Salvage Stereotactic Body Radiation Therapy for Local Prostate Cancer Recurrence After Radiation Therapy A Retrospective Multicenter Study of the GETUG

David Pasquier, Geoffrey Martinage, Guillaume Janoray, Damaris Patricia Rojas, Dario Zerini, Flora Goupy, Renaud de Crevoisier, Emilie Bogart, Gilles Calais, Alain Toledano, et al.

Salvage stereotactic body radiotherapy for local prostate cancer recurrence after radiotherapy: a retrospective multicentre study of the GETUG

David Pasquier*[1,2] MD, PhD, Geoffrey Martinage*[1] MD, Guillaume Janoray[3,4] MD, Damaris Patricia Rojas[5] MD, Dario Zerini[5] MD, Flora Goupy[6] MD, Renaud De Crevoisier[6-8] MD, PhD, Emilie Bogart[9], Gilles Calais[3,4] MD, PhD, Alain Toledano[10] MD, Laurent Chauveinc[10] MD, PhD, Nathaniel Scher[10] MD, Pierre Yves Bondiau[11]MD, PhD, Jean Michel Hannoun-Levi[11]MD, PhD, Marlon Silva[12] MD, Emmanuel Meyer[12] MD, Philippe Nickers[1] MD, PhD, Thomas Lacornerie[13], Barbara Jereczek-Fossa[5] MD, PhD, Eric Lartigau[1,2] MD, PhD

* Both authors contributed equally to this work

1) Academic Department of Radiation Oncology, Centre Oscar Lambret, F-59000 Lille, France

2) CRIStAL UMR CNRS 9189, Lille University, F-59000 Lille, France

3) Oncology-Radiotherapy Department, Henry-S.-Kaplan Cancer Center, CHRU de Tours, 2, boulevard Tonnelle, F-37000 Tours, France

4) University François-Rabelais, F-37000 Tours, France

5) Department of Radiotherapy, European Institute of Oncology and Department of Oncology and Hemato-oncology, University of Milan, Italy

6) Department of Radiotherapy, Centre Eugène Marquis, F-35000 Rennes

7) INSERM 1099 Unit, F-35042 Rennes, France

8) LTSI, Université de Rennes 1, F-35042 Rennes, France

9) Department of Biostatistics, Centre Oscar Lambret, F-59000 Lille, France

10) Department of Radiotherapy, Hartmann Radiotherapy Center, F-92300 Levallois-Perret, France

11) Department of Radiation Oncology, Antoine Lacassagne Cancer Center, University of Cote d'Azur, F-06100 Nice, France

12) Department of Radiation Oncology, Centre François Baclesse, F-14000, Caen, France

13) Department of Medical Physics, Centre Oscar Lambret, F-59000 Lille, France

Running title: SBRT for prostate cancer recurrence

Corresponding author:

David Pasquier, MD, PhD; Department of Radiation Oncology, Centre Oscar Lambret, 3 rue Combemale, 59020 Lille cedex, France.

Email: d-pasquier@o-lambret.fr

Phone: +33 3 20 29 59 11; Fax: +33 3 20 29 59 72

Author responsible for statistical analyses:

Emilie Bogart, Department of Biostatistics, Centre Oscar Lambret, 3 rue Combemale, 59020 Lille cedex, France.

Email: e-bogart@o-lambret.fr

Conflict of interest statement: The authors have no conflict of interest to declare.

No funding to declare.

Acknowlegments: Ms. Jone Iriondo for writing assistance.

Salvage stereotactic body radiotherapy for local prostate cancer recurrence after radiotherapy: a retrospective multicentre study of the XXXXX

Abstract

Background and purpose

To assess the efficacy and safety of salvage stereotactic body radiotherapy (SBRT) in patients with biopsy-proven local prostate cancer recurrence after radiotherapy.

Methods and Materials

Between April 2010 and January 2017, 100 patients were included in 7 centers. Disease extension was assessed by pelvic multiparametric magnetic resonance imaging and choline positron emission tomography in 87% and 94% of patients, respectively. The median time interval between the two treatments was 7.5 years (range, 2-18). Median PSA at recurrence was 4.3 ng/mL (range, 2-38). Median SBRT dose was 36 Gy (range, 25-36.25) in 6 fractions (range, 5-6), every other day. Thirty-four percent of patients were treated by androgen deprivation therapy for a median duration of 12 months. Toxicity was assessed according to CTCAE v.4.03.

Results

Median follow-up was 29.3 months (range, 4–91). Second biochemical recurrence-free survival rate at 3 years was 55% [95% CI: 42%–66%]. The initial D'Amico group, time interval after first radiotherapy and SBRT dose were prognostic factors of biochemical recurrence-free survival in multivariate analysis (p=0.09, p=0.025, p=0.018, respectively). No patient developed acute gastro-intestinal (GI) toxicity of grade > 1; acute genito-urinary (GU) toxicity of grade 2 and 3 were 8% and 1%, respectively. The actuarial 3-year grade ≥2 GU and GI

toxicity was 20.8% (95% CI: 13%-29%) and 1% (95% CI: 0.1%-5.1%), respectively. One patient presented a neuritis of grade 3.

Conclusion

With a short follow up, this study shows that salvage SBRT allows for encouraging control and acceptable toxicity. Further prospective studies are necessary to confirm these preliminary results and to determine late toxicity.

