Treatment of local progression following radiotherapy

Theo M. de Reijke[a], Thomas Wiegel[b]

[a]*Academic Medical Center, Amsterdam, The Netherlands*
[b]*Universitätsklinikum Ulm, Ulm, Germany*

Introduction

The outcome of radiotherapy for localised prostate cancer has improved over past years due to improved radiation techniques resulting in the possibility of delivering higher doses to the prostate and, secondly, due to more precise patient selection. However, there are still many men in follow-up that have been treated with radiotherapy doses which are nowadays considered as insufficient. Although improved staging and patient selection is possible, it is estimated that following surgery or radiotherapy for localised prostate cancer, approximately 40% of men will fail and present with a prostate specific antigen (PSA) relapse (biochemical recurrence) [1].

Since published results of phase III trials, randomising patients with high-risk prostate cancer between radiotherapy alone or radiotherapy plus neo- or adjuvant androgen deprivation therapy, have reported improved survival for the combined approach, these high-risk patients are, in most instances, now treated in first-line with this combination for a period of time up to 3 years [2,3]. Although improved survival rates were accomplished with this combined treatment, a considerable number of patients will still experience a biochemical relapse. The most important issue in case of a demonstrated PSA relapse is the determination of local disease only or distant failure, which has to be approached in a different way.

Following radical prostatectomy, several factors are helpful in defining patients at risk for local recurrence or metastatic disease e.g. time between surgery and PSA relapse, PSA doubling time, and pathological stage and grade [4]. For radiotherapy, these discriminative, predictive factors have not been identified.

PSA evaluation

Definition of PSA relapse

Following radical prostatectomy, the definition of PSA relapse is rather simple since the organ responsible for the majority of PSA production has been removed, although sometimes benign glands can be left behind due to a nerve sparing procedure [5]. The PSA level for recurrence following radical prostatectomy is defined as 0.2 ng/mL followed by a subsequent rise [6]. Recently, however, there were proposals to increase the PSA level to 0.4 ng/mL, because this level better explained the development of distant metastases after controlling for clinical variables and use of secondary treatments [7,8]. Some laboratories provide ultrasensitive methods to determine PSA levels, which could detect PSA relapse at a much earlier stage, but in clinical trials these very low levels have never been confirmed as useful in the definition of biochemical failure (or they have never been used or reported).

In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) agreed that PSA recurrence is an appropriate early endpoint for clinical trials. Biochemical failure after radiation therapy was defined as three consecutive increases in PSA. For clinical trials the date of failure should be the midpoint between post-irradiation PSA nadir and the first of the three consecutive increases [9]. This ASTRO definition was not linked to clinical progression or survival and it performed poorly in patients undergoing androgen deprivation therapy, and backdating biased the Kaplan-Meier estimates of event-free survival. A second Consensus Conference was sponsored by ASTRO and the Radiation Therapy Oncology Group in Phoenix to revise the ASTRO definition [10]. The panel recommended that a rise of 2 ng/mL or more above the nadir PSA be considered the standard definition for biochemical failure after external beam radiotherapy (EBRT) with or without short-term hormone therapy. Nowadays, the two definitions are often reported in most publications.

PSA response and bounce

Following radiotherapy the PSA decline is different compared to radical prostatectomy where an almost immediate disappearance can be observed according to the PSA half-life if radical surgical resection has

been accomplished. Following radiotherapy, a PSA increase can first be observed due to cellular necrosis, inflammatory changes and disruption of the cellular membrane. Later, a rapid decline can be seen, followed by a slower, but more sustained, decrease.

The reason why three, rather than two, consecutive PSA values were proposed in the original ASTRO recommendation for PSA progression was due to the risk of 'bouncing'. This phenomenon results when, during follow-up, one or two increases in PSA are observed followed by a sustained decrease. The effect of PSA 'bounce' was reported following EBRT and also post-brachytherapy for prostate cancer. It seems that the incidence of the 'bounce' is higher following brachytherapy compared to EBRT (40% versus 12%) [11–14].

