Salvage radiotherapy in patients with persisting/rising PSA after radical prostatectomy for prostate cancer

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Introduction

Recurrence rates after prostatectomy

Radical prostatectomy (RP) and radiation therapy (RT) are two of the existing first-line therapeutic options for patients with prostate cancer, with best results achieved in patients with organ-confined disease. There are clearly defined risk factors predicting the outcome after RP (i.e., Gleason score, prostate-specific antigen [PSA] level before surgery, tumour stage, infiltration of the seminal vesicles or positive surgical margins) [1–4]. However, progression of the disease is a common event even in patients with good prognostic factors.

Monitoring PSA levels is a sensitive means of assessing the result of RP for prostate cancer. Following RP, the PSA should become undetectable within 4 to 6 weeks, because the serum half-life of PSA is approximately 2 to 3 days [5]. Therefore, persistent serum PSA levels after RP indicate residual prostatic tissue, be it malignant disease or benign prostatic hyperplasia (BPH). In the former case such levels predate clinically evident disease and do correlate well with disease progression.

A PSA increase of $\geqslant$0.2 ng/mL is a common definition of progression of the disease following RP. It occurs in up to 50% of patients with pT3 tumours and this value ranges up to 70% in case of pT3 tumours with positive surgical margins [6,7].

Using biopsies from the urethrovesical anastomosis, vital tumour tissue was found by different examiners in 35–55% of all patients with PSA elevation after RP without clinical findings suggestive of recurrent tumour [8–10].

Remaining BPH tissue after RP

Fowler and colleagues evaluated the results of transrectal ultrasound (TRUS)-guided anastomotic biopsies in the presence of PSA relapse after RP. In 10% (6 of 62) of the patients, biopsies only revealed BPH tissue [11]. Theoretically, residual benign tissue may result from unintentional disruption of the prostatic capsule during surgery and may account for a detectable postoperative PSA, although several observations indicate that undetected carcinoma may coexist with benign tissue. In this series, the level of PSA ranged from 0.6 to 4.8 ng/mL when only BPH tissue was present in the biopsy. Considering that every gram of BPH tissue produces an average of 0.31 ng/mL PSA [12,13], it seems rather unlikely that around 2–15 g of BPH tissue was left in place after surgery or was otherwise capable of such a fast regrowth.

Godoy and colleagues evaluated a select group of 331 patients that underwent an open radical retropubic prostatectomy with extremely low-risk disease as determined by the preoperative and pathological factors, including a preoperative PSA level $<$10 ng/mL, T1c or cT2a, a Gleason score of $\leqslant$6, an estimated cancer volume in the specimen of $<$5%, and no evidence of positive surgical margins. In this cohort any measurable PSA level would be highly suspicious for a benign origin. At 3 months to 6 years of follow-up (mean 36.2 months), 0.6% and 0.3% of patients had developed a measurable PSA level or biochemical recurrence, respectively. The single patient with biochemical recurrence responded to salvage radiotherapy, strongly suggesting a malignant etiology for the recurrence. These results provide compelling evidence that retained benign prostatic elements are an unlikely source of elevated PSA levels in men who have undergone RP [14]. However, it is important to look specifically at the pathological specimen in order to see if there were benign glands in the margin, especially if a nerve-sparing procedure had been performed. This could in some cases explain a low detectable, non rising PSA following surgery.

Treatment options for persisting/rising PSA after RP

It remains uncertain whether a PSA increase after RP indicates isolated local disease, distant metastatic progression, or both [10]. Therefore, the best treatment for recurrent prostate cancer in patients with increasing or persisting PSA without clinical evidence of disease remains controversial. However, only RT can offer the hope of cure to patients with truly localised malignant disease after RP.

There are indicators for a higher likelihood of local recurrence, e.g. slow PSA rise (PSA doubling time $\geqslant$12 months), more than 1 year between RP and the demonstration of PSA in the serum, Gleason score <7 and negative surgical margins [15]. On the other hand, there are also indicators suggesting metastatic disease such as short PSA doubling time (<12 months) or Gleason score at RP from 8 to 10 [16,17]. Some authors tried to define combinations of risk factors. For example, patients with a combination of PSA <1 ng/mL before RT, pre-RP Gleason score <7, and a long PSA doubling time after progression have a high risk of local disease [18]. Recently, a predictive model for the outcome of RT for PSA progression after RP has been established [19]. Assuming a local nature of the underlying disease, salvage radiotherapy (SRT) of the prostatic bed has widely been used to treat patients in the absence of biopsy-proven local recurrence. An established standard is conformal radiotherapy to the prostatic fossa with a dose of about 66 Gray (Gy), aiming to irradiate the presumed local recurrence and hence to reduce the risk of a "second wave of metastasis" leading to clinical progression of disease [20]. In the light of these well-known problems in detecting local recurrence in the prostatic bed, radiotherapy to the prostatic fossa is one of the rare therapies in which most radiation oncologists irradiate without histological proof of tumour recurrence.

Adjuvant versus salvage radiation therapy

At the present time, there are no published randomised trials to compare adjuvant versus salvage radiotherapy. Although the three randomised adjuvant RT trials encouraged salvage treatment in those who failed after observation, the parameters for salvage treatment were not predetermined. This makes a direct comparison of adjuvant versus salvage radiation flawed. There is a recently activated study designed to answer this question as well as the potential role of concomitant androgen deprivation (AD) [21]. The Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) trial is an effort to evaluate adjuvant versus salvage radiation. Patients will be randomised after surgery to early or delayed radiation. Delayed radiation will be given when there are two consecutive rises with a PSA >0.1 ng/mL or three consecutive rises. The planned accrual is 2600 patients with the primary outcome being cause-specific survival. There will be a second randomisation regarding AD, which will be discussed later.