Introduction

Prostate cancer is the most frequent cancer in developed countries and the third cause of cancer-related deaths in men [1]. The most common site of first recurrence after external beam radiotherapy (EBRT) for prostate cancer is the prostate [2]. Currently, there is no standard of local treatment for these recurrences, and no proof exists on the improvement in survival after the early use of androgen deprivation therapy (ADT). Several options can be proposed including surveillance, surgery, high-intensity ultrasound (HIFU), brachytherapy or cryotherapy. These treatment options, however, are limited by their availability and operator-dependency; salvage radical prostatectomy (SRP) after radiotherapy is feasible but there are high levels of complications [4-12]. As a consequence, less than 2% of the patients with a local recurrence undergo a new local treatment [13]. Stereotactic body radiotherapy (SBRT) is an option for the treatment for primary low- and intermediate-risk prostate cancer [3,14,15]. SBRT allows administering a high dose per fraction with an elevated dose gradient. The high doses per session are particularly interesting for the treatment of prostate cancer due to the low alpha:beta ratio, which allows a shorter overall treatment time [14,15]. Currently, few data are available on the use of this technique as salvage treatment after definitive radiotherapy. A prospective study and a few small retrospective series have been published [16-22]. Techniques such as 3-dimensional conformal radiotherapy (3D CRT) and intensity-modulated radiotherapy (IMRT) seem to be associated with a higher rate of severe late-term toxicities and poor local biochemical control [23]. We undertook this study to assess the efficacy and safety of salvage SBRT in patients with biopsy-proven local prostate cancer recurrence after radiotherapy.

Materials and methods

Between April 2010 and January 2017, 100 prostate cancer patients treated by salvage SBRT after radiotherapy were included in six centers from the xxxxx and in the xxxx. Inclusion criteria were: histologically-proven history of prostate cancer, initially irradiated with curative intent (EBRT ± brachytherapy boost, exclusive brachytherapy), biochemical recurrence according to the Phoenix criteria occurring at least 2 years after external radiotherapy, histologically-proven local recurrence, absence of pelvic or distant metastasis (choline positron emission tomography [PET] and/or whole body computed tomography [CT]), absence of residual toxicity of grade >2. Patients who had undergone prostatectomy were not included. The study complies with the reference methodology adopted by the XXXXXX Data Protection Authority. The study was part of the retrospective research on prostate cancer notified to the Ethical Committee of XXXXX, XXXXX, XXXXX (notification XXXXX). All patients gave consent for the use of their anonymized data for research and educational purposes.

The primary objective was to evaluate the efficacy of salvage SBRT. The primary endpoint was second biochemical recurrence-free survival defined according to the Phoenix criteria (nadir + 2 ng/mL). Prostate-specific antigen (PSA) bounce was defined as an increase of PSA > PSA nadir + 0.4 ng/mL followed by a spontaneous decrease. Secondary objectives were to evaluate acute and late-term tolerance according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03) and overall survival.

SBRT was delivered with a CyberKnife®-type robotic accelerator (Accuray, Inc., Sunnyvale, CA) in all centers except XXX, where patients were treated either with CyberKnife®, Vero® (Mitsubishi Heavy Industries, Ltd., Japan and BrainLab AG, Feldkirchen, Germany) or RapidArc® (Varian Medical Systems, Palo Alto, CA) systems, the technical

characteristics of which have been published elsewhere [18]. All patients were asked to empty the bowel (oral and written instructions for diet and enema were given) and to have full urinary bladder for simulation CT and all treatment fractions. In cases of partial treatment, the gross tumor volume (GTV) was defined on multiparametric magnetic resonance imaging (mpMRI) and/or choline PET/CT, and with topography of positive biopsies. The clinical target volume (CTV) was defined as GTV with a margin of 2 mm to 5 mm. According to the topography of the positive biopsies, the CTV could be half or the whole prostate. The choice of whole or partial prostate SBRT was left to the discretion of the physician. The planning target volume (PTV) was defined as CTV with a margin of 1 to 2 mm in this context of salvage radiotherapy. The dose was prescribed to the 80% isodose. The most commonly used schema was a total dose of 36 Gy in 6 fractions every other day. Priority was given to either the organs at risk (OAR) or the coverage of the target volume depending of the clinical context. Patients were followed at 3 months and every 6 months thereafter with a clinical examination and a PSA assay. Our series comprises the updated data of some patients that were included in a previous report [18,22]. A few patients (n=19) are part of the XXX series in which the biopsy was optional [24]. In our series, all patients had a biopsy-proven intraprostatic recurrence and none had been treated by prostatectomy.

Survival curves were estimated using the Kaplan-Meier method. After having checked the proportional hazard assumption, multivariate analysis was performed using the Cox regression model. The association between the toxicity and the risk factors was analyzed by an exact Fisher test for qualitative variables and by a Wilcoxon Mann Whitney for quantitative variables. A p value <0.05 was chosen as the significance threshold. Statistical analyses were performed using Stata v13.1 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

Patient and treatment characteristics during initial management are described in Table 1. 80% of the patients had received prior EBRT, 17% brachytherapy alone and 3% EBRT and brachytherapy boost. In patients treated with EBRT alone the median dose of the first course was 74.0 Gy (range, 66.8 – 80.0) delivered in 37 fractions (range, 37 – 42). Median PSA nadir was 0.4 ng/mL (range, 0 – 7.1), obtained within a median time interval of 25 months (range, 4-128). Initial ADT was prescribed to 37 patients for a median duration of 33 months (range, 3-72).

