Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: A retrospective study regarding toxicity, biochemical outcome and quality of life

Max Peters [a,*], Metha Maenhout [a,*], Jochem R.N. van der Voort van Zyp [a], Marinus A. Moerland [a], Maaike R. Moman [b], Lotte M.G. Steuten [c], Marijke J.H. van Deursen [a], Marco van Vulpen [a]

[a] Department of Radiation Oncology, University Medical Center Utrecht; [b] Department of Radiology, Meander Medical Center, Amersfoort; and [c] Department of Health Technology and Services Research, University of Twente, Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 16 June 2014
Accepted 16 June 2014
Available online xxxx

Keywords:
Focal salvage
Prostate cancer
I125 brachytherapy
Toxicity
Biochemical failure
Quality of life

ABSTRACT

Purpose: Whole-gland salvage for recurrent prostate cancer (PCa) shows high failure and toxicity rates. Early and adequate localization of recurrences enables focal salvage, thereby potentially improving functional outcomes, while maintaining cancer control.

Materials and methods: Retrospective analysis yielded 20 focal salvage I125 brachytherapy patients for locally recurrent PCa after primary radiotherapy. Tumor was defined by multiparametric MRI and correspondence with transrectal biopsies. Dose data were obtained intra-operatively. The tumor was prescribed $\geqslant$144 Gy. Toxicity was scored by the Common Terminology Criteria for Adverse Events version 4 (CTCAE-4). Biochemical failure (BF) was defined using the Phoenix criteria (PSA-nadir + 2.0 ng/ml). Quality of life (QoL) was measured by SF-36 Health Survey and European Organization of Research and Treatment of Cancer (EORTC) C30+3 and PR25 questionnaires.

Results: With a median follow-up of 36 months (range 10–45), six patients experienced BF, of which three had no initial response. Grade 3 genitourinary (GU) toxicity occurred in one patient (a urethral stricture). The five previously potent patients retained erectile function. QoL remained decreased with regard to urinary symptoms.

Conclusion: Focal salvage I125 brachytherapy showed one grade 3 GU toxicity in the 20 treated patients. Biochemical response and QoL were acceptable.

 Radiotherapy and Oncology xxx (2014) xxx–xxx

Patients treated with external beam radiotherapy or brachytherapy for prostate cancer (PCa) are at risk of recurrent disease, distant metastases and subsequently death. Individual risk depends on risk factors such as tumor stage, Gleason differentiation grade, initial PSA value, PSA-doubling time (PSADT) and time to biochemical failure (BF) after primary treatment [1–3]. For the highest risk groups, biochemical failure (BF) rates can exceed 60% after 10 years [4–7]. The advancements in diagnostic modalities have brought forth the expectation that many of these biochemical recurrences will be due to organ-confined disease, with pathology studies suggesting that most recurrences are located at the site of the primary (dominant) lesion [8–10]. This (index) lesion is thought to drive the natural metastatic progression of PCa, with possibly a monoclonal origin of metastases [11–13].

Recurrences can be curatively treated with whole-gland salvage, such as prostatectomy, cryosurgery, brachytherapy and high intensity focused ultrasound (HIFU) [14–16]. However, all salvage therapies show high failure and toxicity rates, and superiority of any one of these salvage modalities has not been shown [14–16]. Palliative androgen deprivation therapy (ADT) is therefore generally used. Theoretically, targeting only the recurrent localized lesion might reduce the severe morbidity associated with whole-gland salvage and can prevent or postpone the use of ADT.

The aim of this retrospective analysis is to evaluate focal salvage I125 brachytherapy regarding technical aspects and to describe toxicity, biochemical outcome and quality of life (QoL).

Materials and methods

Patients

Institutional review board approval was obtained for this retrospective analysis and the analysis of the QoL data. From March

* Corresponding authors. Address: University Medical Center Utrecht, Department of Radiotherapy, HP. Q00.118, Heidelberglaan 100, 3584CX Utrecht, The Netherlands.

E-mail addresses: m.peters-10@umcutrecht.nl (M. Peters), M.maenhout@umcutrecht.nl (M. Maenhout).

http://dx.doi.org/10.1016/j.radonc.2014.06.013
0167-8140/

2009 until October 2012, 20 patients were treated with focal salvage I-125 brachytherapy. In addition, patients were considered eligible for focal salvage if they met the following criteria: 1. BF ⩾ two years after primary treatment, 2. unilateral biopsy-proven recurrence after systematic transrectal biopsies of both prostate lobes, 3. no extra-capsular extension or seminal vesicle involvement on MRI, 4. local recurrence evident on multiparametric MRI, 5. correlation between biopsy results and findings on MRI sequences, 6. pre-treatment PSA < 20 ng/ml, 7. no ADT at time of salvage, 8. no lymph-node or distant metastases on pelvic-CT or bone scan.

F18-Choline Positron Emission Tomography (PET) scans were performed for 10 of the patients to exclude metastatic disease.

Treatment planning and procedure

A pre-operative 3 Tesla MRI was acquired for all 20 patients. This included a T1-weighted, T2-weighted, dynamic contrast enhanced (DCE) and diffusion weighted imaging (DWI)-sequence. This combination is regarded as predictive for the localization of recurrent PCa [17]. DCE-MRI is especially promising regarding recurrent PCa [18]. No endorectal coil was used. The gross tumor volume (GTV) was delineated on T2W-MRI combining biopsy results and multiparametric MR image(s). On MRI scans, an area was considered as tumor if either of the following were present: a hypo-intense signal on T2W, increased contrast enhancement on DCE-MRI, diffusion restriction on DWI, or a combination of the above. All MRI scans were reviewed by an experienced radiologist and radiation oncologist. The MR-images were imported in the brachytherapy planning software, the Sonographic Planning of Oncology Treatment (SPOT, $n = 18$) or OnCentra Prostate (OCP, $n = 2$) (Nucletron BV, Veenendaal, the Netherlands). The GTV and prostate were delineated on MRI and manually registered to the real-time TRUS during the intra-operative procedure. Furthermore, the organs at risk (OAR: rectum and urethra) were also delineated on the real-time TRUS.

