Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Comparison of genitourinary and gastrointestinal toxicity among four radiotherapy modalities for prostate cancer: Conventional radiotherapy, intensity-modulated radiotherapy, and permanent iodine-125 implantation with or without external beam radiotherapy

Shinya Sutani [a], Toshio Ohashi [a,b,*], Masanori Sakayori [a], Tomoya Kaneda [a], Shoji Yamashita [b], Tetsuo Momma [c], Takashi Hanada [a], Yutaka Shiraishi [a], Junichi Fukada [a], Mototsugu Oya [d], Naoyuki Shigematsu [a]

[a] *Department of Radiology, Keio University School of Medicine;* [b] *Department of Radiology;* [c] *Department of Urology, National Hospital Organization Saitama Hospital; and* [d] *Department of Urology, Keio University School of Medicine, Japan*

ARTICLE INFO

Article history:
Received 28 May 2015
Received in revised form 6 August 2015
Accepted 6 August 2015
Available online xxxx

Keywords:
Prostate cancer
Radiotherapy
Brachytherapy
IMRT
Toxicity

ABSTRACT

Purpose: To compare late genitourinary (GU) and gastrointestinal (GI) toxicity following different prostate cancer treatment modalities.
Materials and methods: This study included 1084 consecutive prostate cancer patients treated with conventional radiotherapy, intensity-modulated radiotherapy (IMRT), permanent iodine-125 implantation (PI) alone, and PI combined with external beam radiotherapy (PI + EBRT). The effects of treatment- and patient-related factors on late grade $\geqslant 2$ (G2+) GU/GI toxicity risk were assessed.
Results: The median follow-up was 43 months (range, 12–97 months). Compared to the PI + EBRT, there was significantly less G2+ GU toxicity in the conventional radiotherapy (hazard ratio [HR] = 0.39; 95% CI, 0.20–0.77) and the IMRT (HR = 0.45, 95% CI, 0.27–0.73). Compared to the PI + EBRT, there was significantly more G2+ GI toxicity in the IMRT (HR = 2.38; 95% CI, 1.16–4.87). In PI-related groups, prostate equivalent dose in 2 Gy fractions was a significant predictor of G2+ GU toxicity ($p = 0.001$), and the rectal volume receiving more than 100% of the prescribed dose was a significant predictor of G2+ GI toxicity ($p = 0.001$).
Conclusion: The differences in the late G2+ GU/GI risk cannot be explained by the differences in treatment modalities themselves, but by the total radiation dose to the GU/GI tract, which had a causal role in the development of late G2+ GU/GI toxicity across all treatment modality groups.
 Radiotherapy and Oncology xxx (2015) xxx–xxx

Definitive radiotherapy (RT) modalities for non-metastatic prostate cancer include external beam RT (EBRT), brachytherapy, or a combination of the two with or without hormone therapy, in accordance with the National Comprehensive Cancer Network (NCCN) treatment guidelines [1]. In clinical practice, several different treatment modalities are applied for patients with similar risk factors [2–4]. Because the guidelines do not specify one RT modality over another, consideration of the late genitourinary (GU) and gastrointestinal (GI) toxicity risks among the modalities is important when counseling patients with prostate cancer.

Since the Japanese government approved the use of the iodine-125 seed source in July 2003, permanent iodine-125 implantation alone (PI alone) and PI combined with EBRT (PI + EBRT) has become a standard treatment option in Japan. However, it remains controversial whether PI + EBRT leads to increased late GU/GI toxicity. Some studies reported that the use of supplemental EBRT did not increase toxicity compared with PI alone [5–7], whereas others reported increased toxicity after the combination regimen [8–10]. Moreover, to our knowledge, data are relatively sparse comparing the late GU/GI toxicities of PI + EBRT and EBRT alone [11,12]. Of these studies, Wong et al. reported GU/GI toxicities following four different radiation modalities, including PI + EBRT [11]; however, toxicity outcomes were represented as crude rates.

* Corresponding author at:. Department of Radiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail address: ohashi@rad.med.keio.ac.jp (T. Ohashi).

http://dx.doi.org/10.1016/j.radonc.2015.08.019
0167-8140/

The aim of this study was to analyze the late GU/GI toxicities as time-to-event outcomes in patients treated with four different modalities: conventional RT, intensity-modulated radiotherapy (IMRT), PI, and PI + EBRT.

Materials and methods

Patient population and treatment strategy

A total of 1084 consecutive patients with non-metastatic prostate cancer (cT1–T4, N0, M0) were included in this retrospective study. The patients were treated with one of four definitive RT modalities from June 2006 through July 2013 at either Keio University School of Medicine or National Hospital Organization Saitama Hospital with a minimal follow-up time of 12 months.

Patients were classified into risk groups according to NCCN guidelines. PI was initiated in January 2007. PI alone was offered only to low-risk patients (T1–T2a, prostate specific antigen [PSA] <10 ng/ml, and Gleason score $\leqslant$6) and low-tier intermediate-risk patients (T2b–c, PSA <10 ng/ml, and Gleason score of 3 + 4 with a biopsy positive core rate <1/3). PI + EBRT was administered primarily to intermediate- to high-risk patients. Conventional RT and IMRT were administered to patients in all risk categories. IMRT was initiated in December 2007. Since then, the use of conventional RT was largely replaced by IMRT. There were no treatment policy discrepancies between the two participating institutes. The institutional review board at each institution approved this study.

