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Original Research Article

# Salvage radiotherapy after radical prostatectomy: Long-term results of urinary incontinence, toxicity and treatment outcomes

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ABSTRACT

*Purpose:* For patients with local recurrent disease after radical prostatectomy (35–54%) salvage radiotherapy (SRT) is the treatment of choice. In the post prostatectomy setting, SRT may impose risk at increased toxicity. As data on long-term toxicity, especially on urinary incontinence, are scarce, we report on the long-term treatment outcomes, toxicity and urinary incontinence rates after SRT.

*Materials and methods:* Patients with biochemically recurrent prostate cancer after radical prostatectomy, who were treated with SRT (3D-CRT) at our institution between 1998 and 2012, were included in this retrospective cohort analysis. Primary endpoint was urinary incontinence rate. Secondary endpoints were acute and late grade ≥2 genitourinary (GU) and gastrointestinal (GI) toxicity rates, biochemical progression-free survival (bPFS), distant metastasis-free survival (DMFS), disease specific survival (DSS), and overall survival (OS).

*Results:* 244 patients were included. Median follow-up after SRT was 50 months (range: 4–187 months). Before start of SRT 69.7% of patients were continent for urine. After SRT de novo urinary incontinence complaints (grade ≥ 1) occurred in the respective acute and late phase in 6.1% and 17.6% of patients. Respective acute grade ≥2 GU and GI toxicity was 19.2% and 17.6%. Late grade ≥2 toxicity for GU was 29.9% and for GI was 21.3%, respectively. The respective 5-year bPFS, OS, DSS and DMFS rates were 47.6%, 91.8%, 98.8% and 80.5%.

*Conclusions:* Experience at our institution with SRT demonstrates that this results in good long-term biochemical control. However, toxicity and urinary incontinence rates were high.



## Introduction

Radical prostatectomy is an effective primary treatment for localized prostate cancer. However, in 15–40% of patients, depending on tumor stage and risk group, PSA rises within 5 years after radical prostatectomy [1–3]. For patients with local recurrent disease (35–54%) salvage radiotherapy (SRT) is the treatment of choice [1,2]. SRT eradicates the microscopic prostate cancer left after radical prostatectomy. Nevertheless, biochemical progression does occur after SRT, which probably results from microscopic regional or distant metastases. Known predictive factors for biochemical progression after SRT are high PSA levels (> 0.5 ng/mL) before start of SRT, pathologic stage, and Gleason score [4–8]. Even with biochemical progression after SRT, patients can achieve long-term survival; thus late SRT-related toxicity is relevant. Previous studies have reported late (i.e. ≥90 days after start of SRT) grade ≥2 GI toxicity in 2–10% of patients. For late GU toxicity this is 2–16% reportedly. The median follow-up of these patients was ranging from 23.1 to 60 months [12–14]. However, relevant data on (late) urinary incontinence rates after SRT are scarce and underreported, since this is not part of the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) [11–14]. Urinary incontinence has a serious impact on the quality of life of patients. Here, we

*Abbreviations:* AMS, American medical systems; bPFS, biochemical progression-free survival; CTCAE, common terminology criteria for adverse events; DMFS, distant metastasis–free survival; DSS, disease specific survival; GI, gastrointestinal; GU, genitourinary; Gy, gray; IMRT, intensity-modulated radiotherapy technique; OS, overall survival; PSA, prostate specific antigen; RTOG, radiation therapy oncology group; SRT, salvage radiotherapy.

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report on the long-term incontinence and toxicity rates, and treatment outcomes after SRT for biochemically recurrent prostate cancer after radical prostatectomy.

## Materials and methods

### *Patient selection and treatment*

In this retrospective cohort study, patients with biochemically recurrent prostate cancer after radical prostatectomy, who were treated with SRT between 1998 and 2012 in the Erasmus Medical Center, Rotterdam, the Netherlands were included. Patients with high PSA levels (≥5 ng/mL) before start of SRT and/or with positive pathologic lymph node evaluation after radical prostatectomy were excluded. Radical prostatectomies were performed between 1992 and 2011 in several hospitals in the Netherlands. Patients were treated with 3-dimensional conformal radiation therapy (3D-CRT) until 2010, when intensity-modulated radiotherapy technique (IMRT) was introduced. SRT was given to the prostate bed. Maximal volume of the rectum receiving 65 Gy was restricted to 30% of the rectal volume (V65 Gy < 30%). No dose constraints for the bladder were included in the treatment protocol. Data on toxicity and treatment outcome after SRT were determined by physician assessment during regular follow-up visits (typically every 3 months for the first 2 years, and every 6 months thereafter), and collected from electronic patient records until April 1, 2018.