There have been multiple retrospective studies that have looked at the clinical question of how adjuvant or salvage radiation affects local control [22–25] or failure from biochemical failure (FFBF) [26–31]. Consistent improvements in local control and FFBF have been observed in patients treated adjuvantly compared to those treated for salvage. The 5-year FFBF rates were approximately 69% to 89% after adjuvant radiotherapy and 39% to 68% after salvage radiotherapy. Local control was 96% to 100% after adjuvant radiotherapy and 79% to 93% after salvage radiotherapy.

Recently, Trabulsi and colleagues studied a group of patients undergoing adjuvant RT by comparing them with a matched control group undergoing salvage RT after biochemical failure. Using a multi-institutional database of 2299 patients, 449 patients with pT3–4 N0 disease were eligible for inclusion, including 211 patients receiving adjuvant radiotherapy and 238 patients receiving SRT. Adjuvant radiotherapy significantly reduced the risk of long-term biochemical progression after RP compared with SRT (5-year FFBF was 73% after adjuvant radiotherapy, compared with 50% after SRT; $P = 0.007$). Gleason score $\geqslant$8 was a significant predictor of FFBF [32].

Role of investigations in the case of persistingrising PSA

A local recurrence is more likely to be confirmed with biopsy when abnormal soft tissue in the post-radical prostatectomy bed is detected with either digital rectal exam (DRE) or imaging [18]. Imaging modalities that can detect post-radical prostatectomy recurrence and potentially guide biopsy include transrectal ultrasonography (TRUS), magnetic resonance imaging (MRI), and nuclear medicine methods; these modalities can also aid in monitoring disease progression or planning salvage radiation therapy.

TRUS is the most available and most commonly performed imaging technique used in post-radical prostatectomy patients with suspected recurrence. The main role of TRUS is in detecting sites of suspected recurrence and directing biopsies. The sensitivity of

TRUS-guided biopsies (66–75%) has been shown to be greater than that of DRE-guided biopsies (29–50%) in the post-radical prostatectomy patient [33,34]. The sensitivity of TRUS-guided biopsies increases with higher PSA levels at the time of recurrence [10], obviously related to larger tumour volume. A recent study showed that only 25% of patients with PSA <1 ng/mL had biopsy proven recurrence, compared with 53% of patients with PSA levels >2 ng/mL [34]. More recent advances in TRUS of post-radical prostatectomy patients include the use of colour and power Doppler to detect areas with increased vascularity. Both these techniques have been shown to improve sensitivity and specificity [35].

The advantages of MRI over TRUS are its superior soft-tissue resolution and its ability to cover the entire post-prostatectomy fossa and detect recurrences that are located beyond the region routinely imaged on ultrasound. The combination of an external and an endorectal coil improves the ability to detect local recurrence of prostate cancer [36]. The anatomic detail and wide coverage of the pelvis by MRI facilitates its increasing use in directing salvage radiation therapy when a recurrence is demonstrated [37]. Additionally, pelvic lymph adenopathies and osseous metastases, the most common early metastatic sites from prostate cancer, are routinely evaluated on MRI.

The reported sensitivity and the specificity of MRI for depicting local recurrences are 95–100% and 100%, respectively [38,39].

Advancements in MRI techniques, including magnetic resonance spectroscopy and DCE-MRI, have not yet been systematically evaluated for detection of post-RP recurrence.

A variety of nuclear medicine techniques are currently being evaluated in post-RP patients with a PSA relapse. These studies include evaluation for local recurrence and for metastatic disease in the pelvis with combined positron emission tomography (PET)/computed tomography (CT), utilising various tracers. Older studies using the radiotracer ^{18}F-fluorodeoxyglucose (FDG), which is commonly used in cancer imaging, showed a low sensitivity and specificity [40]. However, with the clinical introduction of newer image reconstruction algorithms, newer generations of PET scanners with higher spatial resolution, and the use of combined PET/CT, this has changed. Although ^{18}F-FDG continues to be a suboptimal radiotracer for the detection of local recurrence, disease can be detected in selected patients, with the probability of detection depending on PSA level and PSA doubling time [41]. New, experimental radiotracers, including ^{11}C or ^{18}F choline, ^{11}C or ^{18}F acetate or anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, appear more promising for the detection of both local and metastatic recurrent prostate cancer [42,43].

Salvage radiotherapy

There have been an increasing number of studies published on percutaneous RT for patients with PSA elevation out of the undetectable range or persisting PSA after RP, attesting to the importance of this clinical issue. In most of the retrospective studies, the response rate is defined as a decreasing of PSA, but not as achieving an undetectable PSA after SRT [44]. In these circumstances, approximately 70–75% of patients had a decrease of their serum PSA. However, a substantial proportion of these patients, initially responding to SRT, later developed increasing PSA values as biochemical evidence of progression of disease again. Therefore, only about 20–30% of all patients have no progression of the disease at 8–10 years [16,45].

The most critical questions are: In how many patients will it be possible to reduce an elevated PSA level after RP into the undetectable range by SRT? And furthermore, in how many patients will the PSA level stay undetectable in follow-up? Probably only the latter patients have a chance of cure.

Many retrospective studies describe the outcome of patients treated with SRT for both PSA increase and persistent PSA after RP [22,45,46]. Up to now there have been no data from a prospective randomised trial for SRT after biochemical failure of RP.

Pazona and colleagues demonstrated, in a retrospective series of 223 patients, that patients with a complete response defined as a PSA <0.3 ng/mL (162 of 223) had a 5-year biochemical no-evidence-of-disease (bNED) rate of 55% compared with all patients (40%). The median follow-up was 50 months [16]. However, a statistical comparison of these groups was not done and only 223 of 307 men were followed because most of these patients were irradiated in other parts of the US. Additionally, the patients were treated inhomogeneously. The undetectable range (<0.3 ng/mL) in this series was relatively high.

