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

Lisanne F. van Dessel a,*, Sarah H.M. Reuvers b, Chris H. Bangma b, Shafak Aluwini c

a Department of Experimental Urology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands
b Department of Urology, Erasmus MC, Erasmus University Medical Center, Rotterdam, The Netherlands
c Department of Radiation Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

A R T I C L E   I N F O

Article history:
Received 14 February 2018
Revised 10 May 2018
Accepted 10 May 2018

Keywords:
Radiotherapy
Salvage therapy
Toxicity
Urinary incontinence
Prostatic neoplasms

A B S T R A C T

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.

© 2018 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 underestimated, 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
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

| Variable                          | n   | % of total |
|-----------------------------------|-----|------------|
| Age at start SRT (years)          |     |            |
| Median                            | 66  | 25.4       |
| Range (45–79)                     |     |            |
| Age at time of RP (years)         |     |            |
| Median                            | 64  | 26.7       |
| Range (44–76)                     |     |            |
| SRT dose (Gy)                     |     |            |
| 68                                | 12  | 4.9        |
| 70                                | 4   | 1.6        |
| 72                                | 22  | 9.2        |
| 74                                | 2   | 0.8        |
| 78                                | 1   | 0.4        |
| SRT fractions                     |     |            |
| Median                            | 36  | 15.3       |
| Range (32–39)                     |     |            |
| Interval RP–SRT (months)          |     |            |
| Median                            | 22  | 9.1        |
| Range (2–168)                     |     |            |
| iPSA before RP (ng/mL)            |     |            |
| PSA < 10                          | 104 | 42.6       |
| PSA 10–20                         | 67  | 27.5       |
| 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.
All statistical analyses were performed using STATA version 14.1. P values < 0.05 were considered significant. 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 or after 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 were 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

| Phase                          | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|-------------------------------|---------|---------|---------|---------|
|                               | n (%)   | n (%)   | n (%)   | 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) |

n: number of patients, SRT: salvage radiotherapy. Numbers do not add up to 244 patients due to missing values.
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 $\geq 7$ 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
serious impact on the quality of life of patients, but is often under-reported 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 $\geq 2$ urinary incontinence in patients with grade $\geq 1$ before SRT of 10.7%. By contrast, late grade $\geq 2$ urinary incontinence was reported by 19.4% (44/227) of our patients with grade $\geq 1$ 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 $\geq 2$ GU and GI toxicity was comparable to other studies [9,13]. However, our late grade $\geq 2$ 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

### 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)        |              | 1 (0.4)      |              |
| Diarrhea              | 22 (9.0)       |              |              |              |
| Mucous discharge      | 12 (4.9)       | 1 (0.4)      | 31 (12.7)    | 11 (4.5)     | 2 (0.8)      |
| Bleeding              | 1 (0.4)        | 1 (0.4)      |              |              |
| Infection             | 1 (0.4)        |              |              |              |
| Abdominal distension  | 1 (0.4)        |              |              |              |
| Frequency             | 5 (2.0)        |              |              |              |
| Genitourinary Nocturia| 13 (5.3)       | 8 (3.3)      | 1 (0.4)      |              |
| Frequency             | 13 (5.3)       | 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 obstr. | 2 (0.8) |              | 18 (7.4)     | 1 (0.4)      |
| Small bladder capacity|              |              |              |              |
| 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 $\geq 0.5$ ng/mL     | 1.96              | 0.045            |                 |                 |
|                                  | 1.01–3.77         |                  |                 |                 |
| Gleason score $\geq 7$           | 3.16              | 0.015            |                 |                 |
|                                  | 1.25–7.94         |                  |                 |                 |
| Age at start of SRT $\geq 70$    | 2.26              | 0.021            |                 |                 |
|                                  | 1.13–4.53         |                  |                 |                 |
| Interval between RP and SRT (months) | 0.99           | 0.013            |                 |                 |
|                                  | 0.97–0.99         |                  |                 |                 |

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 $\geq 7$        | 2.96       | 0.047   | 1.02–8.64 |         |                 |         |                 |         |
| Seminal vesicle invasion      | 1.95       | 0.001   | 1.32–2.89 |         |                 |         |                 |         |
|                               | 2.15       | 0.038   | 1.04–4.42 |         |                 |         |                 |         |
| Interval between RP and SRT (months) | 0.99      | <0.001  | 0.96     | 0.003  | 0.99      | 0.044  | 0.98–0.99 |         |
|                               | 0.98–0.99  | 0.93–0.99 |         |         |          |         |         |         |

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.
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), Soverby 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 GI 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.