### *Toxicity and urinary incontinence*

Toxicity was scored according to the toxicity criteria of the RTOG [15]. Urinary incontinence before and after SRT was scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [16]. The score of '0' indicates 'no incontinence' (Supplementary Table 1). Acute toxicity/urinary incontinence was defined as treatment related toxicity/urinary incontinence that occurred within 90 days after completing SRT. Toxicity/urinary incontinence scored at or after 90 days after completing SRT was considered late toxicity/urinary incontinence.

### *Treatment outcome*

For treatment outcome analyses, data on biochemical progression, hormonal therapy use, development of distant metastasis and survival were collected. Biochemical progression after SRT was defined as a successive rise in PSA level of ≥0.2 ng/mL. Biochemical progression-free survival (bPFS) was defined as the time from end of SRT until the occurrence of biochemical progression or death without biochemical progression. Time to start hormonal therapy was defined from end of SRT until start of hormonal therapy. Distant metastasis–free survival (DMFS) was defined as the time from end of SRT until the occurrence of distant metastases or death without distant metastases. Development of distant metastases was determined by bone scintigraphy or CT-scan. Disease specific survival (DSS) and overall survival (OS) were defined as the time from end of SRT until death due to prostate cancer (DSS) or death from any cause (OS).

### *Endpoints and statistical analysis*

The primary endpoint was urinary incontinence rate. Secondary endpoints were acute and late toxicity rates, bPFS, DMFS, DSS, and OS. Survival rates were analyzed by the Kaplan Meier method. Follow-up time was calculated from end of SRT until date of last known PSA or death. To identify potentially relevant predictors for

**Table 1**
Patient and tumor characteristics.

| Variable | n | % of total | Variable | n | % of total |
|---|---|---|---|---|---|
| *Age at start SRT (years)* | | | *Gleason score* | 62 | 25.4 |
| Median | 66 | | <7 | 120 | 49.2 |
| Range | 45–79 | | 7 | 60 | 24.6 |
| | | | >7 | | |
| *Age at time of RP (years)* | | | *Seminal vesicle invasion* | | |
| Median | 64 | | No | 185 | 75.8 |
| Range | 44–76 | | Yes | 58 | 23.8 |
| *SRT dose (Gy)* | | | *pT-stage*[1] | | |
| 68 | 12 | 4.9 | T2a | 16 | 6.6 |
| 70 | 4 | 1.6 | T2b | 14 | 5.7 |
| 72 | 225 | 92.2 | T2c | 58 | 23.8 |
| 74 | 2 | 0.8 | T3a | 83 | 34.0 |
| 78 | 1 | 0.4 | T3b | 54 | 22.1 |
| | | | T4 | 10 | 4.1 |
| *SRT fractions* | | | *Positive resection margin* | | |
| Median | 36 | | No | 87 | 35.7 |
| Range | 32–39 | | Yes | 154 | 63.1 |
| *Interval RP-SRT (months)* | | | Hormonal therapy | | |
| Median | 22 | | No | 180 | 73.8 |
| Range | 2–168 | | Yes | 63 | 25.8 |
| *iPSA before RP (ng/mL)* | | | Interval SRT-Hormonal therapy (months) | | |
| PSA < 10 | 104 | 42.6 | Median | 32 | |
| PSA 10–20 | 67 | 27.5 | Range | −2 to 166 | |
| PSA > 20 | 45 | 18.4 | | | |
| *PSA before SRT (ng/mL)* | | | | | |
| PSA < 0.5 | 121 | 49.6 | | | |
| PSA 0.5–1.0 | 76 | 31.1 | | | |
| PSA > 1.0 | 46 | 18.9 | | | |