Biochemical disease recurrence after RP often prompts SRT, but no studies have had sufficient numbers of patients or follow-up to determine whether SRT improves survival, and if so, which subgroup of men will most likely benefit.

Recently, Trock and colleagues published a retrospective analysis of a cohort of 635 men who experienced biochemical and/or local recurrence and

Table 1
Risk factors for freedom from biochemical failure (FFBF) after salvage radiotherapy

Covariate	CP	FFBF (%)*	CP	FFBF (%)*	Refs
Pre-RT PSA	⩽1	63	>1	28	[15,18,51,55,57,58]
SVI	No	48	Yes	18	[18,51]
Margin	Neg.	58	Pos.	31	[18,57]
GS	⩽7	56	8 to 10	13	[18,51,54,57]
PSADT	>1 year	42	<1 year	26	[53,57]

Pre-RT PSA, preradiation prostate specific antigen; SVI, seminal vesicle involvement; GS, Gleason score; PSADT, prostate-specific antigen doubling time; CP, cut point.
*Approximate 5-year values shown.

received no salvage treatment ($n = 397$), salvage radiotherapy alone ($n = 160$) or salvage radiotherapy combined with hormonal therapy ($n = 78$). With a median follow-up of 6 years after recurrence, SRT alone was associated with a significant 3-fold increase in prostate cancer-specific survival relative to those who received no salvage treatment (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.17–0.69; $P = 0.003$). The increase in prostate cancer-specific survival with SRT was limited to men with a PSA doubling time of less than 6 months. SRT also was associated with a significant increase in overall survival [47].

Prognostic factors

Many authors were able to demonstrate that SRT results in an initial treatment response with decreasing PSA levels in up to 60–75% of patients [48,49]. There is less information about the number of patients who achieved an undetectable PSA after SRT and the prognostic value of this endpoint on the one hand and the definition of "undetectable" PSA on the other hand. Threshold values of PSA <0.3 ng/mL, <0.2 ng/mL, or even lower have been used [19]. Many patients with decreasing PSA develop an increase of PSA later, thus indicating further progression of disease. Only about 20–30% of the patients remain without evidence of disease at 10 years [16]. Therefore, it is of relevance to define factors that likely predict those patients with a good chance of responding best to SRT and to define subgroups of patients who will need additional therapy (e.g. hormonal treatment or irradiation of the pelvic lymph nodes) [19].

A consistent predictor of outcome after salvage treatment is the PSA level before radiotherapy. Multiple studies have shown that the lower the PSA at the time of salvage therapy, the better the results [50–56]. Various cut-off points have been used, ranging from PSA 0.5 to 4.0 ng/mL. The relationship between the pre-radiotherapy PSA and patient outcome is consistent [19], and no specific cut-off point has been identified as being better than another at predicting failure, although overall failure rates are high when the PSA is >1.0 ng/mL (Table 1). The lower the pre-radiotherapy PSA is when salvage RT is given, the better the chance of disease control.

Recently, Wiegel and colleagues reported on a retrospective study with the analysis of 162 patients which was different from most other studies because no patient had hormonal treatment before SRT – nearly 90% of the patients were treated homogeneously with 66.6 Gy and, of special interest, patients had careful follow-up to detect whether the patients achieved an undetectable PSA after SRT below 0.1 ng/mL, and especially in more than 90% of them, a value below 0.05 ng/mL [59]. They were the first to demonstrate that achieving an undetectable PSA below 0.1 ng/mL is an independent highly significant predictor for long-term biochemical outcome [59]. These data indicate that the definition of biochemical progression with a PSA of more than 0.3 ng/mL, or more than 0.4 ng/mL, as proposed by others [19] remains questionable.

Other factors shown to herald poor response to salvage treatment are a short PSA doubling time and time to failure. A PSA doubling time of less than 10 to 12 months predicts for increased failure, as does a time to biochemical failure of less than 2 to 3 years [27,60–62].

A nomogram was developed predicting biochemical failure after SRT. Stephenson and colleagues [19] created a nomogram from a pooled multi-institutional database comprising 1818 patients with a median follow-up of 53 months after SRT. The factors included pre-surgery PSA, Gleason score, seminal vesicle involvement, extracapsular extension, surgical margins, lymph node status, PSA at salvage radiation therapy, PSA doubling time, time to recurrence, time from recurrence to radiation, radiation dose, and neo-adjuvant androgen deprivation.

Timing of radiotherapy

There is a major controversy concerning the best time to start irradiation (i.e. the best PSA cut-off level). In former times, the recommended cut-off level was below 1.5 ng/mL (American Society for Therapeutic Radiology and Oncology), but a lower cut-off level was clearly correlated with a better biochemical outcome. For example, various cut-off points had been selected [15,18,48,49,55]; for example, 1.5 ng/mL [48] or 1.1 ng/mL [55]. More recent series recommended start of treatment at PSA levels <0.5 ng/mL [18]. The results by Wiegel and colleagues, as from other groups, suggested that patients with low pre-SRT PSA levels (i.e. <0.5 ng/mL) may be the ones who benefit most from SRT. Their data strongly indicate that a PSA <0.33 ng/mL was an independent prognosticator of achieving an undetectable PSA after SRT, thus giving the chance of a durable long-term response [59]. On the other hand, the best level for start of irradiation remains uncertain as there is a risk for overtreatment in the case of benign glands only. Stephenson and colleagues suggested the best level lies between 0.2 ng/mL and 0.4 ng/mL [19], but the question remains unresolved. It seems possible that the ideal time of treatment could be the first detected and confirmed rise of the PSA value out of the undetectable range; however, this strategy would be associated with a growing proportion of patients being over-treated. Interestingly, a reanalysis of the Southwest Oncology Group 8794 Trial (subgroup analysis of a randomised phase III trial comparing adjuvant RT versus "wait and see") demonstrated a clearly significant benefit for patients with a PSA level <0.2 ng/mL for bNED, local recurrence, and distant failure compared with a PSA level >0.2 ng/mL <1.0 ng/mL [63], thus raising the question of a superiority of adjuvant RT after RP for high-risk patients over the strategy of SRT at the time of PSA elevation [64]. Three randomised phase III trials demonstrated a nearly 20% absolute benefit in case of bNED for 60 Gy compared with "wait and see" only [65–67]. Because there are no randomised data comparing adjuvant RT and SRT, the best time to start irradiation remains under discussion [68].