Patient and SBRT characteristics at recurrence are described in Table 2. Before salvage SBRT, 8 patients experienced gastrointestinal (GI) residual toxicities (7 grade 1 and 1 grade 2); 23 patients experienced residual genitourinary (GU) toxicities (21 grade 1 and 2 grade 2). Recurrence was histologically-proven in all patients. The Gleason score could not be assigned in 26 patients due to changes after radiotherapy. Nevertheless, the histological report unambiguously confirmed the presence of adenocarcinoma. The median time interval between the two radiotherapy treatments was 7.5 years (range, 2-18).

Median follow up was 29.3 months (range, 4 – 91). Sixty-three patients received 36 Gy in 6 fractions (considering an alpha:beta ratio= 2 Gy, BED= 144 Gy). Seventy-seven patients were treated with a BED >120 Gy (35 or 36.25 Gy in 5 fractions and 36 Gy in 6 fractions) and 23 with a BED ≤120 Gy.

Median nadir PSA in the overall population was 0.5 ng/mL (range, 0 – 17.0), obtained after a median time interval of 10.3 months (range, 1.5 – 40.8) from salvage SBRT. Sixty-four patients were treated with salvage SBRT without ADT. For these patients, median nadir PSA was 0.71 ng/mL (range, 0.02 – 17), obtained after a median time interval of 11.0 months

(range, 1.4-41). Seven patients (9%) presented a PSA bounce. The median bounce value was 1.8 ng/mL and was obtained after a median time interval of 20.2 months (range, 5.4-55.0) after the re-irradiation. Second biochemical recurrence-free survival rates at 2 and 3 years were 73% (95% CI: 62%–81%) and 55% (95% CI: 42%–66%), respectively, and median biochemical recurrence-free survival was 48 months (95% CI: 31-57) (Figure 1). Overall survival rates at 2 and 4 years were 96% (95% CI: 89%-99%) and 94% (95% CI: 85%-98%), respectively. Four and six patients presented with a second intraprostatic recurrence diagnosed on choline PET/CT, inside the PTV and at another site, respectively. Seven patients presented with extra pelvic metastatic disease: bone, lymph node or visceral. One death was caused by the prostate cancer.

The D'Amico classification, the time interval between the initial radiotherapy and recurrence, and the SBRT scheme were prognostic factors of biochemical recurrence-free survival in multivariate analysis (p=0.009, p=0.025 and p=0.018, respectively) (Table 3). PSA before SBRT did not appear to be significantly associated, (HR=1.02 [95% CI: 0.96-1.07], p=0.547).

No patient presented acute GI toxicity of grade >1, 8 patients (8%) developed acute GU toxicities of grade 2 and 1 patient (1%) developed an acute GU toxicity of grade 3. The actuarial 3-year grade ≥2 GU and GI toxicity was 20.8% (95% CI: 3.1%-29.7%) and 1% (95% CI: 0.1%-5.1%), respectively (Figure 3). One (1%) patient presented a neuritis and GU events of grade 3 (cystitis and fistula). This patient presented severe urinary toxicity, after a salvage SBRT of the whole prostate for a locally advanced tumor and after transurethral resection for obstructive symptoms. Long-term GU toxicities of grade 2 included cystitis/micturition pain (10%), retention (1%), hematuria (2%) and incontinence (3%). A BED >120 Gy was

associated with late grade ≥2 GU toxicity in univariate analysis (p=0.007) but not in multivariate analysis. In univariate and multivariate analysis BED >120 Gy was associated with late grade ≥1 GU toxicity (HR=2.96, [95% CI: 1.35%-6.5%], p=0.007). No other factor appeared to be significantly associated with toxicity. In particular, no differences in toxicity were observed depending on the treated volume (i.e. whole-prostate vs partial SBRT), PTV volume, kind of first treatment (external radiation therapy vs brachytherapy or brachytherapy boost).

Discussion

We report here the largest retrospective multicenter series of patients re-irradiated by stereotactic radiotherapy for a histologically proven intra-prostatic recurrence. With a short follow-up, this multicenter retrospective study shows that salvage SBRT allows for second biochemical recurrence-free survival rates at 2 and 3 years of 73% (95% CI: 62%–81%) and 55% (95% CI: 42%–66%), respectively, with acceptable toxicity. A systematic literature review [4] reported that the probability of second biochemical relapse–free survival following salvage radical prostatectomy (RP) in prostate cancer patients ranged from 47% to 82% after 5 years. Compared to primary RP, salvage-RP is associated with a significantly higher rate of GU and GI morbidity. The review above reported that the most frequent complications were anastomotic stricture (7%-41%) and rectal injury (0%-28%). Post-operative urinary continence ranged from 21%-90% [4]. In a different series, 290 men with biopsy-confirmed recurrent prostate cancer after radiotherapy, were treated with salvage HIFU [9]. At 7 years, the cancer-specific survival rate was 80% and the metastasis-free survival rate was 79.6%. Half of the patients also received ADT. Recto-urethral fistula occurred in 0.4% of patients and 23% had grade 2/3 urinary incontinence.

Philippou et al. [5] recently compared the efficacy and tolerance results of different salvage therapy options. Oncologic outcomes were comparable for salvage RP and all three nonsurgical salvage modalities. No significant differences in toxicity outcomes among modalities were found; however, salvage RP appears to be associated with worse rates of urinary incontinence than brachytherapy, cryotherapy and HIFU. A meta-regression analysis showed no significant difference in biochemical relapse between salvage RP and the nonsurgical salvage modalities [5].

