxicities were observed in 16 patients: inconsistency or urinary frequency after a median of 4.8 (range: 1.2–6.5) years in 8, grade 2/3 urinary obstruction or dysuria after a median of 3.2 (range: 0.3–11.4) years in 4, and grade 2 urinary bleeding due to radiation cystitis after a median of 2.8 (range: 1.2–6.6) years in 4 patients. Treatment for urinary obstruction consisted of intermittent self-catheterization (n = 1) and conservative therapy (n = 3), and treatment for urinary bleeding consisted of conservative therapy (n = 4). The cumulative incidence rates of grade ≥ 2 late GU toxicities were 10.5% (95% CI: 5.6–17.3) at 5 years and 14.7% (95% CI: 8.6–22.3) at 10 years

(Fig. 3). No grade 4 or higher late GU toxicities were observed. During follow-up, grade 2 late GI toxicities, which consisted of rectal bleeding, were observed in seven patients after a median of 2.0 (range: 0.9–4.5) years, and no grade 3 or higher late GI toxicities were observed. Among them, hemorrhoid was considered as a cause of rectal bleeding in one case. All toxicities were ultimately resolved (decreased to grade 0 or 1). The cumulative incidence rate of grade ≥ 2 late GI toxicities was 5.8% (95% CI: 2.3–11.4) at 5 years and remained unchanged at 10 years (Fig. 3).

Discussion

We retrospectively evaluated the long-term clinical outcomes of IMRT in patients with IR PCa at a single institution. Our institutional treatment protocol specifies IMRT (70–78 Gy in 35–39 fractions) combined with short-term NA-ADT alone (combined androgen blockage for 6 months). Approximately 90% of our cohort has maintained long-term disease-free status, and no severe treatment-related toxicities have been observed. Of note, late recurrence (> 5 years after IMRT) was rarely observed (2.8%). These results support the validity of our treatment strategy for IR PCa.

Although a dose escalation to 74–80 Gy has significantly improved disease control [3], decreases in the failure-free survival rate over long-term follow-up, specifically more than 5 years after EBRT, have been described in many prospective trials or retrospective studies [4-8]. In the EORTC 22991 trial, which included approximately 75% IR PCa patients in the study cohort, the BF-free survival rates of the EBRT (70–78 Gy in 35–39 fractions) plus 6-month ADT arm were 82.6% at 5 years and approximately 70% at 8 years [7]. Similarly, in a Dutch multicenter randomized controlled trial using three-dimensional conformal radiotherapy (68 vs. 78 Gy with 2 Gy per fraction, with or without ADT), an approximately 20% decrease in the BF-free rate was observed from 5 to 10 years among IR PCa patients treated with 78 Gy [6]. Based on this background, the current treatment strategy regarding EBRT is progressing towards further dose escalation. However, we question the validity of uniformly increasing the intensity of local treatments. In the current study, excellent disease control was demonstrated using

IMRT (up to 78 Gy) with short-term ADT (BF rate: 11.3% at 10 years), although we did not apply a high-precision technique such as imaged-guided radiation therapy (IGRT). Promising outcomes of modern IMRT using IGRT have been reported, which support further improvement in disease control with the introduction of IGRT [15,16]. According to the study of IMRT (78 Gy in 39 fractions) with daily image guidance and short-term NA-ADT (3–6 months), Wilcox et al. reported that the BF-free survival rate was 95.5% at 5 years in patients with IR PCa [15]. These results suggest that satisfactory disease control would be achieved with modern IMRT using a dose of 78 Gy in most IR PCa cases, although a subgroup of patients who would truly benefit from further dose escalation exists. We need to wait for further results to confirm long-term treatment outcomes.

A late occurrence of BF was observed in only 2.8% (n = 3) of our cohort. This incidence was considerably lower than that reported previously [1,9]. In the current study, a wide PTV margin (9–10 mm) was added to the CTV. We hypothesize that this wide PTV margin for EBRT may have contributed to the low BF incidence in our cohort, which may be sufficient to correct the error derived from inter-/intra-fractional motion even though no IGRT was applied. According to Engels et al. who investigated the relationship between BF and the PTV margin, disease control was significantly worse among patients treated with a smaller margin (3–5 mm) than those treated with a wider margin (6 mm) during daily IGRT using implanted markers (5-year freedom from BF rate: 74% vs. 96%, p = 0.04) [17]. They concluded that the combination of a smaller PTV margin and a distended rectum at planning CT

may have resulted in the poorer disease control. Those results imply that the quality of IMRT planning also dramatically affects disease control.