Positive surgical margins, indicating residual disease in the prostatic bed, as the target for RT was a predictor of better outcome after SRT in previous studies [18,44]. PSA doubling time (PSADT) is an important prognosticator of bNED [17,59].

A major point of discussion is the best definition of progression after RT for an elevated PSA after RP. There are many different definitions by different authors, thus leading to problems with comparing the results [44]. Besides the American Society for Therapeutic Radiology and Oncology guidelines [69], other authors used two consecutive increases of PSA after SRT [52,69], or two consecutive increases from nadir [51,70]. Stephenson and colleagues reported the results of a multi-institutional cohort with 1540 patients from 17 North American tertial referral centres and defined progression as a PSA value of 0.2 ng/mL or more above the post-RT nadir followed by another rise [18,19]. Others defined a single PSA value greater than 0.4 ng/mL at least 1 year after RT [17] as progression or not achieving a decrease to less than 0.3 ng/mL (with all patients starting with values higher than 0.3 ng/mL) [16]. However, there is an urgent need to find a uniform definition of biochemical progression after SRT for elevated PSA after RP for better comparisons of the various reports.

The best RT dose in the case of elevated PSA after RP remains uncertain. Total SRT dose was associated with significantly improved bNED in some studies [44,55]. Total doses between 64 Gy and 66 Gy (and 70 Gy) are commonly recommended [18]. However, there is clear evidence in the case of definitive RT of prostate cancer, that doses beyond 72 Gy are needed to cure a macroscopic tumour burden [68]. Therefore, it would be possible that 66 Gy is enough to achieve an undetectable PSA in many cases, but not enough for durable cure and higher doses are needed for curative treatment.

Persisting PSA after RP

Most published studies report together on data of patients with an increasing PSA and patients with persistent PSA – within the detectable range – after RP. However, it is unclear whether postoperatively persisting PSA values have to be interpreted in the same way as an increase out of the undetectable range or whether this is rather a sign of occult metastatic tumour spread [72]. Current data support both the latter and the former views, but all the relevant studies involve only small patient groups.

Positive pelvic lymph nodes

Whether the pelvic lymphatics should be treated in primary RT for prostate cancer is still not clear at all, and the first large-scale, and therefore adequately powered, phase III study on that topic which has been fully published has not provided helpful conclusions [73]. Moreover, in the treatment of a biochemical recurrence, there seems to be a sort of consensus that recurrences in the pelvic lymphatics should be managed as systemic disease not amenable

Table 2
Published reports of radiotherapy for isolated PSA failure after radical prostatectomy

	Schild, 1996 [55]	Pisansky, 2000 [15]	Anscher, 2000 [71]	MacDonald, 2003 [44]	Wiegel, 2009 [59]
No. pts.	46	166	89	60	162
Follow-up (median)	37 mo.	52 mo.	48 mo.	51 mo.	42 mo.
Definition of bio-chemical progression	PSA ⩾0.3 ng/mL	PSA ⩾0.3 ng/mL	Increase ⩾10% on 2 consecutive studies	PSA ⩾0.3 ng/mL	3 consecutive increases in PSA measurements
% bDFS (acturial)	50 (5-yr)	46 (5-yr)	50 (4-yr)	45 (5-yr)	54% (3.5-yr)
Pre-RT PSA (median)	–	0.9 ng/mL	1.4 ng/mL	0.69 ng/mL	0.33 ng/mL
Med. RT dose	64 Gy	64 Gy	66 Gy	64.8 Gy	66.6 Gy
Hormonal treatment before RT	no	no	8 pts.	no	no
Dose–response relationship	RT dose ⩾64 Gy	RT dose ⩾64 Gy	RT dose ⩾65 Gy	RT dose ⩾64.8 Gy	–

No, number; pts, patients; mo, months; PSA, prostate specific antigen; bDFS, biochemical disease-free survival; yr, year; Pre-RT, pre-radiotherapy; Med, median; RT, radiotherapy; Gy, Gray.

to local treatment modalities. Therefore, the rate of patients in whom the pelvic lymph nodes are treated during salvage irradiation is generally very low and below 10% in most published series [15,17,18].

In those patients in whom the pelvic lymphatics are treated by RT, this is mainly with palliative intent due to hormone-insensitive disease causing complaints by obstruction or compression of lymphovascular drainage. Alleviation of the symptoms is often achieved in these patients, but there are only a few published reports dealing with that topic; at least in part this may be due to the limited prognosis of this negatively selected patient population.

Additional use of hormone therapy to SRT

There are prospective randomised data showing the benefit of AD plus radiation for men with high-risk prostate cancer treated definitively. The results in support of postoperative RT + AD are scarce, mostly derived from small retrospective series in which short-term AD was used in the salvage setting [27,74,75]. AD was an independent predictor of outcome in a multi-institutional analysis used to construct a nomogram, by Stephenson and colleagues [19].