The magnitude of PSA increase and the occurrence of PSA 'bounce' were evaluated in several series with respect to subsequent failure. Mitchell and colleagues found a lower rate of subsequent biochemical failure in a prospectively collected database where PSA 'bounce' was defined as a rise of 0.2 ng/mL above an initial PSA nadir with subsequent decline to or below that nadir without treatment. The patients who received neo-adjuvant or adjuvant hormone manipulation were excluded. Biochemical failure was determined using both the ASTRO consensus and Phoenix definitions [15]. Horwitz and colleagues found an increased risk of biochemical failure in patients with a PSA 'bounce' following EBRT, while Crook and colleagues found no relationship with PSA 'bounce' and subsequent biochemical failure following 125-I prostate brachytherapy [13,16]. The reasons for these different findings are not completely understood, but definition and perhaps the use of different PSA kits could be an explanation.

The PSA 'bounce' was independent of age, race, pre-treatment PSA, clinical T-stage, Gleason score and radiation dose although Hanlon and colleagues concluded that 'bouncing' was associated with a lower radiation dose and higher pre-treatment PSA levels [17]. The median time of occurrence for this phenomenon was 9 to 18 months from the time of therapy and the majority of 'bounces' were observed within 36 months. This phenomenon should of course be fully understood by all doctors following patients after radiotherapy for prostate cancer in order to reassure the patient.

PSA levels and nomograms

The initial PSA level is a determining factor for eventual success of radiotherapy. 5-year biochemical relapse rates were reported in 32%, 49% and 69% of patients with an initial PSA of 10–20 ng/mL, 20–30 ng/mL and 30 ng/mL or greater, respectively [18]. The PSA nadir was also a strong prognostic factor, with PSA recurrence-free survival rates of 83%, 68%, 56% and 28% if the PSA nadirs were 0.5 ng/mL or less, 0.6–0.9 ng/mL, 1.0–1.9 ng/mL and 2.0 ng/mL or greater, respectively.

The initially developed nomograms could help to predict the risk of recurrence for EBRT and different forms of brachytherapy by including different baseline characteristics e.g. pre-treatment PSA, Gleason score on biopsies and clinical T-stage. Since an increasing number of patients were treated with combination treatments (neo- and/or adjuvant hormonal therapy for shorter or longer duration), the more recent nomograms also included this as a baseline factor in order to determine the risk of PSA recurrence [19–22]. However, there are so many variables in treatment techniques, durations and schemes of neo- and/or adjuvant treatment that it is questionable if these nomograms are very helpful for the individual patient.

Investigations in case of PSA recurrence

Physical examination

In case of a PSA only relapse, a physical examination, and especially a digital rectal examination (DRE), is usually not helpful in determining the site of relapse. Due to the radiation the prostate has undergone changes and can be displaced, which usually makes a proper digital evaluation not possible. Only in the case of a high-risk patient and a very early PSA relapse or in the case of local symptoms can a local progression be identified by DRE.

Transrectal ultrasound and biopsies

Transrectal ultrasound (TRUS) examination following radiation therapy of the prostate is also not very helpful and certainly no better than DRE. No exact data exist on the sensitivity, specificity, and positive predictive value in case of follow-up after radiotherapy, but these figures will not differ significantly from the data for the initial work-up in case there is suspicion of prostate cancer, approximately 32–85%, 41–89%, and 20–76%, respectively [23]. In the field of TRUS many new developments (e.g. Doppler sonography, contrast-enhanced TRUS, elastography) are now being evaluated in the initial work-up of patients with elevated

PSA. Some of these improved sonographic investigations have already shown promising results but, in the field of evaluation of PSA recurrence following radiation treatment, no data are available yet [24–26].

Following radiation therapy there is no role for routine follow-up prostate biopsies. It is known that it takes up to 3 years for biopsies to convert to negative, so there is no role for taking routine prostate biopsies before 3 year follow-up unless there are other clinical reasons [27].

In case local recurrence is suspected and the demonstration of local recurrence has clinical consequences, prostate biopsies are indicated. However, no prospective data exist on the number and location of the biopsies, but it would be recommendable to target the biopsies to the previously positive location of the biopsies, although this information will frequently be lacking. The number of biopsies should not differ from that of the initial work-up of an elevated PSA, i.e. 12 biopsies. The interpretation of post-irradiation biopsies should be done with great care, especially if radiation was combined with hormonal therapy, because morphological changes may be present that resemble prostate cancer, but in fact these may just be radiation-induced changes [28].

Bone scintigraphy

Bone scans are indicated in the initial work-up in the following cases: PSA is greater than 20 ng/mL, higher clinical stage or Gleason grade. In the situation of a demonstrated PSA relapse following radiation therapy, a rapid slope or a PSA greater than 40 ng/mL are indications to perform bone scintigraphy [29,30]. However, in case a second local therapy is considered, distant metastases should be excluded, and certainly if the PSA relapse occurs early following radiation therapy. In cases of salvage therapy, a complete work-up will usually be performed, including a bone scan.

