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Prostate brachytherapy

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

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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.

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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

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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.

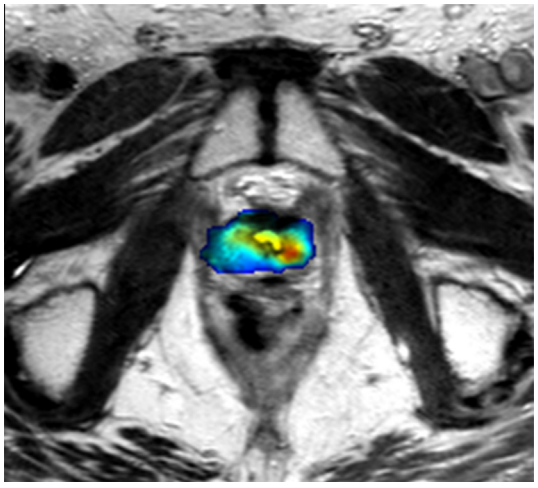

Fig. 1. A transverse image of the prostate is depicted. The DCE-MRI color map (K_{trans}) is projected over the T2-weighted MRI image, where red indicates relatively high and blue relatively low perfusion. The T_2weighted MRI showed a hypointense signal suspect for tumor in that same area (the left lateral 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.

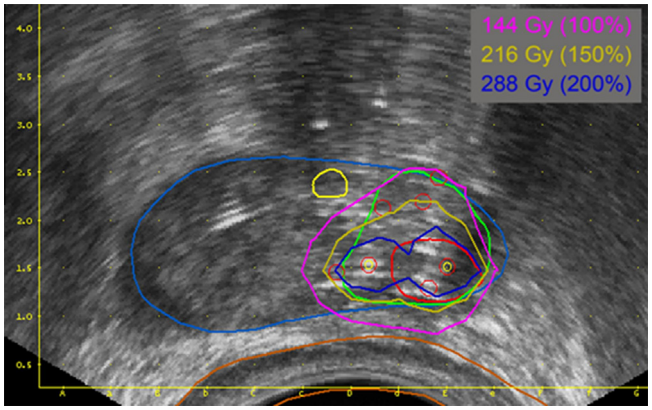

Fig. 2. Intra-operative dose distribution, based on the same patient. The needle positions are indicated, together with the primary GTV (red line), expanded GTV (green line), the urethra (yellow line) and the rectum (brown line). The dose distribution is depicted in purple (100% = 144 Gy), yellow (150%) 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.

A p-value < 0.017 was considered statistically significant, using a Bonferroni correction for multiple testing (0.05/3 measurements). Clinical relevance was defined as a median difference of >10 points compared to baseline [24]. Data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

The median age of the patients was 69 years (range 59–78). Time between primary and salvage treatment varied between 3.5 and 12 years. Median pre-salvage PSA was 4.7 ng/ml (range 0.3–14.0) and median initial PSA before primary treatment was 12.9 ng/ml (range 5.4–51). The median PSADT before focal salvage was 19 months (range 6.1–90). Two patients had a PSADT < 10 months, but did not fail treatment. The median follow-up was 36 months (range 10–45). The initial tumor stage of the patients was T3 in 50% and both T1 and T2 in 25%. Of the primary tumors 12 (60%) were Gleason 4–6 (G1), six (30%) Gleason 7 (G2) and two (10%) Gleason 8–10 (G3). Eight (40%) patients received hormonal therapy ranging from 6 to 36 months before focal salvage. A median of 10 (range 6–13) biopsy cores were taken. All biopsy regiments were bilateral. Most tumors were present in the left peripheral mid and base of the prostate (total 60%). A median of 15% (range 5–80%) tumor load was found (in 11 patients). 6 patients (30%) had multiple (2–5) unilateral tumor localizations. The implants for these patients were expanded up to half of the prostate accordingly. 14 patients (70%) had a single unilateral recurrence. For additional patient and treatment characteristics, see Table 1.

Biochemical outcomes and survival

Three patients (15%) failed treatment after 24 (n = 1) and 36 months (n = 2). Three patients did not respond to treatment and developed metastatic disease, including the only patient with a pre-salvage PSA > 10.0 ng/ml (14 ng/ml). These six patients were treated with ADT after biochemical failure.

The Kaplan–Meier 3-year BdFS estimates are 71% and 60% excluding and including non-responders, respectively (Fig. 3, Supplementary material). One patient died 6 months post-treatment caused by a cardiac arrest, unrelated to the PCa or treatment. The median initial PSA of patients with a biochemical recurrence was 19 ng/ml (range 6.7–51) versus 12.1 ng/ml (range 4.7–39.5) in the group without a biochemical recurrence. The pre-focal salvage PSA for these groups was median 5.4 ng/ml (range 2.5–14) and 4.6 ng/ml (range 0.3–10), respectively. Even though there is an absolute median difference between the two groups, no statistically significant difference was observed (p = 0.628 and p = 0.336, respectively).