[1] According to the 2009 TNM classification [24,25]. %: percentage, Gy: Gray, iPSA: initial PSA, n: number of patients, RP: radical prostatectomy, SRT: salvage radiotherapy. Numbers do not add up to 244 patients due to missing values.

toxicity or treatment outcome, the following variables were tested: initial PSA before radical prostatectomy ≥10.0 ng/mL; PSA before SRT ≥0.5 ng/mL; Gleason score ≥7 (determined on prostatectomy sample); seminal vesicle invasion; positive resection margins; age at start of SRT >70 years; interval between surgery and SRT; and date of first SRT before 2010. These variables were tested in univariate analysis for toxicity, bPFS, no PSA nadir after SRT, development of distant metastases, and death from any cause either with logistic regression for dichotomous outcomes or using the Cox proportional hazards model for time to event outcomes. Univariate variables, that appeared to be associated with the tested endpoint (P value < 0.10) were subsequently included in a multivariate stepwise backward selection model. P values < 0.05 were considered significant. All statistical analyses were performed using STATA version 14.1.

## Results

Between 1998 and 2012 244 patients were treated with SRT in our institution for biochemically recurrent prostate cancer after radical prostatectomy. One hundred and thirteen patients started with SRT before 2010 and were thus treated conventionally. Median follow-up time after SRT was 50 months (range: 4–187 months). Patient and tumor characteristics are described in Table 1. Median initial PSA before radical prostatectomy was 10.0 ng/mL (range: 1.3–86.0). Median PSA before start of SRT was 0.5 ng/mL (range: 0.01–4.80) and 27 patients (11.1%) started SRT at a PSA level of <0.2 ng/mL. The median SRT dose was 72 Gy (range: 68–78 Gy).

A total of 63 patients (25.8%) received hormonal therapy during (n = 1) or after (n = 62) completion of SRT. Reasons to start hormonal therapy were PSA progression (n = 34/63; 54.0%), lymph node and/or bone metastasis (n = 17/63; 27.0%), and as part of a clinical trial (1/63; 1.6%). For 11 patients (11/63; 17.5%) the exact reason to start hormonal therapy was unclear from the patient records.

### *Urinary incontinence*

In 74 patients (30.3%), urinary incontinence was reported after radical prostatectomy (Table 2). One patient with grade 3 urinary incontinence received an artificial urinary sphincter (AMS prosthesis) just before start of SRT and remained continent during follow-up.

Acute urinary incontinence after SRT was reported in a total of 88 patients (36.1%; Table 2). In 71 patients (29.1%) pre-existent urinary incontinence complaints were unchanged, 2 patients (0.8%) experienced progression of urinary incontinence and 15 patients (6.1%) experienced de novo urinary incontinence (grade ≥ 1; Fig. 1 and Supplementary Fig. 1).

Late urinary incontinence after SRT was reported in a total of 122 patients (50.0%; Table 2). In 54 patients (22.1%) pre-existent urinary incontinence complaints (i.e. before start of SRT) remained unchanged. In 24 patients (9.8%) progression of urinary incontinence complaints or persistent acute de novo incontinence were reported. In one patient (0.4%) acute de novo incontinence complaints improved, although this patient remained incontinent during follow-up. In 43 patients (17.6%) de novo urinary incontinence complaints were reported (grade ≥ 1; Fig. 1 and Supplementary Fig. 1).

Seventeen patients (7.0%) with grade 3 urinary incontinence had one or more interventions, including artificial urinary sphincter surgery (AMS prosthesis; n = 13), urethral bulking (Bulkamid injections; n = 4), urethral sling surgery (n = 3), and suprapubic catheter placement (n = 2). Follow-up data of 9 patients on late urinary incontinence complaints were missing.

### *Acute toxicity*

Twenty-five patients (10.2%) experienced acute grade 2 GU toxicity and 22 patients (9.0%) experienced acute grade 3 GU toxicity. Acute grade 2 GI toxicity was reported in 41 patients (16.8%) and 2 patients (0.8%) experienced acute grade 3 GI toxicity. For both GU and GI no acute grade 4 toxicity was detected. Toxicity symptoms are shown in Table 3.