In the current study, none of our FIR PCa patients has developed disease failure during follow-up. Although this is the result from a small number of the cohort (n = 26), our results may suggest that ADT can be omitted or at least shortened in this risk group. Currently, the long-term outcomes of RTOG 9910 trial, investigating the optimal duration of ADT for IR PCa (16 weeks vs. 36 weeks) combined with EBRT using 70.2 Gy, was published, in which the prolonged ADT (36 weeks) did not show the improvement of disease control [18]. In addition, the current NCCN Clinical Practice Guidelines does not recommend to add ADT for FIR PCa cases [2]. The appropriate duration of combining ADT should be further investigated, especially in the setting of prospective trials.

Severe radiation-induced adverse events were relatively rare in the current study. Only 5.7% (n = 6) of our patients developed grade 2 rectal bleeding at 10 years, and no GI toxicities higher than grade 3 were observed. Grade 2 rectal bleeding occurred within 4 years after IMRT, and no cases of bleeding occurred after 4 years, which was consistent with previous reports [1,19]. In contrast, we observed a continuous increase in GU toxicities, and the cumulative incidence rate of grade 2/3 GU toxicities was 14.7% at 10 years. However, these GU toxicities included urinary inconsistency or urgency, which may have developed due to aging. Similarly, most of the previous reports may have categorized these toxicities as late GU toxicities, rendering it difficult to truly evaluate radiation-induced GU toxicities [1,11,19].

Therefore, we also evaluated the occurrence of urinary bleeding and obstruction separately. As a result, we observed a continuous increase in the rate of urinary bleeding and obstruction. Notably, one patient developed urinary obstruction requiring self-catheterization at a very late phase (11.4 years after IMRT). Despite the considerably low rate, this case highlights the importance of long-term follow-up with special attention paid to radiation-induced GU toxicities.

Our study had several limitations. This was a single-institution retrospective study and patients were enrolled in daily clinical practice, although the treatment was based on a uniform and predetermined protocol. We could not perform analyses to detect factors affecting the prognosis due to the small number of events. Furthermore, because our study cohort consisted of Japanese patients, our results may not apply directly to other ethnic groups due to reported differences in the sensitivity to ADT among ethnicities [20]. Nevertheless, we believe that our study provides benchmark data for patients with IR PCa treated with IMRT for comparison with prostatectomy and brachytherapy, because we evaluated long-term clinical outcomes in a form that can truly determine the frequency of late recurrence as long as intractable late GU toxicities.

In conclusion, IMRT combined with short-term NA-ADT resulted in excellent long-term disease-free outcomes with acceptable morbidities in patients with IR PCa. Satisfactory disease control may be achieved by modern IMRT using a maximum dose of 78 Gy in most IR PCa cases, and the incidence of late recurrences was very low. Further investigations in a larger cohort with a longer

follow-up are warranted to confirm our findings.

Acknowledgements:

This work was supported, in part, by JSPS KAKENHI Grant Number 16K10390. The funding programs had no effects on the study design, analysis, and interpretation of the data of this manuscript.

Conflict of Interest Disclosure Statement:

The authors declare that they have no competing interests.

References:

1. Alicikus ZA, Yamada Y, Zhang Z, et al. (2011) Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer 117 (7):1429-1437. doi:10.1002/cncr.25467

2. National Comprehensive Cancer network (2019) NCCN Guidelines; prostate cancer version 2.2019. In: The category of prostate cancer (Accessed April 17 2019). https://wwwnccnorg/professionals/physician_gls/pdf/prostatepdf

3. Zaorsky NG, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB (2015) What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. Radiother Oncol 115 (3):295-300. doi:10.1016/j.radonc.2015.05.011

4. Pasalic D, Kuban DA, Allen PK, et al. (2019) Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial. Int J Radiat Oncol Biol Phys 104 (4):790-797. doi:10.1016/j.ijrobp.2019.02.045

5. Dearnaley DP, Jovic G, Syndikus I, et al. (2014) Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 15 (4):464-473. doi:10.1016/S1470-2045(14)70040-3

6. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV (2014) Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 110 (1):104-109. doi:10.1016/j.radonc.2013.09.026