Toxicity

Frequencies of GU and GI toxicity and ED are presented in Table 2 (Supplementary material). One urethral stricture was observed two years post-treatment. This was scored as severe (grade 3) GU toxicity. After endoscopic incision of the stricture, the patient recovered, with some urinary incontinence remaining (grade 2). Grade 1 urinary incontinence occurred in 4 patients. In the remaining 15 patients no urinary incontinence was observed. The most frequent GU toxicity was urinary frequency (grade 1–2), often present before focal salvage due to primary radiotherapy. This was managed predominantly with medication, after which most patients recovered. One patient experienced radiation

Table 1
Baseline characteristics, diagnostic and treatment related parameters.

Variable	N = 20
Median (range) age, years	69 (59–78)
Primary therapy	
I-125 brachytherapy (T1–T2), 145 Gy	7 (35%)
EBRT, 70 Gy (T3), 35 fractions	6 (30%)
IMRT, 76 Gy (T3), 35 fractions	7 (35%)
Median (range) time between primary treatment and focal salvage, months	79 (42–144)
Initial tumor stage (primary tumor)	
T1	5 (25%)
T2	5 (25%)
T3	10 (50%)
Initial Gleason score (primary tumor)	
Grade 4–6	12 (60%)
Grade 7	6 (30%)
Grade 8–10	2 (10%)
Median (range) initial PSA, ng/ml (primary tumor)	12.9 (5.4–51)
4–10 ng/ml	8 (40%)
10–<20 ng/ml	7 (35%)
20–<50 ng/ml	4 (20%)
>50 ng/ml	1 (5%)
D'Amico risk group (primary tumor)	
Low	5 (25%)
Intermediate	3 (15%)
High	12 (60%)
Area of primary tumor	
Left	6 (30%)
Right	5 (25%)
Bilaterally	8 (40%)
Unknown	1 (5%)
Gleason score recurrence	
Grade 4–6	7 (35%)
Grade 7	6 (30%)
Undefinable	7 (35%)
Median (range) PSA before focal salvage, ng/ml	4.7 (0.3–14.0)
0–4 ng/ml	8 (40%)
4–<10 ng/ml	11 (55%)
10–<20 ng/ml	1 (5%)
Median (range) PSADT before focal salvage, months	19 (6.1–90)
F18-choline PET-scan	
Yes	10 (50%)
No	10 (50%)
Hormonal therapy before focal salvage	8 (40%)
Zoladex	5 (25%)
Casodex	3 (15%)
Median (range) duration, months	36 (6–36)
Median (range) nadir PSA after focal salvage, ng/ml	0.4 (0.2–3.8)
Biopsy area of recurrence (+T_2W/DCE/DWI-MRI localization)	
Left peripheral base	6 (30%)
Left peripheral mid	6 (30%)
Left peripheral apex	2 (10%)
Right peripheral base	4 (20%)
Right peripheral mid	2 (10%)
Right peripheral apex	3 (15%)
Total cores, median (range)	10 (6–13)
Tumor load in positive biopsies (n = 11), median (range)	15 (5–80)
Patients with multiple (2–5) positive biopsies (unilateral) of recurrence	6 (30%)
Single unilateral recurrence	14 (70%)
Median (range) follow-up after focal salvage, months	36 (10–45)
Vital parameters after focal salvage	
Non-responders	3
Biochemical failure (months)	3 (24–36)
Death, unrelated to PCa	1
Treatment related parameters	
Median (range) prostatic volume, cc	24 (11–75)
Median (range) number of needles	9 (6–12)
Median (range) number of seeds	32 (17–46)
Median (range) % of prostate considered GTV	23 (6–50)
Median (range) V100 percentage of prostate	45 (27–56)

Abbreviations: I-125 = iodine-125; EBRT = external beam radiotherapy; IMRT = intensity modulated radiotherapy; Gy = Gray; PSA = prostate specific antigen; PSADT = PSA doubling time. PCa = prostate cancer; V100 = volume that receives 100% (145 Gy) dose.

cystitis (grade 2) one year post-treatment, for which he successfully received hyperbaric oxygen therapy. The most frequently observed GI toxicity consisted of short rectal/perirectal pain and diarrhea. A few patients had minor (grade 1) GI toxicity before focal salvage. Two patients suffered from radiation proctitis (grade 2) before focal salvage. One patient was successfully treated with laser therapy, the other recovered spontaneously.

Grade 2 ED was present in 10 and grade 3 in 5 patients pre-salvage. The 5 initially potent patients retained potency during follow-up. One patient experienced a slight decrease (grade 1), but did not need therapy for adequate sexual functioning.