More recently, salvage radiation therapy series have been reported in the literature. Re-irradiation with techniques such as 3D CRT or IMRT with standard fractionation appears to be associated with a high toxicity rate. In Zilli et al.'s series including 14 patients, mean (SD) 5-year grade ≥3 GU and GI toxicity-free survival rates were 77.9% ± 11.3% and 57.1% ± 13.2%, respectively [23]. It is important to note that the median follow-up in this series was 94 months (range, 48-172), longer than that in any other series of salvage SBRT to date. The median follow-up in published salvage SBRT series ranges from 9 to 26 months, which is short to quantify late-term toxicities [16-22,24]. The follow-up of our series is among the longest in this context. Indeed, many salvage SBRT series have recently been published, the first one being Milan's study, which revealed promising preliminary results [17]. A recent retrospective series included twenty-three patients which underwent reirradiation to the prostate, prostatic bed, or prostate and local recurrence. Re-treatment consisted of a median total dose of 25 Gy in 5 fractions using volumetric modulated arc therapy. Thirteen patients were treated for intraprostatic recurrence, without histological evidence, but the small number of patients prevented subgroup analyses [25]. Only one prospective study has been published to date. Twenty-nine patients with biopsy-proven recurrent local prostate cancer were treated with 34 Gy in 5 fractions, delivering a heterogeneous, high dose-rate-

like dose-escalation pattern on the whole gland. With a median 24-month follow-up (range, 3-60 months) the actuarial 2-year biochemical disease-free survival rate was 82%. Grade >1 toxicity was limited to the genitourinary domain, with 18% grade ≥2 and 7% grade ≥3 [16]. While the short follow up prevents drawing definite conclusions, these toxicity rates, as well as ours, seem to compare favourably with those of whole prostate salvage brachytherapy. The results of a phase II trial of brachytherapy for locally recurrent prostate cancer (NRG Oncology/RTOG -0526) were recently published. Ninety-two patients had a median follow-up of 54 months and twelve patients (14%) reported late grade 3 GI/GU events with no treatment-related grade 4 or 5 toxicity. Only higher V100 (% of prostate enclosed by prescription isodose) predicted late toxicity [26].

To date, other than Fuller et al.'s prospective study [16], the total number of patients with histologically-proven recurrence treated with SBRT reported in retrospective series is around 30 [17,18,22]. The multicenter nature of this study allows precising the results in terms of tumor control and toxicity and investigating prognostic factors. Biochemical recurrence-free survival rates are comparable to those reported in the literature with other salvage treatments [5] and in small SBRT series [16-22,24]. With a short follow up, the rates of GU and GI toxicities were acceptable, and also comparable to those reported in the literature [5,16-22]. Selecting the patients with no residual toxicity or disabling urinary symptoms appears important.

One of the predictive factors for biochemical recurrence-free survival evidenced in our series is the D'Amico group during the first treatment, similarly to what has been shown with other salvage treatments, either surgical or not [4,5,9,21]. This can be linked to a diminished local control or to a sensitivity fault for detecting distant or pelvic micro-metastatic disease. New tracers such as prostate specific membrane antigen (PSMA) could allow for better

patient selection [27]. The main limitations of our study are the duration of the follow-up (29.3 months), the retrospective nature and the heterogeneity in dose prescription.

Many questions remain unanswered concerning the implementation of salvage SBRT, including patient selection, the pre-therapeutic assessment, delineation of target volume in case of partial treatment, the prescribed dose and doses to OAR. These issues also arise for salvage brachytherapy. In a Delphi consensus study on salvage brachytherapy, eighty-four percent of the participants regarded life expectancy as a criterion. No consensus was reached on the duration of life expectancy (5 or 10 years), but the majority (67%) chose a life expectancy of at least 5 years. Most participants advocated for the use of choline PET (75%) and/or bone scintigraphy (65%) and MRI (78%) in addition to ultrasound for the evaluation of local disease. Opinions were divided concerning the treatment volume for salvage treatment: the percentage of participants supporting whole gland treatment, hemi-gland treatment or treatment to only intraprostatic lesions were 41%, 12% and 47%, respectively [28].

A common problem with focal treatments is the target volume delineation. Few reports have been published on the correlation between PET, multiparametric MRI and anatomo-pathological data [29]. In Kanoun et al.'s study, both multiparametric MRI and choline PET were shown to have limited sensitivity but good specificity for the detection of local cancer recurrence after radiation therapy [30]. The integration of guided biopsy with MRI is feasible and alters delineation of the tumour target boundary in a substantial proportion of patients considering focal salvage [18]. Multiparametric MRI has greater accuracy in the detection of recurrent prostate cancer after radiation therapy than T2-weighted imaging alone [32]. Salvage SBRT has to be evaluated prospectively and a phase I/II (GETUG AFU 31) has been recently launched [33].

Conclusion

With a short follow up, this study shows that salvage SBRT allows for encouraging biochemical control and acceptable toxicity, with the key advantage of non-invasiveness of SBRT. So far, this treatment is not a standard of care, and should not be considered for routine practice. It has to be administered with caution in competent centers. Further prospective studies are necessary to confirm these preliminary results.

References

[1] Torre LA, Bray F, Siegel RL, *et al*. Global Cancer Statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.

[2] Zumsteg ZS, Spratt DE, Romesser PB, *et al*. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose-Escalation Era for Prostate Patients Undergoing External Beam Radiotherapy. *J Urol* 2015;194:1624–30.