7. Bolla M, Maingon P, Carrie C, et al. (2016) Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. J Clin Oncol 34 (15):1748-1756. doi:10.1200/JCO.2015.64.8055

8. Michalski JM, Moughan J, Purdy J, et al. (2018) Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol 4 (6):e180039. doi:10.1001/jamaoncol.2018.0039

9. Abu-Gheida I, Reddy CA, Kotecha R, et al. (2019) Ten-Year Outcomes of Moderately Hypofractionated (70 Gy in 28 fractions) Intensity Modulated Radiation Therapy for Localized Prostate Cancer. Int J Radiat Oncol Biol Phys 104 (2):325-333. doi:10.1016/j.ijrobp.2019.01.091

10. Spratt DE, Zumsteg ZS, Ghadjar P, et al. (2014) Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU Int 114 (3):360-367. doi:10.1111/bju.12514

11. Mizowaki T, Norihisa Y, Takayama K, et al. (2016) Ten-year outcomes of intensity-modulated radiation therapy combined with neoadjuvant hormonal therapy for intermediate- and high-risk patients with T1c-T2N0M0 prostate cancer. Int J Clin Oncol 21 (4):783-790. doi:10.1007/s10147-016-0954-4

12. Zhu S, Mizowaki T, Nagata Y, et al. (2005) Comparison of three radiotherapy treatment planning protocols of definitive external-beam radiation for localized prostate cancer. Int J Clin Oncol 10 (6):398-404. doi:10.1007/s10147-005-0519-4

13. Roach M, 3rd, Hanks G, Thames H, Jr. , et al. (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65 (4):965-974. doi:10.1016/j.ijrobp.2006.04.029

14. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48 (3):452-458. doi:10.1038/bmt.2012.244

15. Wilcox SW, Aherne NJ, McLachlan CS, McKay MJ, Last AJ, Shakespeare TP (2015) Is modern external beam radiotherapy with androgen deprivation therapy still a viable alternative for prostate cancer in an era of robotic surgery and brachytherapy: a comparison of Australian series. J Med Imaging Radiat Oncol 59 (1):125-133. doi:10.1111/1754-9485.12275

16. Zelefsky MJ, Kollmeier M, Cox B, et al. (2012) Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 84 (1):125-129. doi:10.1016/j.ijrobp.2011.11.047

17. Engels B, Soete G, Gevaert T, Storme G, Michielsen D, De Ridder M (2014) Impact of planning target volume margins and rectal distention on biochemical failure in image-guided radiotherapy of prostate cancer. Radiother Oncol 111 (1):106-109. doi:10.1016/j.radonc.2014.02.009

18. Pisansky, TM, Hunt, D, Gomella, LG, et al. (2015) Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial

9910. J Clin Oncol 33(4): 332-339.

19. Aizawa R, Takayama K, Nakamura K, et al. (2019) Ten-year outcomes of high-dose intensity-modulated radiation therapy for nonmetastatic prostate cancer with unfavorable risk: early initiation of salvage therapy may replace long-term adjuvant androgen deprivation. Int J Clin Oncol. doi:10.1007/s10147-019-01478-y

20. Cooperberg MR, Hinotsu S, Namiki M, Carroll PR, Akaza H (2016) Trans-Pacific variation in outcomes for men treated with primary androgen-deprivation therapy (ADT) for prostate cancer. BJU Int 117 (1):102-109. doi:10.1111/bju.12937

Tables

Table 1. Patient and treatment characteristics.

