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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.