[3] https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Acceded 10th February 2019

[4] Chade DC, Eastham J, Graefen M, *et al*. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. *Eur Urol* 2012;61:961-71.

[5] Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for

Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. *Eur Urol Focus* 2016;2:158–71.

[6] de Castro Abreu AL, Bahn D, Leslie S, *et al*. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. *BJU Int* 2013;112:298–307.

[7] Lian H, Yang R, Lin T, *et al*. Salvage cryotherapy with third-generation technology for locally recurrent prostate cancer after radiation therapy. *Int Urol Nephrol* 2016;48:1461–6.

[8] Yutkin V, Ahmed HU, Donaldson I, *et al*. Salvage High-intensity Focused Ultrasound for Patients with Recurrent Prostate Cancer after Brachytherapy. *Urology* 2014;84:1157–62.

[9] Crouzet S, Murat FJ, Pommier P, *et al*. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. *Radiother Oncol* 2012;105:198–202.

[10] Chen CP, Weinberg V, Shinohara K, *et al*. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. *Int J Radiat Oncol Biol Phys* 2013;86:324–9.

[11] Yamada Y, Kollmeier MA, Pei X, *et al*. A phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. *Brachytherapy* 2014;13:111–6.

[12] Wojcieszek P, Szlag M, Głowacki G, *et al*. Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. *Radiother Oncol* 2016;119:405–10.

[13] Tran H, Kwok J, Pickles T, Tyldesley S, Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. *Urol Oncol* 2014;32:701–6.

[14] King CR, Collins S, Fuller D, *et al*. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys* 2013;87:939–45.

[15] Katz A, Formenti SC, Kang J. Predicting Biochemical Disease-Free Survival after Prostate Stereotactic Body Radiotherapy: Risk-Stratification and Patterns of Failure. *Front Oncol* 2016;6:168.

[16] Fuller DB, Wurzer J, Shirazi R, *et al*. High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. *Pract Radiat Oncol* 2015;5:e615–23.

[17] Jereczek-Fossa BA, Beltramo G, Fariselli L, *et al*. Robotic Image-Guided Stereotactic Radiotherapy, for Isolated Recurrent Primary, Lymph Node or Metastatic Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2012;82:889–97.

[18] XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

[19] Janoray G, Reynaud-Bougnoux A, Ruffier-Loubière A, *et al*. Stereotactic body re-irradiation therapy for locally recurrent prostate cancer after external-beam radiation therapy: Initial report. *Cancer Radiother* 2016;20:275–81.

[20] Mbeutcha A, Chauveinc L, Bondiau PY, *et al*. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. *Radiat Oncol* 2017;12:49.

[21] Loi M, Di Cataldo V, Simontacchi G, *et al*. Robotic Stereotactic Retreatment for Biochemical Control in Previously Irradiated Patients Affected by Recurrent Prostate Cancer. *Clin Oncol* 2018;30:93–100.

[22] XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

[23] Zilli T, Benz E, Dipasquale G, Rouzaud M, Miralbell R. Reirradiation of Prostate Cancer Local Failures After Previous Curative Radiation Therapy: Long-Term Outcome and Tolerance. *Int J Radiat Oncol Biol Phys* 2016;96:318–22.

[24] XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

[25] D'Agostino GR, Di Brina L, Mancosu P, Franzese C, Iftode C, Franceschini D, et al. Reirradiation of Locally Recurrent Prostate Cancer With Volumetric Modulated Arc Therapy. Int J Radiat Oncol Biol Phys. 2019 Feb 27 *In press*

[26] Crook JM, Zhang P, Pisansky TM, Trabulsi EJ, Amin MB, Bice W, et al. A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy (NRG Oncology/RTOG-0526). Int J Radiat Oncol Biol Phys. 2019 Feb 1;103(2):335–43

[27] Meredith G, Wong D, Yaxley J, *et al*. The use of 68 Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. *BJU Int* 2016;118(Suppl 3):49–55.

[28] Kaljouw E, Pieters BR, Kovács G, Hoskin PJ. A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study. *Radiother Oncol* 2016;118:122–30.

[29] Pucar D, Hricak H, Shukla-Dave A, *et al*. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic

resonance imaging and step-section pathology evidence. *Int J Radiat Oncol Biol Phys* 2007;69:62–9.

[30] Kanoun S, Walker P, Vrigneaud JM, *et al*. 18F-Choline Positron Emission Tomography/Computed Tomography and Multiparametric Magnetic Resonance Imaging for the Detection of Early Local Recurrence of Prostate Cancer Initially Treated by Radiation Therapy: Comparison With Systematic 3-Dimensional Transperineal Mapping Biopsy. *Int J Radiat Oncol Biol Phys* 2017;97:986–94.

[31] Ménard C, Lupati D, Publicover J, *et al*. MR-guided prostate biopsy for planning of focal salvage after radiation therapy. Radiology 2015;274:181–91.

[32] Donati OF, Jung SI, Vargas HA, *et al*. Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? *Radiology* 2013;268:440–50.