The implantation of I125 seeds was performed under spinal anesthesia with a TRUS-guided, transperineal approach. Needles were inserted through a template. The TRUS probe and template were mounted on a stepper. This implantation procedure is equivalent to conventional I125-brachytherapy [19]. The number of needles and seeds depended on the GTV-volume. Treatment margins were expanded up to half of the prostate to account for uncertainties in the definition and delineation of the GTV, and the uncertainty in matching of the MRI and ultrasound images (Figs. 1 and 2).

A dose of ⩾144 Gy was prescribed to the target area. Dose constraints for the OAR were according to ESTRO/EAU/EORTC-recommendations for primary brachytherapy: urethra D_{10} < 150% (<216 Gy = dose received by 10% of the structure), rectum D_{2cc} < 100% (<144 Gy = dose received by 2 cc of the structure) and $D_{0.1cc}$ < 200 Gy [20]. No bladder constraints were applied during treatment, as none are available for I-125 brachytherapy.

Toxicity assessment and PSA measurements

Genitourinary (GU), gastrointestinal (GI) toxicity and erectile dysfunction (ED) were evaluated with the Common Terminology Criteria for Adverse Events version 4 (CTCAE-4). Toxicity was considered severe if ⩾grade 3. Toxicity is commonly evaluated at baseline, 1 and 6 months postoperatively, and annually thereafter. PSA-measurements were performed 4 weeks and 3 months postoperatively, and subsequently every 6 months or annually. BF was defined according to the Phoenix definition (PSA nadir + 2.0 ng/ml). Biochemical disease free survival (BdFS) was estimated using Kaplan–Meier analysis. Patients were censored after their last follow-up moment or death. The initial and pre-focal salvage PSA-values of patients with biochemical failure were tested against those patients who stayed in (biochemical) remission. Because of the non-Gaussian distribution of the data, a Wilcoxon-signed rank test was used to analyze the data for significance. A p-value < 0.05 was considered to indicate statistical significance.

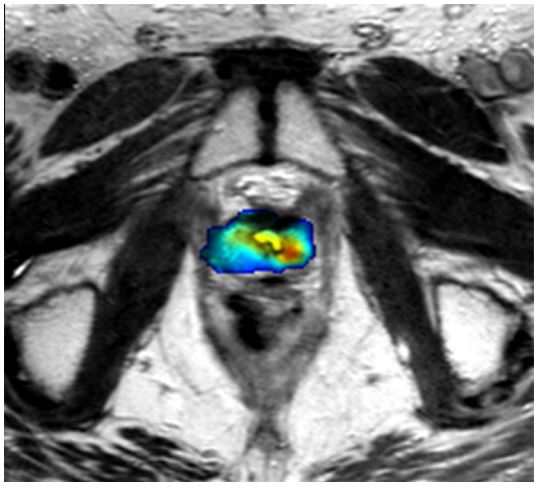

Fig. 1. A transverse image of the prostate is depicted. The DCE-MRI color map (K_{trans}) is projected over the T2-weighted MRI image, where red indicates relatively high and blue relatively low perfusion. The T_2weighted MRI showed a hypointense signal suspect for tumor in that same area (the left lateral dorsal base of the prostate). On the apparent diffusion coefficient (ADC) map of the diffusion weighted image (DWI), a diffusion restriction was observed in this same area, which is also indicative of tumor.

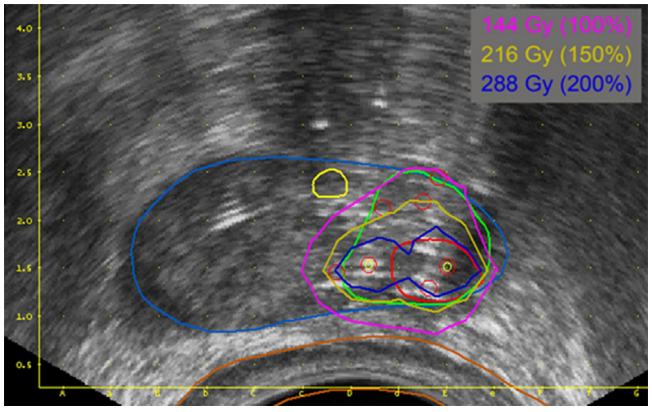

Fig. 2. Intra-operative dose distribution, based on the same patient. The needle positions are indicated, together with the primary GTV (red line), expanded GTV (green line), the urethra (yellow line) and the rectum (brown line). The dose distribution is depicted in purple (100% = 144 Gy), yellow (150%) and blue (200%). The primary GTV received a dose of approximately 200%. The rectum and urethra remain beneath the 100% dose line. *Abbreviations:* GTV = gross tumor volume.

Quality of life

QoL is measured at baseline, 1 month, 6 months and then annually after focal salvage treatment as a standard of care monitoring instrument. Three validated questionnaires are used: the RAND-36 [21], the European Organization of Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30(+3)) [22], and the prostate-specific EORTC QLQ-PR25 [23]. A Wilcoxon signed rank test was performed to compare each value to the value at baseline.

Please cite this article in press as: Peters M et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: A retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.06.013