Conventional RT

For two-dimensional RT, treatment fields were simulated and designed on plane films using bony structures and a contrast-filled Foley catheter balloon. The initial dose of 30 Gy was delivered via two opposed anterior–posterior/posterior–anterior fields, measuring up to 10 $\times$ 10 cm, and the final 30–36 Gy dose was delivered via rotational fields technique or four-field box technique. For three-dimensional conformal RT (3D-CRT), the clinical target volume (CTV) included the entire prostate only, or the prostate and seminal vesicles depending on the risk category of the disease. The planning target volume (PTV) was defined by adding a 1-cm margin around the CTV, except posteriorly at the rectum interface, where a 6-mm margin was used. A four-field box technique was used, in which a multileaf collimator-defined radiation beam aperture conformed to the PTV with the appropriate margins. All treatments were delivered using 6–10 MV photons. The median dose was 70 Gy (range, 60–76 Gy) in 2.0 Gy fractions at isocenter. Daily positioning was performed based on skin markings.

IMRT

In CT simulation and treatment, the patient was immobilized with a vacuum pillow in the supine position. The CTV included the entire prostate only, or the prostate and proximal portion of the seminal vesicles depending on the risk category of the disease. The PTV was defined by adding a 7-mm margin around the prostate except posteriorly at the rectal interface, where a 6-mm margin was used, and by adding a 5-mm margin around the seminal vesicles. The rectum and entire bladder were delineated as solid organs. The rectum was contoured from 4 mm above the PTV to 4 mm below the PTV. A five to seven fields step-and-shoot IMRT plan was created using 10-MV photons. The prescribed radiation dose represented the minimum dose to 95% of the PTV. The median doses were 76 Gy (range, 70–78 Gy) for low-risk patients, 78 Gy (range, 70–80 Gy) for intermediate-risk patients, and 78 Gy (range, 70–80 Gy) for high-risk patients. Dose constraints included a maximum dose to the PTV (PTV Dmax) $\leqslant$107% of the prescribed dose, mean dose to the PTV (PTV Dmean) $\geqslant$100% of the prescribed dose, the dose delivered to 95% of the PTV (PTV D95%) $\geqslant$100% of the prescribed dose, maximum dose to the rectum (rectum Dmax) $\leqslant$107% of the prescribed dose, the dose delivered to 1% of the rectum (rectum D1%) $\leqslant$78 Gy, the dose delivered to 5% of the rectum (rectum D5%) $\leqslant$76 Gy, the dose delivered to 20% of the rectum (rectum D20%) $\leqslant$60 Gy, the dose delivered to 40% of the rectum (rectum D40%) $\leqslant$40 Gy, and the maximum dose to the bladder (bladder Dmax) $\leqslant$107% of the prescribed dose.

In February 2010, daily cone-beam computed tomography-based image-guided radiotherapy (IGRT), which was based on soft-tissue alignment without implanted markers, was implemented. One hundred and three patients (33.1%) were treated with non-IGRT before implementation of the IGRT and 208 patients (66.9%) were treated with IGRT.

PI/PI + EBRT

The techniques and dose constraints used for the PI and PI + EBRT groups have been previously described in detail [13–15]. The PI dose calculation was performed in accordance with NIST-99 calibration standards, the AAPM TG-43 formula, and the TG-43 update [16–18]. The prescribed dose was 160 Gy (TG-43) for PI alone and 110 Gy (TG-43) for PI + EBRT. PTV was defined as the prostate itself. Dose constraints included V100 >95%, V150 <50%, 110% < D90 < 130%, urethral volume receiving 150% of the prescribed dose <0.1 cc, and rectal volume receiving 100% of the prescribed dose <0.1 cc. Post-implant CT dosimetry was performed 1 month after implantation, and the minimal dose received by 90% of the prostate (prostate D90) and rectal volume receiving more than 100% of the prescribed dose (RV100) in the PI were calculated. In the PI + EBRT group, approximately 4–8 weeks after seed implantation, supplemental EBRT was initiated using 3D-CRT with 10 MV photons to a median dose of 45 Gy in 1.8 Gy fractions at isocenter.

Calculation of equivalent dose in 2 Gy fractions

The prostate biological effective dose (BED) was calculated from the EBRT prescribed dose and the prostate D90 using an α/β ratio of 2 (Gy2), as described by Stock et al. [19]. The total BED values for the PI + EBRT regimen were obtained by summing the BEDs computed for each treatment. The equivalent dose in 2 Gy fractions (EQD2) was calculated as

$$\mathrm{EQD2} = \mathrm{BED}/[1 + 2/(\alpha/\beta)]$$

with an α/β ratio of 2, which is the same as that used in the calculation of BED.

Follow-up

Clinical follow-up evaluations included obtaining an interval history and performing a physical examination at 3-month intervals during the first 2 years and every 6 months thereafter. Post-treatment GU/GI toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) scoring system modified by Wong et al. [11]. While the use of the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE-IV) would have made the results of the present study more reproducible, it could be subjective depending on evaluator interpretation. To reduce the uncertainty that exists between evaluators, we adopted the modified RTOG scale, which is similar to the CTCAE-IV, and more detailed and specific for radiotherapy-induced toxicities than the CTCAE-IV.

Please cite this article in press as: Sutani S et al. Comparison of genitourinary and gastrointestinal toxicity among four radiotherapy modalities for prostate cancer: Conventional radiotherapy, intensity-modulated radiotherapy, and permanent iodine-125 implantation with or without external beam radiotherapy. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.08.019