Computer tomography (CT)-scan

In spite of improvements in imaging techniques, a CT-scan is not the most sensitive technique for identifying prostate cancer or excluding the presence of metastatic disease. The diagnostic accuracy ranges between 50 and 60%. Johnstone and colleagues concluded that only in the case of a rapidly increasing PSA could a CT-scan be of any value [30].

Magnetic resonance imaging (MRI)

Thanks to the technical improvements and introduction of the endorectal coil, the diagnostic accuracy of MRI increased, compared to CT-scans, to 60–70%. MR-spectroscopy is evaluating metabolism properties of different areas in the prostate, choline/citrate ranges, which can increase the diagnostic accuracy again to 70–90%. However, these data are obtained in the initial work-up of patients suspected for the presence of prostate cancer; if these figures are also to apply for patients presenting with PSA relapse, further research is needed. For the evaluation of lymphogenous spread, ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MRI seems very promising with a detection limit for lymph node metastases of 4 mm [31].

Positron emission tomography (PET)-scan

The role of PET-scan is not clearly defined at this moment due to conflicting reports on the accuracy of demonstrating local and/or distant recurrences. Different techniques are being used at this moment which makes interpretation of the published data difficult.

[18]fluorocholine PET/CT can be performed to exclude distant metastases in patients with PSA levels greater than 4 ng/mL and 11C-choline PET/CT seems a valuable tool to demonstrate recurrent prostate cancer, but the limited positive predictive value warrants careful interpretation of these data [32,33]. Further studies using these techniques have to be awaited before PET-scans can be introduced in the work-up of patients who are candidates for salvage treatment following radiation treatment.

Timing of salvage treatment

Once a PSA relapse has been demonstrated the most important question is if the patient is a candidate for salvage treatment with curative intent or not. It has to be realised that combination treatment also implies a higher risk of morbidity.

In order to discuss salvage treatment the patient should have a good performance status, the morbidity of the initial radiotherapy should have been minimal, the metastatic work-up should be negative and the life expectancy should be at least 10 years.

In case of a biochemical relapse following radical prostatectomy, it has been shown that it takes at least 8 years before metastatic disease is demonstrated without any treatment and another 5 years until patients die [34]. In the survival analysis, time to PSA recurrence, Gleason score and PSA doubling time were predictive factors of the probability and time to metastatic disease. Whether the same is true for PSA relapse following radiotherapy is not known, but these facts should be taken into consideration when counselling a patient for a salvage procedure.

Salvage treatments

In early publications it was reported that salvage treatments had a poor outcome, due to the observation that many patients had marginal positive disease and/or lymph node metastases in the pathological specimen. Also, an increase in Gleason score and aneuploid tumours was found and this resulted in a poor outcome [35,36]. However, due to the introduction of PSA, radio-recurrent disease can be detected earlier and patients treated initially have been better staged and possibly had lower prostate cancer volume; these factors could result in better outcomes for patients once treated with a salvage treatment.

Salvage radical prostatectomy

Apart from a biochemical recurrence the reason for salvage radical prostatectomy could also be indicated if there is severe toxicity, e.g. incontinence, radiation cystitis or a contracted bladder. The proposed indications for salvage surgery are a PSA <10 ng/mL, PSA doubling time >12 months, $\leqslant$T3a stage and N0M0 [37].

The series of salvage surgery reported in the literature comprise only small numbers of patients; the oncological outcome with a median follow-up of 2–92 months showed a 5-year failure-free survival of 31–83% [38]. The reported morbidity was considerable: urinary incontinence: 17–67%, rectal injury: 4–8%, erectile dysfunction: 100%, bladder neck stricture: 0–41%, and mortality: 0–4%. These data have to be interpreted with great care because of patient selection, the small number of patients and short follow-up.

Following interstitial radiotherapy, only small series have been reported, but the outcome does not seem different from patients treated following EBRT [39].

Salvage radical prostatectomy is nowadays also feasible via the laparoscopic approach [40].. It is clear that these salvage procedures should be performed in centres of excellence and the data should be collected prospectively in order to obtain conclusions on which patients are best suitable for salvage radical prostatectomy.