Univariate analysis for acute GU toxicity showed that Gleason score, interval between radical prostatectomy and start of SRT and date of first SRT before 2010 were significantly associated (Supplementary Table 2). Univariate analysis for acute GI toxicity showed no significant associations. Multivariate analysis supported that a longer interval between radical prostatectomy and SRT reduced the risk of acute GU toxicity slightly but significantly (Table 4a).

### *Late toxicity*

Late grade 2 GU toxicity was reported in 28 patients (11.5%) and 44 patients (18.0%) experienced late grade 3 GU toxicity. Late grade 4 GU toxicity was reported in 1 patient (0.4%); this patient required an ileal conduit urinary diversion because of a vesicorectal fistula and severe frequency complaints. Thirty-eight patients (15.6%) experienced late grade 2 GI toxicity and 12 patients (4.9%) experienced late grade 3 GI toxicity. Late grade 4 GI toxicity was reported in 2 patients (0.8%), who both required a colostomy because of a severe hemorrhagic rectal ulcer. Toxicity symptoms are shown in Table 3.

Univariate analysis for late GU toxicity showed that Gleason score and seminal vesical invasion was significantly associated (Supplementary Table 2). PSA level before SRT, Gleason score and age at start of SRT were significantly associated with late GI toxicity in the univariate analysis (Supplementary Table 2). Multivariate analysis showed no significant associations for late GU toxicity. Multivariate analysis supported that a PSA ≥ 0.5 ng/mL before SRT, a Gleason score ≥ 7 and age at start of SRT > 70 years increased the risk of late GI toxicity (Table 4a).

### *Treatment outcomes*

PSA nadir of <0.2 ng/mL after SRT was reached in 183 patients (75.0%) after a median follow-up of 6 months (range: 0–36

**Table 2**
Urinary incontinence.

| Phase | Grade | | | |
|---|---|---|---|---|
| | Grade 0<br>n (%) | Grade 1<br>n (%) | Grade 2<br>n (%) | Grade 3<br>n (%) |
| *Pre-SRT* | 170 (69.7) | 57 (23.4) | 12 (4.9) | 5 (2.0) |
| *Acute urinary incontinence* | 156 (63.9) | 66 (27.0) | 16 (6.6) | 6 (2.5) |
| *Late urinary incontinence* | 113 (46.3) | 62 (25.4) | 34 (13.9) | 26 (10.7) |

%: percentage, n: number of patients, SRT: salvage radiotherapy. Numbers do not add up to 244 patients due to missing values.