Two randomised trials from the RTOG were designed to more directly address the question of AD use in the postoperative setting. One study was RTOG 9601 (radiation therapy alone versus radiation therapy plus 2 years of bicalutamide at 150 mg/d) which has completed accrual and results are now pending. The other was RTOG p-0011, a 3-arm adjuvant radiation therapy trial that was terminated because of poor accrual. Another postoperative RTOG trial (05-34), a 3-arm trial, was activated in 2007. This SRT trial compares prostate bed radiation therapy alone versus prostate bed plus 4 to 6 months of AD versus whole pelvis and prostate bed radiation therapy plus 4 to 6 months of AD, and has a planned accrual of about 1700 patients; the primary endpoint is biochemical failure (PSA nadir >2 ng/mL). As mentioned earlier, the RADICALS trial will also investigate the role of AD in the postoperative setting. This trial incorporates a second randomisation for all patients receiving radiation to either no AD, 6 months of AD, or 2 years of AD.

Technical aspects of external RT

Traditionally, a 4-field technique has been used. The conventional RT treatment volumes were typically very generous, being approximately 10×10 cm in the anterior-posterior fields with the inferior border at the ischial tuberosities. The lateral fields extended from the anterior aspect of the pubic symphysis and split the rectum posteriorly.

In 3-dimensional conformal radiation therapy (3D-CRT), the target volume should include the bladder neck (pulled into the prostate bed), periprostatic tissues/clips, and the seminal vesicle bed (including any seminal vesicle remnants if present). There are some anatomic landmarks that are useful in maximising coverage of the surgical bed. Inferiorly, the vesical-urethral anastomosis should be included. The anastomosis is the most frequent area of positive prostate biopsies [33,76,77]. By placing the inferior field edge at the top of the bulb of the penis (best seen on MRI) and adding margins for uncertainties, there should be adequate coverage. Laterally, the field should extend to about the medial aspect of each obturator internus

muscle. Although the rectum is a landmark posteriorly, the relative position of the rectum appears to shift after the prostate is removed as well as during RT [78–81]. For this reason, a generous margin posteriorly is recommended, such as setting an 8-mm margin with image guidance [82]. The superior margin is more subjective. The former prostate can extend above the pubic symphysis, but it is recommended that the anterior bladder be avoided at this level because this is the least likely area for extracapsular extension and positive margins. Treatment of the seminal vesicle bed behind the bladder is advised. If vascular clips were used at prostatectomy, they are likely to be seen in this region. The level of the posterior-superior clinical target volume is somewhat subjective and should be guided by the extent of disease at the prostate base and whether the seminal vesicles were involved.

Given the potential for late toxicity after postoperative radiotherapy, the use of intensity-modulated radiotherapy (IMRT) is appealing [83]. As with 3D-CRT, generous definition of the prostate bed target volume and adequate margins to account for target motion (due to different rectal and bladder filling) and setup uncertainties are critical. The theoretical advantages of IMRT are that dose falloff is more geometrically rapid than for 3D-CRT, and there is better conformation of dose to irregularly shaped targets (e.g. the superior-posterior aspect of the postoperative field). There should be greater sparing of the superior-anterior bladder, the posterior rectum, and the erectile tissues using IMRT, despite using the same field borders [84]. The prostate bed has been shown to move relative to the skeletal anatomy [80]. Weekly localisation using, at a minimum, ultrasound is recommended [85,86]. However, ultrasound is difficult to use without a prostate to target, and alternative image-guided RT methods could be considered [82,87,88].

Side effects and toxicity

SRT is generally associated with a low rate of severe acute and late side effects. Urinary incontinence in 0–5% of the cases, moderate proctitis in 0–10% and mild to moderate cystitis in up to 10% may result from this procedure [18,48,70,89]. Severe late effects are rare events affecting 3–6% or fewer of the patients [70]. In our study, SRT was well tolerated with only a few severe effects: only four patients (2.4%) had grade 3 cystitis. Four of 162 patients (2.4%) had urethral strictures after RP followed by SRT.

A low rate of side effects is of particular importance for a therapy without histological confirmation. As literature data attest, doses up to 66 Gy given in the frame of three-dimensional RT treatment planning are rarely associated with serious long-term side effects (grade 3/4 according to the RTOG-EORTC grading system) involving the rectum and bladder. Although in general, side effects tend to be underreported in retrospective analyses, a proportion of <3% seems to be a realistic estimate. Fairly higher rates of 10% genitourinary grade 3 complications, namely anastomotic strictures and bladder neck contractures requiring dilatation, reported in a series of 115 patients from the Memorial Sloan-Kettering Cancer Center, need to be interpreted with caution [74]. It may be difficult to differentiate side effects of RT from pre-existing disabilities and sequelae of RP. At least equivalent rates of severe genitourinary complications following RP alone have been reported in a Surveillance, Epidemiology, and End Results (SEER) database analysis of 11,522 patients published by the same institution [90]. When postoperative RT is performed in a three-dimensionally planned, multiple-field technique with fields individually shaped to spare the bladder and rectum, RTOG grade 1/2 side effects occur in up to 25% of patients, but they do not have a relevant negative impact on quality of life [91]. Formenti and colleagues investigated the rate and degree of incontinence and erectile dysfunction after nerve-sparing RP with or without adjuvant RT. Unfortunately, follow-up examinations only comprised a questionnaire with inherent weaknesses. No difference was found between 72 patients who underwent both RP and RT and 138 patients who underwent RP only when total doses of 45–54 Gy were applied [92]. In a randomised study comprising 100 patients, there was no difference in the number of fully continent patients after 24 months between the group receiving 60 Gy and the group under observation [93]. Similar results were obtained in a retrospective study of the Mayo Clinics [94]. However, with doses exceeding 70 Gy, the rates, as well as the degree of side effects, increased markedly [91,95].

Conclusions

Salvage radiotherapy should be offered to patients with persisting PSA after RP provided distant metastases have been adequately ruled out. Of these patients, 30–70% will experience a decrease in their PSA to an undetectable range, and in about 40–50% of these patients, the PSA will remain stable after 5 years. This patient group, therefore, has a curative chance with SRT that otherwise would not exist.