Salvage radiation treatment

Since many patients that are in follow-up have been treated with doses that are nowadays considered insufficient, there could be room for salvage radiation treatment. Different scenarios are possible in this case: patients treated with EBRT could be treated with salvage EBRT or brachytherapy and vice versa. Of course, patients qualifying for salvage radiation therapy should not have radiation-induced toxicity from the initial treatment.

The series on salvage brachytherapy reported are again small; oncological outcome with a median follow-up of 19–64 months showed a 5-year failure-free survival rate ranging from 20–89%. The morbidity was considerable: urinary incontinence: 0–31%, rectal grade 3–4 toxicity: 0–24%, genito-urinary grade 3–4 toxicity: 0–47%, and prostatic-rectal fistula: 0–12% [38]. The series are difficult to compare since different forms of brachytherapy were used (palladium, iodine and iridium). Salvage brachytherapy and salvage EBRT following initial brachytherapy are incidentally reported and no clear recommendations can be made from these small, highly selected series [41].

Salvage cryotherapy

The technique for cryotherapy has been improved considerably in recent years, especially the introduction of the transperineal ultrasound-guided implantation technique using thin needles which has reduced toxicity and improved outcome for the treatment of primary diagnosed prostate cancer [42].

The technique has now also been introduced for salvage procedures because it has the theoretical advantage of no radiation being used and the formation of the ice ball can be monitored accurately. The median follow-up of the series reported in the literature ranges from 12–82 months. Different cryotherapy techniques were used in these series resulting in a failure-free survival rate of 18–77%. Different PSA criteria were used for defining success, which makes comparison difficult. The reported percentages for morbidity were: urinary incontinence 4–96%, tissue sloughing 0–55%, bladder neck stricture 0–55%, and fistula 0–11% [38]. In a recent series using up-to-date equipment the 5-year biochemical relapse-free survival was 73%, 45%, and 11% for low-, intermediate-, and high-risk patients, respectively, with a median follow-up of 33.5 months [43]. The reported morbidity figures were: urinary incontinence 13%, erectile dysfunction 86%, lower urinary tract symptoms 16%, and fistula 1%.

New minimally invasive salvage procedures

High intensity focused ultrasound (HIFU)

HIFU is a relatively new technique combining an imaging and treatment modality using ultrasound.

It destroys tissue with rapid heat elevation, which essentially "cooks" the tissue. Ultrasound energy is focused when transrectal ultrasound is guided at a specific location and at that focal point the temperature rises to 90ºC in a matter of seconds. This technique is applied in some centres for the primary treatment of localised prostate cancer. Long-term data are still lacking, but the technique seems feasible. Recently, a retrospective analysis was published on the application of HIFU in radio-recurrent disease [44].

Local cancer control with negative biopsies was achieved in 122/167 patients (73%) with a short median follow-up (18.1 months). Urinary incontinence rates were considerable (49.5%) and in 18 patients an artificial urinary sphincter prosthesis was implanted. Five patients developed a recto-urethral fistula. This technique should not be applied in patients that present with a PSA relapse following brachytherapy with permanent seed implants, because the recto-urethral fistula rate is then increased, probably due to impaired blood supply near the rectum or HIFU-associated near-field heating of the rectal wall [45].

Vascular targeted photodynamic therapy

Photodynamic therapy for prostate cancer has only been used in a small cohort of patients and only early reports have been published on this new technique. This technique applies photosensitisers that are activated on different wavelengths. Several agents have been explored in phase I/II studies and showed minimal morbidity. Following a phase I trial exploring photosensitiser and light doses, Trachtenberg and colleagues reported on 28 patients treated with this technique [46,47]. In this series, avascular areas could be created based on MRI images and the tumour burden could be decreased based on the outcome of 6-month biopsies. This is an evolving technique that should be explored in well-defined studies in order to demonstrate reproducibility and to produce long-term outcome data. The treatment can be given in an outpatient setting and the authors concluded that the morbidity of this salvage therapy was low, although two recto-urethral fistulas were seen.

Focal therapy

Since the follow-up of patients with localised prostate cancer treated with potential curative intent is more stringent and early relapses are diagnosed at an earlier stage, the question arises if salvage treatment should entail the whole prostate once PSA only recurrence has been demonstrated. Due to improvements in imaging modalities, recurrent tumour areas within the prostate can possibly be identified and, hopefully in the near future, the dominant tumour area within the prostate can also be identified using new molecular techniques. The possible advantages of focal therapy are the reduction of toxicities using subsequent treatment modalities because that is still a matter of great concern with all existing salvage treatment modalities. In fact, all the described techniques can be used for focal therapy and in the literature the first reports have appeared for using focal therapy as initial treatment or salvage therapy [48–50].