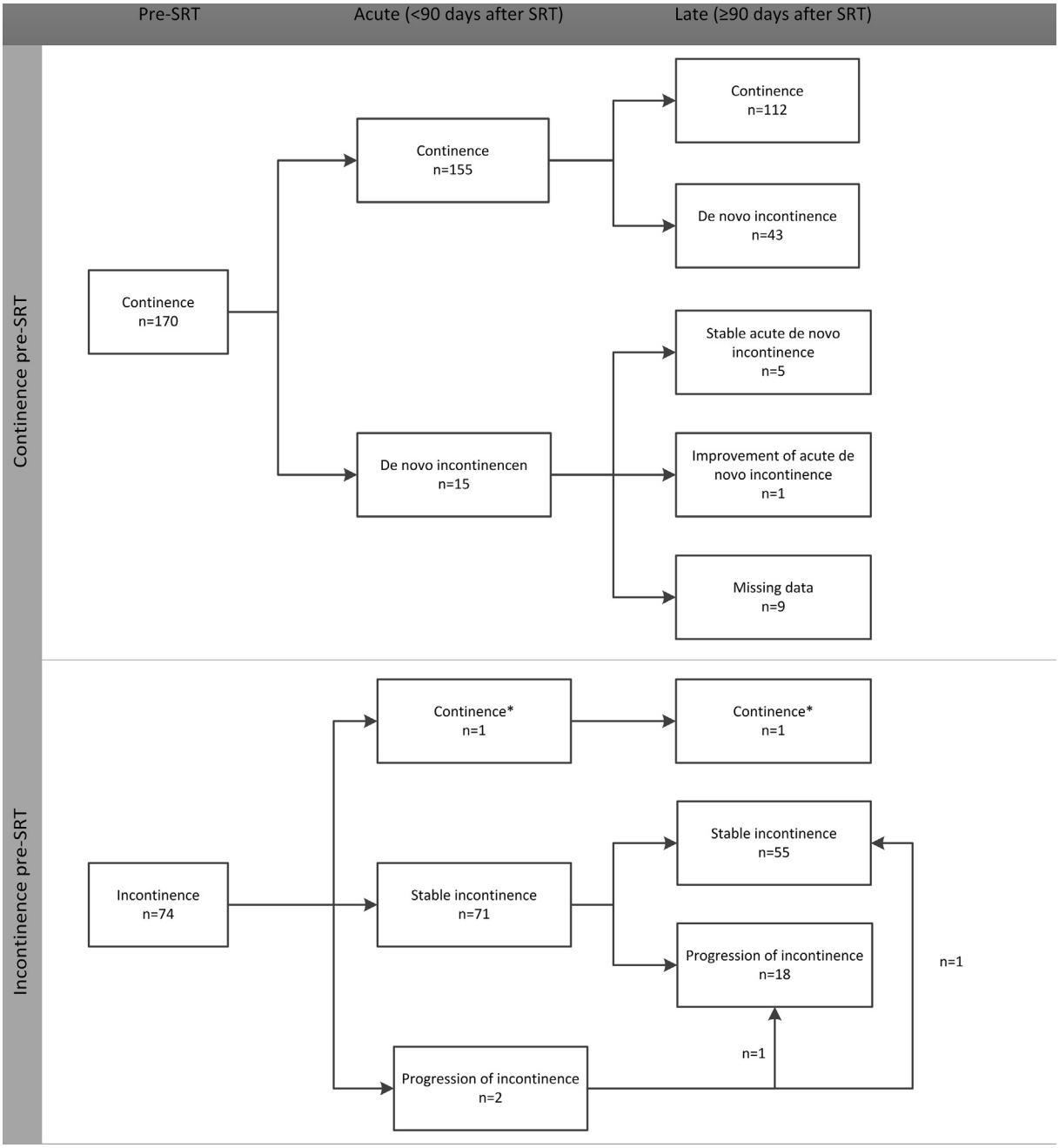


**Fig. 1.** Evolution of urinary incontinence after salvage radiotherapy. The columns divide the phases of urinary incontinence in before start of SRT (pre-SRT), acute urinary incontinence (<90 days after SRT), and late urinary incontinence (≥90 days after SRT). The rows divide the pre-SRT condition of patients in continence and incontinence. Horizontally, the evolution of urine (in)continence can be followed. *This patient received an artificial urinary sphincter (AMS prosthesis) just before start of SRT because of severe urinary incontinence complaints. SRT: salvage radiotherapy, n: number of patients.

months). A total of 111 patients (45.5%) experienced biochemical progression until end of data collection in April 2018. In 26 patients (10.7%) no PSA response was observed at all. The 5-year bPFS, OS, DSS and DMFS were 47.6%, 91.84%, 98.8% and 80.5%, respectively.

The results of the univariate analyses to identify predictors for biochemical progression, no PSA response after SRT, death from any cause and the development of distant metastases are listed in Supplementary Table 3. analysis showed that a longer interval between radical prostatectomy and SRT reduced the risk of biochemical progression, no PSA response after SRT and the development of distant metastases (Table 4b). For seminal vesicle invasion, we found evidence that it increased the risk of biochemical progression, death and the development of distant metastases (Table 4b). Furthermore, multivariate analysis supported that a Gleason score ≥7 increased the risk of death from any cause (Table 4b).

## Discussion

In this single-center retrospective cohort analysis on 244 prostate cancer patients, who received SRT for biochemical progression after radical prostatectomy, we focused our analyses on late toxicity, especially urinary incontinence. Urinary incontinence has a