Dosimetry

In 18 patients, ⩾95% of the GTV was covered with ⩾144 Gy (91% in 2 patients). A median of 45% (range 27–56%) of the prostate received 100% dose (144 Gy). Median D90 for the GTV was 198 Gy (range 150–330). The median D2cc and D0.1cc for the rectum were 68 Gy (range 18–96) and 133 (range 69–207), respectively. The D0.1cc constraint for the rectum was exceeded in 1 patient (207 Gy). Median urethral D10 was 132 Gy (100–240). Two patients exceeded the restriction of 216 Gy (232 and 240 Gy).

Quality of life

QoL data was available for 14 patients. Four weeks post-treatment, patients reported a decrease in QoL regarding global health, general physical discomfort, fatigue and urinary symptoms. After 6 months, only a decrease in urinary symptoms remained. After a median of three years follow-up (range 10–45 months), only urinary symptoms showed a statistically significant and clinically relevant deterioration. Physical functioning, general physical discomfort and treatment related symptoms showed no clinically relevant deterioration (although $p < 0.017$) because the absolute median difference was <10 points [24]. The results regarding QoL are depicted in Table 3 (Supplementary material).

Discussion

Focal I125-salvage seems technically feasible and clinically acceptable. Technical feasibility focused on the implantation procedure and the ESTRO/EAU/EORTC dose prescriptions. The clinical feasibility evaluated biochemical response, toxicity and QoL.

As no guidelines for salvage I-125 brachytherapy exist, dose prescriptions for primary brachytherapy were used [20]. The GTV was often given a high dose (median D90 = 198 Gy (range 150–330)) (Fig. 2). Almost all patient plans met the OAR constraints. This could explain the favorable toxicity rates and could be an indication of the validity of these prescriptions for focal salvage I-125 brachytherapy. Only one patient (5%) underwent an endoscopic intervention for a urethral stricture, which was scored as grade 3 even though no hydronephrosis or renal dysfunction was present. One patient was treated for radiation cystitis (grade 2). ED did not occur for the five initially potent patients. These results are promising compared to the frequent severe toxicity rates associated with whole-gland salvage, which shows high rates of severe incontinence (up to 70%), urinary obstruction/retention (up to 50%), rectal injury and recto-urethral fistula (up to 10%) and frequently nearly 100% ED [14–16]. Grade 3 genitourinary and gastro-intestinal toxicity (requiring operative intervention) for whole-gland salvage are usually estimated around 30% [14–16]. This is probably associated with targeting the entire prostatic volume and reduced repair capacity of surrounding organs and neurovascular bundles after primary radiotherapy. Targeting a smaller prostatic volume in the focal salvage setting seems to reduce the damage to these surrounding structures, with less toxicity as a consequence.

Evidence regarding focal salvage is limited. Eisenberg et al. retrospectively analyzed partial salvage cryosurgery in 19 patients suffering from radio-recurrent PCa. Three-year biochemical recurrence-free survival rates were 50% (ASTRO-criteria) and 79% (Phoenix-criteria), with acceptable treatment-related morbidity: one urethral stricture, one urethral ulcer and one mild stress incontinence. Forty percent (2/5) of previously potent patients remained potent [25]. Another (retrospective) focal salvage cryotherapy study was done by de Castro Abreu et al. regarding salvage total (STC, $n = 25$) or salvage focal cryoablation (SFC, $n = 25$, defined as hemi-ablation) after primary radiotherapy [26]. Five-year biochemical failure-free survival estimates were 54.4% (SFC) and 86.5% (STC). It seems that regarding BF, focal salvage might be inferior to whole-gland salvage for this particular group of patients. However, due to heterogeneity in the patient groups, no statistical comparison was made. The toxicity rates for SFC were satisfactory: no urinary incontinence and no recto-urethral fistulas were found. Twenty-nine percent retained potency (2/7). In the STC group, 13% developed urinary incontinence, 0% retained potency (0/4) and one (4%) developed a recto-urethral fistula.

Ahmed et al. retrospectively analyzed focal salvage HIFU (also hemi-ablation) in 39 patients. The biochemical progression-free survival was 69% at one and 49% at two years (Phoenix) with acceptable continence and potency rates, but with 23% needing surgical or endoscopic intervention under general anesthesia due to adverse events [27].

Prospective studies are also limited. The earliest study is from Shariat et al. who treated 8 patients with radiofrequency interstitial tumor ablation (RITA) [28]. All patients experienced a decrease in PSA after treatment, and in all patients PSA decreased >66% after median 18 months (range 3–33) follow-up, with minor self-limiting or conservatively managed complications. ED is not reported.

Recently, Hsu et al. reported partial salvage permanent prostate implant (PPI) with I-125 seeds for local recurrences after initial PPI ($n = 15$). After 3 years, progression free survival (Phoenix-definition) was 71.4%. Two patients who failed treatment were re-implanted successfully. No grade 3 GI or GU toxicity was observed. Grade 3 ED was observed in 2 patients (13%), while the majority of patients remained potent [29].