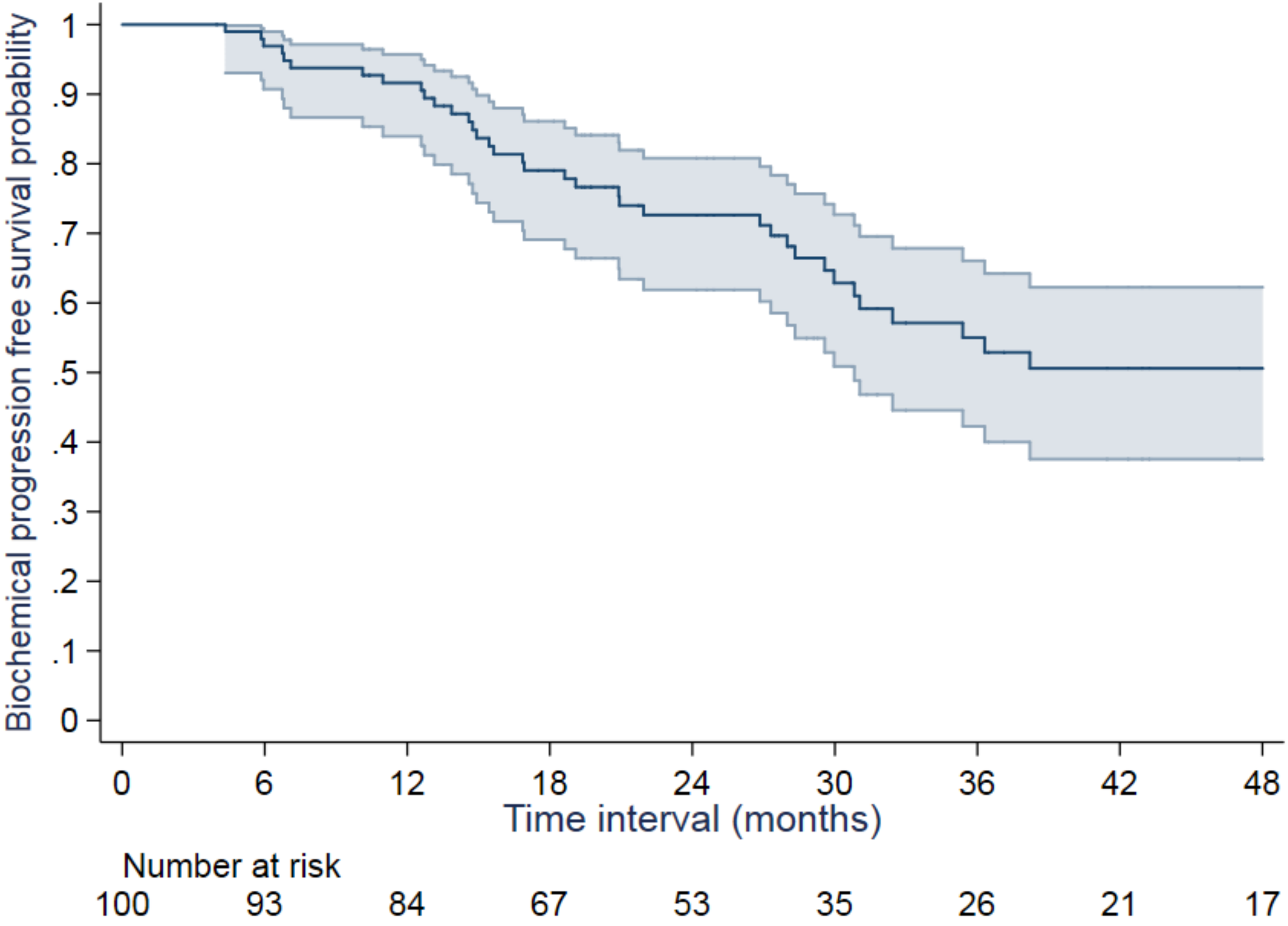
[33] https://clinicaltrials.gov/ct2/show/NCT03438552. Acceded 10th February 2019