**Table 3**
Acute and late toxicity.

| | Symptoms | Acute toxicity | | Late toxicity | | |
|---|---|---|---|---|---|---|
| | | Grade 2 n (%) | Grade 3 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| Gastrointestinal | *Pain* | 8 (3.3) | | | | |
| | *Diarrhea* | 22 (9.0) | | | 1 (0.4) | |
| | *Mucous discharge* | 12 (4.9) | | 3 (1.2) | | |
| | *Bleeding* | 1 (0.4) | 1 (0.4) | 31 (12.7) | 11 (4.5) | 2 (0.8) |
| | *Infection* | 1 (0.4) | | | | |
| | *Abdominal distension* | | 1 (0.4) | | | |
| | *Frequency* | | | 5 (2.0) | | |
| Genitourinary | *Nocturia* | 13 (5.3) | 3 (1.2) | 8 (3.3) | 1 (0.4) | |
| | *Frequency* | 13 (5.3) | 19 (7.8) | 5 (2.0) | 4 (1.6) | 1 (0.4) |
| | *Urgency* | 7 (2.9) | | 3 (1.2) | 1 (0.4) | |
| | *Hematuria* | | | 16 (6.6) | 19 (7.8) | |
| | *Dysuria* | 4 (1.6) | | | | |
| | *Lower urinary tract obstruction* | | 2 (0.8) | 1 (0.4) | 18 (7.4) | |
| | *Small bladder capacity* | | | | 1 (0.4) | |
| | *Retention* | 1 (0.4) | | 1 (0.4) | 2 (0.8) | |
| | *Radiation cystitis* | | | 9 (3.7) | 7 (2.9) | |

%: percentage, n: number of patients.

**Table 4a**
Multivariate stepwise backward selection model for toxicity.[1]

| Variables | Acute GU toxicity | | Late GI toxicity | |
|---|---|---|---|---|
| | OR 95% CI | P value | OR 95% CI | P value |
| *PSA pre-SRT ≥0.5 ng/mL* | | | 1.96<br>1.01–3.77 | 0.045 |
| *Gleason score ≥ 7* | | | 3.16<br>1.25–7.94 | 0.015 |
| *Age at start of SRT >70 years* | | | 2.26<br>1.13–4.53 | 0.021 |
| *Interval between RP and SRT (months)* | 0.99<br>0.97–0.99 | 0.013 | | |

[1] Only significant variables from the univariate analysis (Supplementary Table 2) are shown. CI: confidence interval, GI: gastrointestinal, GU: genitourinary, SRT: salvage radiotherapy, OR: odds ratio, RP: radical prostatectomy, SRT: salvage radiotherapy.

**Table 4b**
Multivariate stepwise backward selection model for treatment outcomes.[1]

| Variables | Biochemical progression | | No PSA response after SRT | | Death from any cause | | Development of DM | |
|---|---|---|---|---|---|---|---|---|
| | HR 95% CI | P value | OR 95% CI | P value | HR 95% CI | P value | HR 95% CI | P value |
| *Gleason score ≥7* | | | | | 2.96<br>1.02–8.64 | 0.047 | | |
| *Seminal vesicle invasion* | 1.95<br>1.32–2.89 | 0.001 | | | 2.15<br>1.04–4.42 | 0.038 | 1.88<br>1.04–3.39 | 0.037 |
| *Interval between RP and SRT (months)* | 0.99<br>0.98–0.99 | <0.001 | 0.96<br>0.93–0.99 | 0.003 | | | 0.99<br>0.98–0.99 | 0.044 |

[1] Only significant variables from the univariate analysis (Supplementary Table 3) are shown. CI: confidence interval, DM: distant metastasis, OR: odds ratio, HR: hazard ratio, RP: radical prostatectomy, SRT: salvage radiotherapy.

serious impact on the quality of life of patients, but is often underreported in clinical studies. Our detailed and person-based analysis on urinary incontinence is unique and adds important information on the late outcome of SRT.

In our cohort nearly one third of patients had urinary incontinence before start of SRT which is comparable to other studies [9–11]. However, our reported urinary incontinence rates after SRT are higher than previously reported. Goenka et al. [13] reported a 5-year risk of CTCAE grade ≥2 urinary incontinence in patients with grade ≤1 before SRT of 10.7%. By contrast, late grade ≥2 urinary incontinence was reported by 19.4% (44/227) of our patients with grade ≤1 before SRT (Supplementary Fig. 1). In the study by Cozzarini et al. grade 3 incontinence rates were nearly half of our cohort (6.0% vs. 10.7%) in a quite similar patient cohort [11].