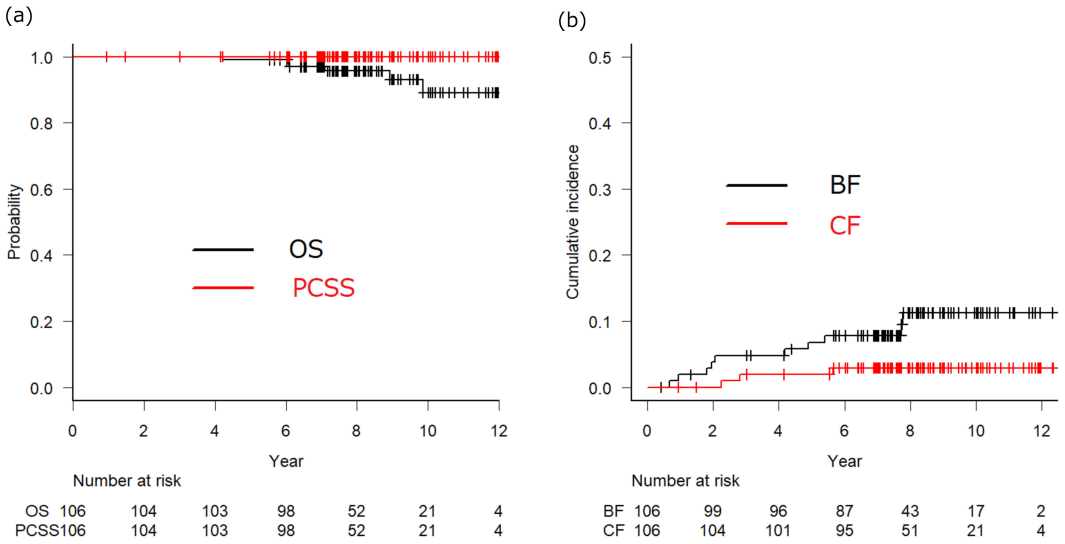
Age (years)	
Median	70
IQR	65–75
Clinical T stage, n (%)	
T1c	35 (33.1)
T2a	33 (31.1)
T2b	24 (22.6)
T2c	14 (13.2)
iPSA (ng/mL)	
Median	10.3
IQR	6.5–12.7
Gleason score, n (%)	
3+3	19 (17.9)
3+4	52 (49.1)
4+3	35 (33.0)
NCCN risk classification, n (%)	
favorable intermediate risk	26 (24.5)
unfavorable intermediate risk	80 (75.5)
Duration of NA-ADT (months)	
Median	6.4
IQR	5.5–7.7
S-ADT, n (%)	7 (6.6)
PSA at S-ADT initiation (ng/mL)	
Median	6.9
IQR	5.2–8.1
IMRT dose, n (%)	
78 Gy	13 (12.3)
74 Gy	68 (64.1)
70 Gy	25 (23.6)

Footnote: IQR, interquartile range; iPSA, pretreatment prostate-specific antigen; NCCN risk classification,

the National Comprehensive Cancer Network risk classification version 2, 2019; NA-ADT, neoadjuvant androgen deprivation therapy; S-ADT, salvage androgen deprivation therapy; IMRT, intensity-modulated radiation therapy.

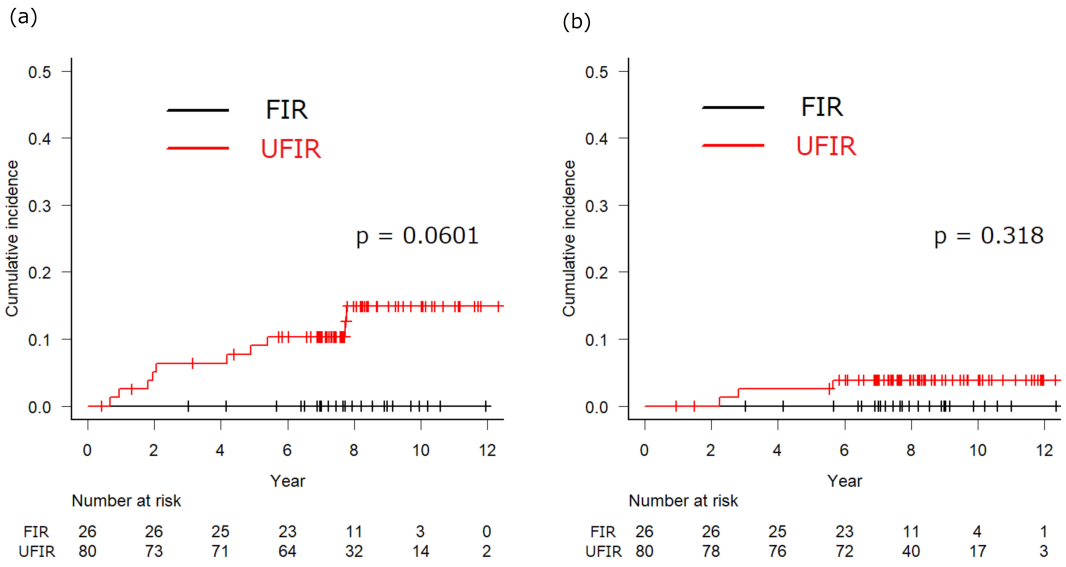
Figures:

Figure 1.