A nomogram is now available as a guide to assessing the therapeutic value of SRT after biochemical failure. When SRT is indicated, it should be initiated as early as possible. Serious side effects are apparently low, thus confirming the suitability of this therapeutic approach. The role of AD after adjuvant or salvage RT remains poorly defined.

Conflict of interest statement

None declared.

References

1 Chun FK, Graefen M, Zacharias M, et al. Anatomic radical retropubic prostatectomy-long-term recurrence-free survival rates for localized prostate cancer. World J Urol 2006;24(3):273–80.
2 Swindle P, Eastham JA, Ohori M, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 2005;174(3):903–7.
3 Salomon L, Anastasiadis AG, Antiphon P, et al. Prognostic consequences of the location of positive surgical margins in organ-confined prostate cancer. Urol Int 2003;70(4):291–6.
4 Pinto F, Prayer-Galetti T, Gardiman M, et al. Clinical and pathological characteristics of patients presenting with biochemical progression after radical retropubic prostatectomy for pathologically organ-confined prostate cancer. Urol Int 2006;76(3):202–8.
5 Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317(15):909–16.
6 Morgan WR, Bergstralh EJ, Zincke H. Long-term evaluation of radical prostatectomy as treatment for clinical stage C (T3) prostate cancer. Urology 1993;41(2):113–20.
7 Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172(3):910–4.
8 Lightner DJ, Lange PH, Reddy PK, Moore L. Prostate specific antigen and local recurrence after radical prostatectomy. J Urol 1990;144(4):921–6.
9 van den Ouden D, Bentvelsen FM, Boeve ER, Schroder FH. Positive margins after radical prostatectomy: correlation with local recurrence and distant progression. Br J Urol 1993;72(4):489–94.
10 Shekarriz B, Upadhyay J, Wood DP, Jr., et al. Vesicourethral anastomosis biopsy after radical prostatectomy: predictive value of prostate-specific antigen and pathologic stage. Urology 1999;54(6):1044–8.
11 Fowler JE, Jr., Brooks J, Pandey P, Seaver LE. Variable histology of anastomotic biopsies with detectable prostate specific antigen after radical prostatectomy. J Urol 1995;153(3 Pt 2):1011–4.
12 Patel A, Dorey F, Franklin J, deKernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol 1997;158(4):1441–5.
13 Richardson TD, Wojno KJ, Liang LW, et al. Half-life determination of serum free prostate-specific antigen following radical retropubic prostatectomy. Urology 1996;48(6A Suppl):40–4.
14 Godoy G, Tareen BU, Lepor H. Does benign prostatic tissue contribute to measurable PSA levels after radical prostatectomy? Urology 2009.
15 Pisansky TM, Kozelsky TF, Myers RP, et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. J Urol 2000;163(3):845–50.
16 Pazona JF, Han M, Hawkins SA, Roehl KA, Catalona WJ. Salvage radiation therapy for prostate specific antigen progression following radical prostatectomy: 10-year outcome estimates. J Urol 2005;174(4 Pt 1):1282–6.
17 Ward JF, Zincke H, Bergstralh EJ, Slezak JM, Blute ML. Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. J Urol 2004;172(6 Pt 1):2244–8.
18 Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291(11):1325–32.
19 Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25(15):2035–41.
20 Coen JJ, Zietman AL, Thakral H, Shipley WU. Radical radiation for localized prostate cancer: local persistence of disease results in a late wave of metastases. J Clin Oncol 2002;20(15):3199–205.
21 Parker C, Sydes MR, Catton C, et al. Radiotherapy and androgen deprivation in combination after local surgery (RADICALS): a new Medical Research Council/National Cancer Institute of Canada phase III trial of adjuvant treatment after radical prostatectomy. BJU Int 2007;99(6):1376–9.
22 Morris MM, Dallow KC, Zietman AL, et al. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 1997;38(4):731–6.
23 Pacholke HD, Wajsman Z, Algood CB, Morris CG, Zlotecki RA. Postoperative adjuvant and salvage radiotherapy for prostate cancer: impact on freedom from biochemical relapse and survival. Urology 2004;64(5):982–6.
24 Do LV, Do TM, Smith R, Parker RG. Postoperative radiotherapy for carcinoma of the prostate: impact on both local control and distant disease-free survival. Am J Clin Oncol 2002;25(1):1–8.
25 Petrovich Z, Lieskovsky G, Langholz B, Jozsef G, Streeter OE, Jr., Skinner DG. Postoperative radiotherapy in 423 patients with pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys 2002;53(3):600–9.
26 Vicini FA, Ziaja EL, Kestin LL, et al. Treatment outcome with adjuvant and salvage irradiation after radical prostatectomy for prostate cancer. Urology 1999;54(1):111–7.
27 Lee AK, D'Amico AV. Utility of prostate-specific antigen kinetics in addition to clinical factors in the selection of patients for salvage local therapy. J Clin Oncol 2005;23(32):8192–7.
28 Vargas C, Kestin LL, Weed DW, Krauss D, Vicini FA, Martinez AA. Improved biochemical outcome with adjuvant radiotherapy after radical prostatectomy for prostate cancer with poor pathologic features. Int J Radiat Oncol Biol Phys 2005;61(3):714–24.
29 Valicenti RK, Gomella LG, Ismail M, et al. The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: a matched-pair analysis. Int J Radiat Oncol Biol Phys 1999;45(1):53–8.
30 Leibovich BC, Engen DE, Patterson DE, et al. Benefit of adjuvant radiation therapy for localized prostate cancer with a positive surgical margin. J Urol 2000;163(4):1178–82.