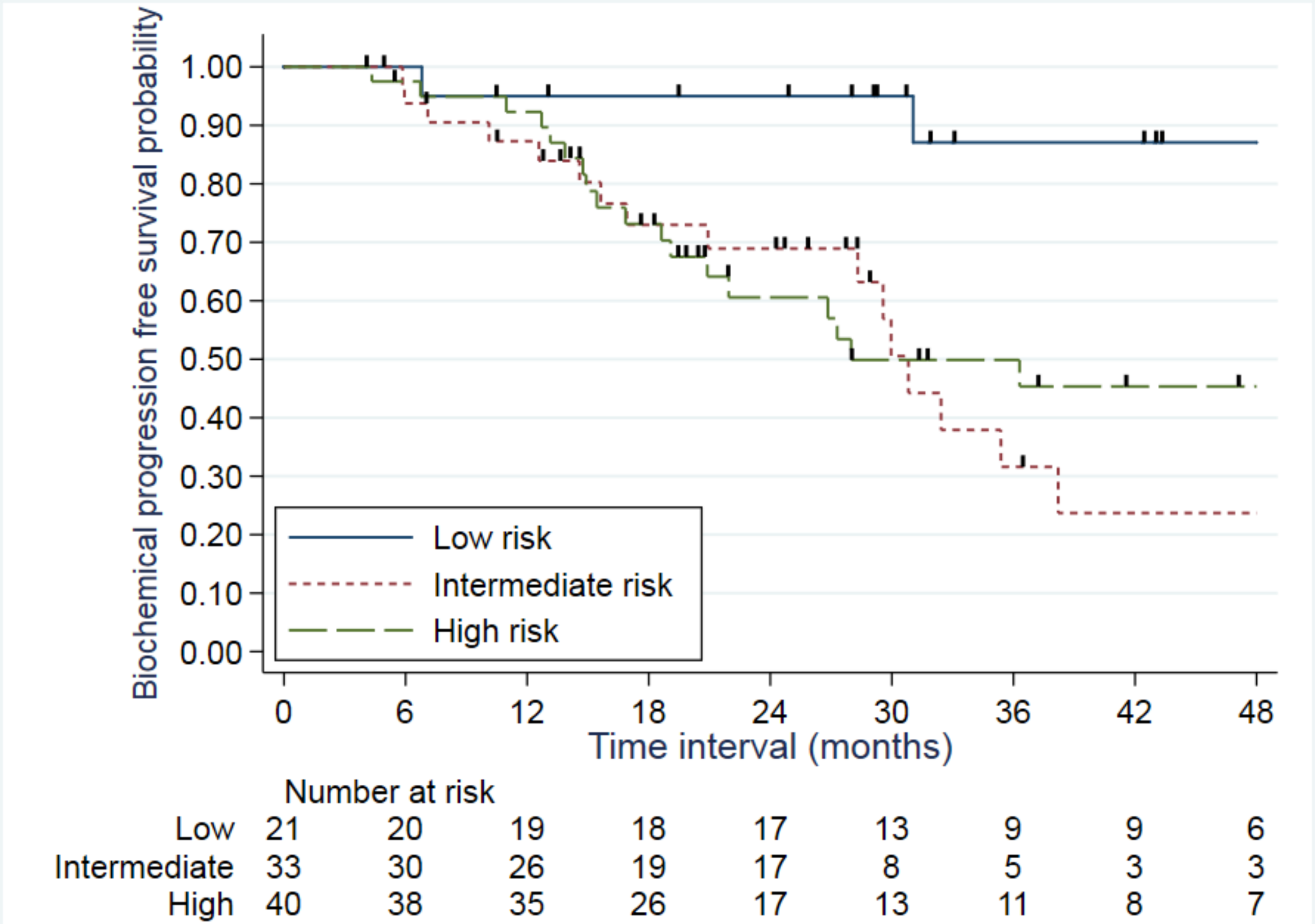
Figure captions

Figure 1. Biochemical recurrence-free survival (95% CI) after salvage SBRT for prostate cancer.

Figure 2. Biochemical recurrence-free survival after salvage SBRT according to the initial D'Amico group

Figure 3. Actuarial grade ≥2 genito-urinary toxicity


Biochemical progression free survival probability
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
0
6
12
18
24
30
36
42
48
Time interval (months)
Number at risk
100
93
84
67
53
35
26
21
17



Number at risk

Low	21	20	19	18	17	13	9	9	6
Intermediate	33	30	26	19	17	8	5	3	3
High	40	38	35	26	17	13	11	8	7