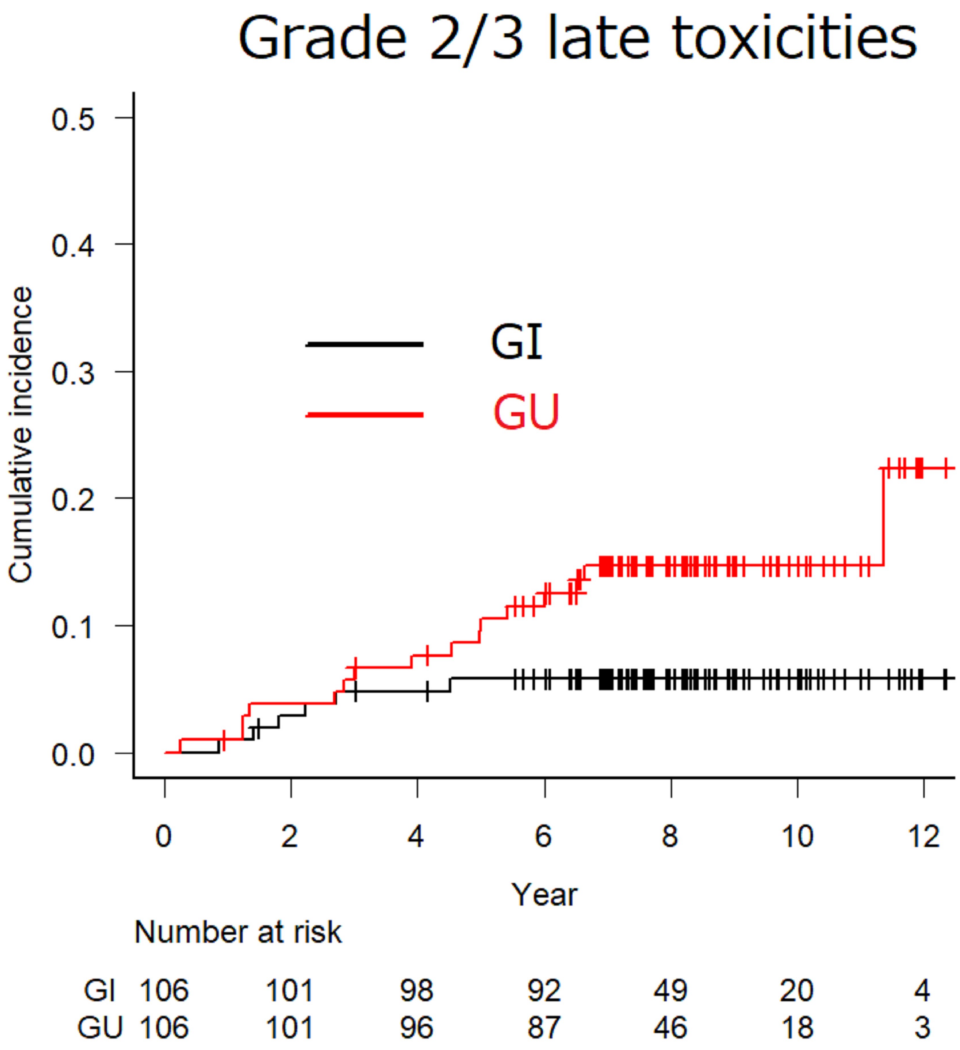
Kaplan–Meier curves for overall survival and prostate cancer-specific survival rates after intensity-modulated radiation therapy (a). Cumulative incidence rates of biochemical failure and clinical failure after intensity-modulated radiation therapy (b). OS, overall survival; PCSS, prostate cancer-specific survival; BF, biochemical failure; CF, clinical failure.

Figure 2.



Cumulative incidence rates of biochemical failure (a) and clinical failure (b) after intensity-modulated radiation therapy according to the National Comprehensive Cancer Network risk classification (version 2, 2019). FIR, favorable intermediate risk (FIR) and unfavorable intermediate risk (UFIR).

Figure 3.



Cumulative incidence rates of grade 2/3 late genitourinary (GU) and gastrointestinal (GI) toxicities after intensity-modulated radiation therapy. GU, genitourinary; GI, gastrointestinal.