Acknowledgment

We would like to thank Maxime P. Look and Esther Oomen-de Hoop for their help with the statistical analyses.

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.

References

[1] Ward JF, Moui JW. Rising prostate-specific antigen after primary prostate cancer therapy. Nat Clin Pract Urol 2005;2:174–82.
[2] Hsing W, Partin AW, Zahurak M, Piantadosi S, Epstein J, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003;169:517–23.
[3] Pound CR, Partin AW, Ensenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591–7.
[4] Briganti A, Barnes RJ, Joniau S, Boorjian SA, Cozzarini C, Gandaglia G, et al. Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. Eur Urol 2014;66:476–89.
[5] Stephenson AJ, Scardino PT, Kattan MW, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035–41.
[6] Siegmann A, Bottke D, Faehndrich J, Lohm G, Miller K, Bartkowiak D, et al. Dose escalation for patients with decreasing PSA during radiotherapy for elevated PSA after radical prostatectomy improves biochemical progression-free survival: results of a retrospective study. Strahlenther Onkol 2011;187:467–72.
[7] Wiegel T, Lohm G, Bottke D, Hoch S, Miller K, Siegmann A, et al. Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome—results of a retrospective study. Int J Radiat Oncol Biol Phys 2009;73:1009–16.
[8] Goenka A, Magasanik JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. Int J Radiat Oncol Biol Phys 2012;84:1142–8.
[9] Ghadjar P, Hayoz S, Bernhard J, Zwaalhen DR, Holscher T, Gut P, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: first results of the randomized trial SAKK 09/10. J Clin Oncol 2015;33:4158.
[10] Coelho RF, Rocco B, Patel MB, Orvieto MA, Chauhan S, Faricca V, et al. Retropubic, laparoscopic, and robotic-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010;24:2003–15.
[11] Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, et al. Clinical factors predicting late severe urinary toxicity after posterior prostate radiotherapy for prostate cancer: a single-institution analysis of 742 patients. Int J Radiat Oncol Biol Phys 2012;82:191–9.
[12] Peterson JL, Buskirk SJ, Heckman MG, Crook JE, Ko SJ, Wehle MJ, et al. Late toxicity after postprostatectomy salvage radiation therapy. Radiother Oncol 2009;93:203–6.
[13] Goenka A, Magasanik JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol 2011;60:1144–8.
[14] Apicella G, Beldi D, Marchioro G, Torrente S, Tunesi S, Magnani C, et al. Postoperative radiotherapy in prostate cancer: analysis of prognostic factors in a series of 282 patients. Rep Pract Oncol Radiother 2015;20:113–22.
[15] Cox JD, Stetz J, Paijak TF. Toxicity criteria of the radiation-therapy oncology group (RTOG) and the European-organization-for-research-and-treatment-of-cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[16] Services USDoHalt Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009, p. 80.
[17] Feng M, Hanlon AL, Pisansky TM, Kuban D, Catton CN, Michalski JM, et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1417–23.
[18] Soverby RJ, Gani J, Yim H, Radomski SB, Catton C. Long-term complications in men who have early or late radiotherapy after radical prostatectomy. Can Urol Assoc J 2014;8:253–8.
[19] Aluwini S, Pos F, Schimmel E, Krol S, van der Toorn PP, de Jager H, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. Lancet Oncol 2016;17:464–74.

[20] Aluwini S, Pos F, Schimmel E, van Lin E, Krol S, van der Toorn PP, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2015;16:274–83.

[21] Cremers RG, van Lin EN, Gerrits WL, van Tol-Geerdink JJ, Kiemeney LA, Vergunst H, et al. Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high-risk patients suited for adjuvant radiotherapy. Radiother Oncol 2010;97:467–73.

[22] Bernard Jr JR, Buskirk SJ, Heckman MG, Diehl NN, Ko SJ, Macdonald OK, et al. Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. Int J Radiat Oncol Biol Phys 2010;76:735–40.

[23] Detti B, Scoccianti S, Cassani S, Cipressi S, Villari D, Lapini A, et al. Adjuvant and salvage radiotherapy after prostatectomy: outcome analysis of 307 patients with prostate cancer. J Cancer Res Clin Oncol 2013;139:147–57.

[24] Mottet N, Bellmunt J, Briers E, Bergh RCNvd, Bolla M, Casteren NJv, et al. EAU Guidelines on Prostate Cancer. 2015.

[25] Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. seventh ed. Wiley-Blackwell; 2009.