The most recent study analyzed 10 patients who underwent focal salvage MRI-guided cryotherapy. Technically, the procedure was feasible, with acceptable side-effects (one patient developed a urethral stricture, which had to be resolved surgically). Follow-up was short: 6 months ($n = 8$) and 12 months ($n = 4$). Three patients had a biochemical recurrence and were successfully re-treated [30].

Our study shows a crude biochemical recurrence-free rate of 70% after median 36 months (range 10–45) follow-up and 82% when excluding the three non-responders. 3-year Kaplan–Meier BdFS estimates are 60% and 71%, respectively. These results, in combination with the results from the literature regarding focal salvage, seem to correlate with oncologic outcomes of whole-gland salvage series [14,15]. However, comparison is hampered by the variability in patient and tumor characteristics, definitions of failure and the concomitant use of ADT, among other factors. A definitive comparison between focal and whole-gland salvage can therefore not be made with this preliminary data and the scarce evidence available for focal salvage therapies. Trials between the two modalities would need to be performed to assess these preliminary results regarding biochemical outcome, toxicity and quality of life.

Although current results are acceptable, long term biochemical and survival outcomes are required. Multifocality of recurrent PCa might be present. One patient with PSA progression suffered from

a pre-salvage PSA > 10 ng/ml. Even though the PSA values of patients with a biochemical recurrence did not differ significantly from patients without a biochemical recurrence in this group, a high pre-salvage PSA could still be an indication of more advanced disease. A larger cohort would need to be analyzed to assess the relation between PSA-values and biochemical outcome in the focal salvage setting. Two other patients also failed, reflecting probable (micro)metastatic disease at the time of focal salvage. Both patients had primary T3-tumors, which could pose an explanation. A short PSADT is also a predictor of (metastatic) disease progression and PCa specific mortality [1]. However, the two patients with a PSADT < 10 months did not fail treatment. In general, low to intermediate risk patients are expected to be ideal candidates for focal ablation of a local recurrence. A more uniform approach in selecting these patients for focal salvage might strengthen these preliminary results.

In patients with a rise in PSA, we expect multifocality can be detected by performing T2W/DCE/DWI-MRI, in combination with systematic biopsies. Previous pathology studies show recurrent tumors to re-grow primarily at the site of the primary (dominant) tumor, usually with a smaller volume [8–10]. In contrast, some pathology data seem to localize recurrences bilaterally (28%) and frequently within 5.0 mm of the urethra, creating obstacles for focal salvage [31]. In addition, biopsy studies seem to indicate that a significant number of additional cancer sites are found when expanding the number of biopsies and when a transperineal approach is used. More than 60% of patients can have bilateral cancer foci in previous TRUS-guided unilateral positive biopsies when expanding to 50 cores with a transperineal approach [32]. It can be questioned, though, if all tumor foci should be treated, or that therapy should target the previously mentioned index lesion [12,13]. It seems that secondary tumor foci do not drive the progression of PCa [12]. This might be of special importance in the focal salvage setting, since secondary tumor foci might have been treated successfully by the primary radiotherapy, leaving only the index lesion as potential malignant remnant. This might have been the case in this particular group of patients, of which the biopsy results before initial radiation were bilaterally positive in 40% ($n = 8$). Furthermore, the index lesion might be the tumor with the biggest volume, thereby reducing the risk of underdetection using conventional transrectal biopsy schemes in combination with multiparametric MRI, as was done in the current study.

QoL was significantly decreased in the domains physical functioning, general physical discomfort, treatment related symptoms and urinary symptoms. Urinary symptoms were frequently encountered in the toxicity data and could be an explanation for the deterioration in these last two domains. Because of multimorbidity and increasing age in a growing number of patients, physical function and general physical discomfort might have decreased independently of the focal salvage treatment. This was exactly what many patients declared during follow-up with regard to their QoL. Furthermore, the only clinically relevant deterioration was present in urinary symptoms (median difference > 10 points) [24]. In the other domains, the median difference was <10 points. The deterioration in these three domains might have been random because of multiple testing.

Focal salvage was performed under spinal anesthesia. Together with the outpatient approach, the burden to the patient is low, which may increase cost-effectiveness. Also, when considering primary focal treatment, repeating focal salvage might be a solution for tumor re-growth during follow-up, especially when toxicity rates remain as low as observed. Therefore PCa might be regarded for some patients as a chronic disease in which only the clinically relevant tumor areas are treated.

Conclusion

Focal multiparametric MRI-TRUS guided I125 salvage is a promising new treatment approach for patients with locally recurrent prostate cancer after radiotherapy. The treatment is technically feasible and biochemical response, toxicity and quality of life are acceptable.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.06.013.

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