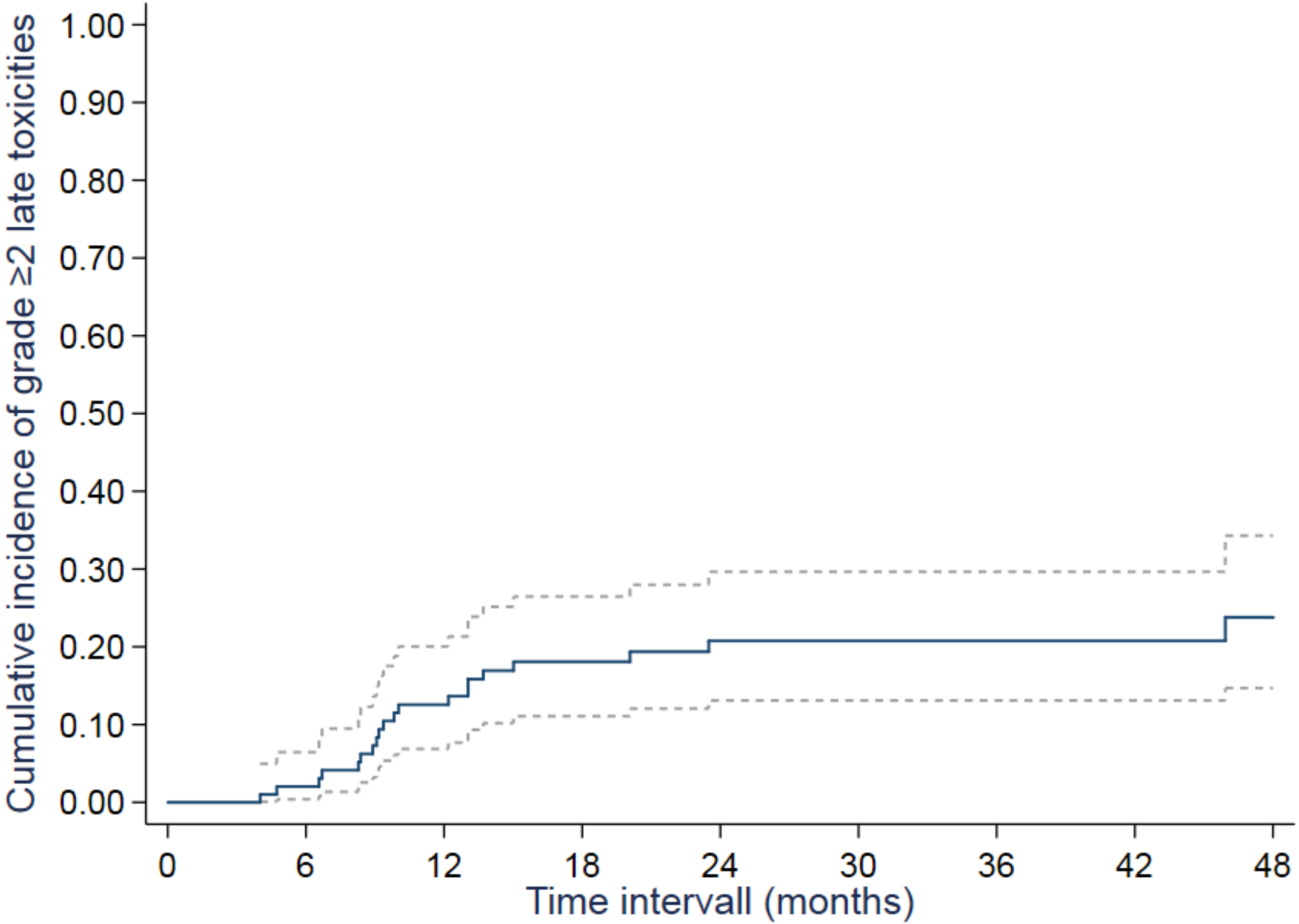

Cumulative incidence of grade ≥2 late toxicities
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
6
12
18
24
30
36
42
48
Time intervall (months)

Table 1. Patient characteristics at the first radiotherapy treatment

Characteristics	**N=100**	
Age at initial diagnosis (years)		
Median (range)	62	(47 - 78)
PSA at initial diagnosis (ng/mL)		
Median (range)	10.2	(2.3 - 120)
Gleason score		
Gleason ≤ 6	46	55%
Gleason 7 (3+4)	14	17%
Gleason 7 (4+3)	17	21%
Gleason 8	4	5%
Gleason 9-10	2	2%
Missing data	*17*	
D'Amico classification		
Low risk	21	22.3%
Intermediate risk	34	36.2%
High risk	39	41.5%
Missing data	*6*	
Characteristics of initial irradiation	**%**	
Type		
External radiation therapy	80	80%
Brachytherapy	17	17%
External radiation therapy + brachytherapy	3	3%
External Radiotherapy dose* (Gy)		
Median (range)	74	(66.6 - 80)
Fraction number		
Median (range)	37	(37-42)

*External radiotherapy alone, without brachytherapy boost

Table 2. Characteristics of patients and treatment during salvage stereotactic body radiotherapy

Data at recurrence	**N=100**	
Age (years)		
Median (range)	71.2	(56-86)
Median (range) PSA before any new treatment (CK, ADT)	4.3	(2.0-38.3)
Median (range) PSA doubling time (months)	12	(3-120)
Median (range) number of biopsies	12	(2-27)
Median (range) number of positive biopsies	4	(1-13)
Gleason score		
Gleason 6	10	14%
Gleason 7 (3+4)	17	22%
Gleason 7 (4+3)	18	23%
Gleason 7*	5	7%
Gleason 8	19	26%
Gleason 9 – 10	6	8%
Scoring not performed	*26*	
MRI	87	87%
Choline PET	94	94%
Extent of disease as assessed by PET		
Normal PET	3	3%
One-sided /unilateral intra prostatic	73	78%
Two-sided /bilateral intra prostatic	17	19%
Missing data	7	
Characteristics of androgen deprivation therapy at recurrence	n	%
Androgen deprivation therapy	33	34%
Missing data	*3*	
Duration of androgen deprivation therapy (months)		
Median – (Range)	12	(3-72)

Data at recurrence	N=100	
Missing data	*1*	
Stereotactic re-irradiation (n=100)	**n**	**%**
Treatment		
Focal (<50% of the prostate)	32	32%
Half-prostate	18	18%
Whole-prostate	49	49%
Seminal vesicles only	1	1%
Cyber-knife®	81	81%
Vero® and Rapidarc®	19	19%
PTV volume (cm^3)		
Median - (Range)	33.9	(2.6-131)
Missing data	*6*	
Use of a rectal spacer		
No	91	91%
Yes (balloon)	9	9%
Dose (Gy)		
Median - (Range)	36	(25-36.25)
Number of fractions		
5	35	35%
6	65	65%
Dose/fraction (Gy)		
Median - (Range)	6	(5-7.25)
BED (Gy)		
Median - (Range)	144.0	(87.5-167.7)
Treatment duration (days)		
Median - (Range)	12	(4-23)
D50% PTV (Gy)		
Median - (Range)	38.0	(15.4-45.1)
Missing data	*16*	

Data at recurrence	N=100	
D2% Rectum (Gy)		
Median - (Range)	26.2	(6.8-34.5)
D2% Bladder (Gy)		
Median - (Range)	23.4	(2.6-36)

BED: Biologically Effective Dose determined with an alpha/beta ratio; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PTV: Planning target volume. Dx% represents the dose received by x % of the specified structure. * Gleason grades not specified

Table 3. Prognostic factors of second biochemical recurrence-free survival in multivariate Cox regression analysis.

Factors	***HR* (95% CI)**	**p**
D'Amico classification		**0.009**
Intermediate risk vs Low risk	4.39 (1.65-11.72)	
High risk vs Low risk	3.92 (1.47-10.48)	
Time interval between initial radiotherapy and recurrence	0.87 (0.77-0.98)	**0.025**
PSA before SBRT	1.02 (0.96-1.07)	0.547
Scheme (BED ≤ 120 Gy vs > 120 Gy)	0.41 (0.20-0.86)	**0.018**

BED: Biologically Effective Dose determined with an alpha/beta ratio = 2 Gy; SBRT: Stereotactic Body Radiation Therapy; CI: confidence interval,