Acute grade ≥2 GU and GI toxicity was comparable to other studies [9,13]. However, our late grade ≥2 GU (29.9%) and GI toxicity (21.3%) rates were substantially higher than reported in other series [11–13,17].

Our relatively high toxicity, including urinary incontinence, might, in part, be explained by differences in radiation dose; our cohort received a median dose of 72 Gy. In the respective studies by Feng et al. [17] and Peterson et al. [12] patients received a median dose of 64 and 65 Gy. Goenka et al. [13] reported that 63% of patients received an SRT dose <70 Gy. However, in the study by Cozzarini et al. [11] patients who received a median SRT dose of

72 Gy reported a late GU toxicity rate of 23.7%, which is lower than our reported rates. The retrospective character of all these series with different toxicity reporting methods could also explains the differences in reported toxicity.

We found that a longer interval between radical prostatectomy and start of SRT is associated with decreased rates of acute GU toxicity. This suggests that a long recovery time after radical prostatectomy is needed for pelvic organs. However, in groups receiving either early or late SRT (mean time 3.6 vs. 30.1 months after radical prostatectomy), Sowerby et al. [18] found similar rates of GU toxicity, including urinary incontinence, bladder neck contracture and urethral stricture.

A high PSA before SRT and a high Gleason score were significantly associated with late GI toxicity in our cohort and this has not been described before in other studies [9,13]. As high PSA before SRT and high Gleason score are indicative of a more aggressive cancer, this might justify a higher SRT dose with consequently a higher risk of toxicity. In addition, age at initiation of SRT >70 years was significantly associated with late GI toxicity in our cohort. This variable has recently been reported as a risk factor for acute and late GU toxicity after primary radiotherapy for prostate cancer [19,20]. Our results suggest that higher age is a risk factor in the SRT setting as well.

Unfortunately, we were unable to analyze potentially relevant predictors for the development of urinary incontinence after SRT. Our patient subgroups with de novo acute and late urinary incontinence were too small and diverse to allow for unbiased and valid interpretation of such results.

Biochemical progression was reported in 45.5% of our patients. This is fairly comparable with published series that reported 41–46% biochemical progression rates [7,21,22]. Of note, the study of Bernard et al. had an extended median follow-up time of 72 months [22]. However, Detti et al. reported in only 31.7% of patients biochemical progression [23]. Remarkably, these patients had more aggressive tumors (at least pT3 and Gleason 7) compared to our patient cohort and these patients received a mean SRT dose of only 67 Gy. We found that a high Gleason score was associated with an increased mortality risk in our cohort. Seminal vesicle invasion was associated with an increased risk to develop biochemical progression and distant metastases. Thus, tumor characteristics seem to predict poor response to SRT and might justify more individual treatment strategies in these patients. On the other hand, patients with a longer interval between radical prostatectomy and start of SRT might represent a subgroup with a favorable outcome, as this variable was associated with a decreased risk of biochemical progression, no PSA response after SRT and the development of distant metastases.

Important limitations of this study are the retrospective design and the lack of use of patient reported questionnaires. All data were gathered from patient records which were not always complete. Numbers on strictures are missing. Missing data could potentially skew the results. However, the relatively high reported toxicity could indicate a reasonable level of accuracy in collecting data from patient records. Despite these limitations, this study adds important information on urinary incontinence and toxicity after SRT. Since most studies use the well-known RTOG criteria [15], which lack urinary incontinence grading, a systematic approach to grade urinary incontinence is often missing. Therefore, we used the CTCAE v4.0 criteria to grade urinary incontinence [16]. Particularly, we focused on the individual evolution of a patient's (in)continence, which gives insight in the development of urinary incontinence on patient-level.

Our study shows that SRT results in good long-term biochemical control. However, toxicity and urinary incontinence rates are higher than previously reported. Toxicity and urinary incontinence after SRT are important factors with a clear impact on the quality of life of patients. Thus, offering upfront radiotherapy as a routine escape therapy for insufficient radical surgery in high risk tumors should at least be accompanied with realistic information to patients, especially on the late phase increase of de novo urinary incontinence. Alternative primary treatments like radiotherapy in combination with ADT should be well considered at that time.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2018.05.001.

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