Hormonal therapy

In case of metastatic disease androgen deprivation therapy is indicated, but based on the outcome of several phase III trials there is also a role for the combination of hormonal therapy with EBRT for specific high-risk patient groups. However, if only biochemical recurrence is found, the role of androgen deprivation has not been clearly defined until now. The important question is if early hormonal therapy is as good as delayed hormonal therapy. Some studies have appeared randomising patients between immediate and delayed hormonal therapy as initial therapy, showing conflicting results. The Medical Research Council (MRC) initially reported that patients with M0 disease as well as M+ disease benefited from early hormonal therapy, but in a later, not published, report it was said that this benefit was only apparent for patients with M0 disease [51,52]. The European Organisation for Research and Treatment of Cancer Genito-Urinary (EORTC GU) group also investigated the role of immediate versus delayed therapy in approximately 1000 patients that were not candidates for primary treatment with curative intent. The trigger to start hormonal therapy in the delayed arm was symptomatic progression and not PSA progression only. It was demonstrated that immediate androgen deprivation resulted in a modest but statistically significant increase in overall survival but no significant difference in prostate cancer mortality or symptom-free survival [53]. In a further analysis of this trial, risk groups for progression in the delayed treatment arm were identified: patients with a baseline PSA greater than 50 ng/mL and/or a PSA doubling time less than 12 months were at increased risk of dying from prostate cancer and might have benefited from immediate androgen deprivation therapy, whereas patients with a baseline PSA less than 50 ng/mL and a slow PSA doubling time (>12 months) were likely

to die of causes unrelated to prostate cancer, and thus could be spared the burden of immediate androgen deprivation [54]. These data do not directly apply to biochemical recurrence following radiation therapy, but this group of patients can be considered to have advanced disease and the criteria identified in this EORTC GU group study could be used to counsel the patient on the timing of hormonal therapy. A specific problem can be the group of patients that have been treated with a period of neo- or adjuvant hormonal therapy and who develop biochemical recurrence. The androgen deprivation treatment could have modified the androgen receptor and this could result in a worse outcome of starting hormonal therapy again. Hormonal therapy in the trials mentioned was given in the form of a chemical (LHRH analogue) or surgical castration. This treatment induces short-term and long-term side effects, which have to be taken into account when discussing immediate therapy, especially if treatment is started at the time of first demonstration of PSA relapse, where most patients will receive androgen deprivation therapy for a (very) long period of time. The recently identified metabolic syndrome and high chance of osteoporosis is especially a risk for this older patient group [55,56]. Because of these issues other forms of hormonal manipulation have been explored, e.g anti-androgen monotherapy, intermittent androgen deprivation and 5-alpha reductase inhibitors alone or in combination. These treatments are all investigational in this setting and no strong recommendations can be made on their role for PSA relapse following radiation treatment.

Conclusion

The treatment of biochemical relapse only following radiation treatment is still controversial and the optimal treatment and timing of treatment are not known. The patient is concerned with the fact that, following unsuccessful initial treatment with curative intent, salvage treatment might induce considerable morbidity, which will have an impact on his quality of life. Based on clinical data and new evolving imaging modalities, local or systemic recurrence can nowadays be predicted in a better, but still not optimal way. In case of local recurrence a salvage treatment can be discussed, although the best modality is not yet known and it is clear from the scarce literature that the salvage procedure will add to the already present toxicity. The patient opting for salvage treatment should have a good life expectancy and a good performance status, but it remains a matter of discussion between the doctor and the patient to decide which treatment is best in each individual case. New developments are being explored and although these are called 'minimally invasive', the morbidity can still be significant in a salvage approach. Well designed clinical trials are necessary in order to define which patients will benefit most from salvage treatment and which technique is the best. Follow-up procedures should be defined and evaluation of outcome parameters of salvage strategies determined, because the used parameters have not been tested in this setting. Besides the evaluation of new imaging procedures and the described salvage techniques, collaboration with molecular biologists, pathologists and others is essential in order to determine which recurrent tumours are at risk, based on molecular/genetic/metabolomic profiles, and need a salvage procedure.

Conflict of interest statement

None declared.

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