31 Choo R, Hruby G, Hong J, et al. Positive resection margin and/or pathologic T3 adenocarcinoma of prostate with undetectable postoperative prostate-specific antigen after radical prostatectomy: to irradiate or not? Int J Radiat Oncol Biol Phys 2002;52(3):674–80.
32 Trabulsi EJ, Valicenti RK, Hanlon AL, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3–4N0 prostate cancer. Urology 2008;72(6):1298–302; discussion 1302–4.
33 Scattoni V, Roscigno M, Raber M, et al. Multiple vesico-urethral biopsies following radical prostatectomy: the predictive roles of TRUS, DRE, PSA and the pathological stage. Eur Urol 2003;44(4):407–14.
34 Deliveliotis C, Manousakas T, Chrisofos M, Skolarikos A, Delis A, Dimopoulos C. Diagnostic efficacy of transrectal ultrasound-guided biopsy of the prostatic fossa in patients with rising PSA following radical prostatectomy. World J Urol 2007;25(3):309–13.
35 Tamsel S, Killi R, Apaydin E, Hekimgil M, Demirpolat G. The potential value of power Doppler ultrasound imaging compared with grey-scale ultrasound findings in the diagnosis of local recurrence after radical prostatectomy. Clin Radiol 2006;61(4):325–30; discussion 323–4.
36 Huch Boni RA, Meyenberger C, Pok Lundquist J, Trinkler F, Lutolf U, Krestin GP. Value of endorectal coil versus body coil MRI for diagnosis of recurrent pelvic malignancies. Abdom Imaging 1996;21(4):345–52.
37 Miralbell R, Vees H, Lozano J, et al. Endorectal MRI assessment of local relapse after surgery for prostate cancer: A model to define treatment field guidelines for adjuvant radiotherapy in patients at high risk for local failure. Int J Radiat Oncol Biol Phys 2007;67(2):356–61.
38 Sella T, Schwartz LH, Swindle PW, et al. Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. Radiology 2004;231(2):379–85.
39 Silverman JM, Krebs TL. MR imaging evaluation with a transrectal surface coil of local recurrence of prostatic cancer in men who have undergone radical prostatectomy. AJR Am J Roentgenol 1997;168(2):379–85.
40 Hofer C, Laubenbacher C, Block T, Breul J, Hartung R, Schwaiger M. Fluorine-18-fluorodeoxyglucose positron emission tomography is useless for the detection of local recurrence after radical prostatectomy. Eur Urol 1999;36(1):31–5.
41 Schoder H, Herrmann K, Gonen M, et al. 2-[18F]fluoro-2-deoxyglucose positron emission tomography for the detection of disease in patients with prostate-specific antigen relapse after radical prostatectomy. Clin Cancer Res 2005;11(13):4761–9.
42 Cimitan M, Bortolus R, Morassut S, et al. [18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. Eur J Nucl Med Mol Imaging 2006;33(12):1387–98.
43 Scattoni V, Picchio M, Suardi N, et al. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Urol 2007;52(2):423–9.
44 Macdonald OK, Schild SE, Vora SA, et al. Radiotherapy for men with isolated increase in serum prostate specific antigen after radical prostatectomy. J Urol 2003;170(5):1833–7.
45 Teh BS, Bastasch MD, Mai WY, Kattan MW, Butler EB, Kadmon D. Long-term benefits of elective radiotherapy after prostatectomy for patients with positive surgical margins. J Urol 2006;175(6):2097–101; discussion 2101–2.
46 Hocht S, Wiegel T, Schostak M, Hinkelbein W. Adjuvant and salvage radiotherapy after radical prostatectomy. Onkologie 2002;25(3):201–6.
47 Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008;299(23):2760–9.
48 Neuhof D, Hentschel T, Bischof M, Sroka-Perez G, Hohenfellner M, Debus J. Long-term results and predictive factors of three-dimensional conformal salvage radiotherapy for biochemical relapse after prostatectomy. Int J Radiat Oncol Biol Phys 2007;67(5):1411–7.
49 Forman JD, Meetze K, Pontes E, et al. Therapeutic irradiation for patients with an elevated post-prostatectomy prostate specific antigen level. J Urol 1997;158(4):1436–9; discussion 1439–40.
50 Catton C, Gospodarowicz M, Warde P, et al. Adjuvant and salvage radiation therapy after radical prostatectomy for adenocarcinoma of the prostate. Radiother Oncol 2001;59(1):51–60.
51 Chawla AK, Thakral HK, Zietman AL, Shipley WU. Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. Urology 2002;59(5):726–31.
52 Garg MK, Tekyi-Mensah S, Bolton S, et al. Impact of postprostatectomy prostate-specific antigen nadir on outcomes following salvage radiotherapy. Urology 1998;51(6):998–1002.
53 Leventis AK, Shariat SF, Kattan MW, Butler EB, Wheeler TM, Slawin KM. Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2001;19(4):1030–9.
54 Mosbacher MR, Schiff PB, Otoole KM, et al. Postprostatectomy salvage radiation therapy for prostate cancer: impact of pathological and biochemical variables and prostate fossa biopsy. Cancer J 2002;8(3):242–6.
55 Schild SE, Buskirk SJ, Wong WW, et al. The use of radiotherapy for patients with isolated elevation of serum prostate specific antigen following radical prostatectomy. J Urol 1996;156(5):1725–9.
56 Wilder RB, Hsiang JY, Ji M, Earle JD, de Vere White R. Preliminary results of three-dimensional conformal radiotherapy as salvage treatment for a rising prostate-specific antigen level postprostatectomy. Am J Clin Oncol 2000;23(2):176–80.
57 Macdonald OK, Schild SE, Vora S, et al. Salvage radiotherapy for men with isolated rising PSA or locally palpable recurrence after radical prostatectomy: do outcomes differ? Urology 2004;64(4):760–4.
58 Zelefsky MJ, Aschkenasy E, Kelsen S, Leibel SA. Tolerance and early outcome results of postprostatectomy three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 1997;39(2):327–33.
59 Wiegel T, Lohm G, Bottke D, 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(4):1009–16.
60 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. J Clin Oncol 2005;23(22):4975–9.
61 Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294(4):433–9.

62 Taylor N, Kelly JF, Kuban DA, Babaian RJ, Pisters LL, Pollack A. Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 2003;56(3):755–63.
63 Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007;25(16):2225–9.
64 Bottke D, Wiegel T. Adjuvant radiotherapy after radical prostatectomy: indications, results and side effects. Urol Int 2007;78(3):193–7.
65 Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005;366(9485):572–8.
66 Thompson IM, Jr., Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006;296(19):2329–35.
67 Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;**27**:2924–39.
68 Bottke D, Wiegel T. Percutaneous radiotherapy for low-risk prostate cancer: options for 2007. World J Urol 2007;25(1):53–7.
69 Song DY, Thompson TL, Ramakrishnan V, et al. Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. Urology 2002;60(2):281–7.
70 Do T, Parker RG, Do C, Tran L, Do L, Dolkar D. Salvage radiotherapy for biochemical and clinical failures following radical prostatectomy. Cancer J Sci Am 1998;4(5):324–30.
71 Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. Int J Radiat Oncol Biol Phys 2000;48(2):369–75.
72 Zietman AL, Edelstein RA, Coen JJ, Babayan RK, Krane RJ. Radical prostatectomy for adenocarcinoma of the prostate: the influence of preoperative and pathologic findings on biochemical disease-free outcome. Urology 1994;43(6):828–33.
73 Roach M, 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21(10):1904–11.
74 Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol 2003;21(3):483–9.
75 King CR, Presti JC, Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? Int J Radiat Oncol Biol Phys 2004;59(2):341–7.
76 Leventis AK, Shariat SF, Slawin KM. Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. Radiology 2001;219(2):432–9.
77 Naya Y, Okihara K, Evans RB, Babaian RJ. Efficacy of prostatic fossa biopsy in detecting local recurrence after radical prostatectomy. Urology 2005;66(2):350–5.
78 Sanguineti G, Castellone P, Foppiano F, et al. Anatomic variations due to radical prostatectomy. Impact on target volume definition and dose-volume parameters of rectum and bladder. Strahlenther Onkol 2004;180(9):563–72.
79 Fiorino C, Foppiano F, Franzone P, et al. Rectal and bladder motion during conformal radiotherapy after radical prostatectomy. Radiother Oncol 2005;74(2):187–95.
80 Kupelian PA, Langen KM, Willoughby TR, Wagner TH, Zeidan OA, Meeks SL. Daily variations in the position of the prostate bed in patients with prostate cancer receiving postoperative external beam radiation therapy. Int J Radiat Oncol Biol Phys 2006;66(2):593–6.
81 Schiffner DC, Gottschalk AR, Lometti M, et al. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007;67(2):610–9.
82 Paskalev K, Feigenberg S, Jacob R, et al. Target localization for post-prostatectomy patients using CT and ultrasound image guidance. J Appl Clin Med Phys 2005;6(4):40–9.
83 Bastasch MD, Teh BS, Mai WY, et al. Post-nerve-sparing prostatectomy, dose-escalated intensity-modulated radiotherapy: effect on erectile function. Int J Radiat Oncol Biol Phys 2002;54(1):101–6.
84 Pinkawa M, Siluschek J, Gagel B, et al. Postoperative radiotherapy for prostate cancer : evaluation of target motion and treatment techniques (intensity-modulated versus conformal radiotherapy). Strahlenther Onkol 2007;183(1):23–9.
85 Morr J, DiPetrillo T, Tsai JS, Engler M, Wazer DE. Implementation and utility of a daily ultrasound-based localization system with intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002;53(5):1124–9.
86 Chinnaiyan P, Tomee W, Patel R, Chappell R, Ritter M. 3D-ultrasound guided radiation therapy in the post-prostatectomy setting. Technol Cancer Res Treat 2003;2(5):455–8.
87 Scarbrough TJ, Golden NM, Ting JY, et al. Comparison of ultrasound and implanted seed marker prostate localization methods: Implications for image-guided radiotherapy. Int J Radiat Oncol Biol Phys 2006;65(2):378–87.
88 Paskalev K, Ma CM, Jacob R, et al. Daily target localization for prostate patients based on 3D image correlation. Phys Med Biol 2004;49(6):931–9.
89 Wiegel T, Bressel M, Carl UM. Adjuvant radiotherapy following radical prostatectomy – results of 56 patients. Eur J Cancer 1995;31A(1):5–11.
90 Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346(15):1138–44.
91 Wiegel T, Steiner U, Hinkelbein W. [Radiotherapy after radical prostatectomy: indications, results and side effects]. Strahlenther Onkol 1997;173(6):309–15.
92 Formenti SC, Lieskovsky G, Simoneau AR, et al. Impact of moderate dose of postoperative radiation on urinary continence and potency in patients with prostate cancer treated with nerve sparing prostatectomy. J Urol 1996;155(2):616–9.
93 Van Cangh PJ, Richard F, Lorge F, et al. Adjuvant radiation therapy does not cause urinary incontinence after radical prostatectomy: results of a prospective randomized study. J Urol 1998;159(1):164–6.
94 Schild SE, Wong WW, Grado GL, et al. The result of radical retropubic prostatectomy and adjuvant therapy for pathologic stage C prostate cancer. Int J Radiat Oncol Biol Phys 1996;34(3):535–41.
95 Schild SE, Wong WW, Grado GL, et al. Radiotherapy for isolated increases in serum prostate-specific antigen levels after radical prostatectomy. Mayo Clin Proc 1994;69(7):613–9.