

# PSA Progression Following Radical Prostatectomy and Radiation Therapy: New Standards in the New Millennium

Bob Djavan<sup>a,\*</sup>, Judd W. Moul<sup>b,1</sup>, Alexandre Zlotta<sup>c</sup>, Mesut Remzi<sup>a</sup>, Vincent Ravery<sup>d</sup>

<sup>a</sup>Department of Urology, University of Vienna, Waehringer Guertel 18-20, Vienna A-1090, Austria

<sup>b</sup>Center for Prostate Disease Research, Uniformed Services University and Walter Reed Army Medical Center, Bethesda, MD, USA

<sup>c</sup>Department of Urology, Brussels, Belgium

<sup>d</sup>Department of Urology, Paris, France

Accepted 22 October 2002

## Abstract

Prostate-specific antigen (PSA) progression following radical treatments of clinically localized prostate cancer is a common problem facing both the patient and the urologist. Not all patients with relapsing disease have an equal risk of death due to prostate cancer.

After surgery, biochemical failure can be defined as persisting detectable levels of PSA after radical prostatectomy or a PSA rise after a period of normalization. On the other hand, definitions of PSA progression after radiation therapy vary and no clear consensus can be found.

This review of the recent international literature updates the knowledge about the diagnostic procedures used in relapsing patients. Predictors of progression are precised leading to a better patient selection, based on currently available tables and nomograms. Indeed, identification of high risk patients may allow a more appropriate treatment decision.

After radical treatment, the analysis of time to recurrence, PSA doubling time, PSA kinetics combined to modern imaging techniques such as <sup>111</sup>In capromab pentitide scan may allow a better identification of the recurrence site. Thus, an optimal treatment strategy may be envisaged such as local irradiation, salvage surgery, hormone therapy or combinations for which indications and results are provided. Alternative options such as cryotherapy still need further investigation.

At last, the use of artificial neural networks will certainly enhance the selection of patients submitted to radical treatments as well as the selection of relapsing patients to allow a more appropriate adjuvant therapy.

© 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Prostate cancer; PSA; PSA progression; Radical prostatectomy; Radiation therapy; Review

## 1. Introduction

Although the incidence rate of prostate cancer (PCa) has decreased somewhat since the early 1990s peak, the American Cancer Society still estimated that there will be approximately 189,000 cases in 2002 [1]. With this large shift in incidence has come an unprecedented stage migration. Radical prostatectomy (RPE) rates increased

from 17.4/100,000 in 1988 to 54.6/100,000 in 1992 [2]. By 1992, 36.6% of localized and regional disease cases were treated with radical prostatectomy and 32.3% were treated with radiation therapy. Furthermore, there has been a shift in the age adjusted rate of these treatments. Most notably, there was a 3–4-fold increase in the rate of radical prostatectomy for men 45–59 and 2 to 3-fold increase for those 60–69 years old [2]. Rates of radiation also increased 1–2-fold for men 45–79 years old.

In the late 1990s clinicians began seeing the effects of the diagnosis [3]. A large number of generally younger men who were treated for clinically localized prostate cancer have already had or are now experiencing

\* Corresponding author. Tel. +43-1-40400-2615; Fax: +43-1-408-9966. E-mail address: bdjavan@hotmail.com (B. Djavan).

<sup>1</sup> The opinions and assessments contained herein are the private views of the author and are not to be construed as reflecting the views of the US Army on the Department of Defence.

recurrence. If approximately 200,000 patients are diagnosed with prostate cancer per year, of which two-thirds are treated with surgery or radiation, and up to 40% may eventually have relapse, up to 50,000 men per year may have prostate-specific antigen (PSA) only early progression. Clearly this is a key issue for clinicians and, perhaps most importantly, for the man and his family. For the patient who has undergone a radical prostatectomy, a persistent PSA value is a sign of residual disease, but an undetectable value does not necessarily mean cure. But what if the PSA value had been undetectable and then becomes detectable and continues to increase? A rising PSA value can predate other signs of progression by months or even years [4]. Misinterpretation of the significance of the change in PSA levels can create havoc for patients who are profoundly concerned with their PSA determinations and for physicians who must address the anxieties and fears of their patients. Unfortunately, documentation of rising values also often triggers a cascade of expensive testing that can prompt the administration of treatments that may be unnecessary and, perhaps, more detrimental to the patient than the disease itself.

Pound et al. [5] recently reported that patients with serum PSA failure within the first 2 years carried the highest risk of developing distant metastases. Recent work from Djavan et al. [6] has suggested that benign prostate glands at the surgical margin are a significant cause of elevated serum PSA levels after radical prostatectomy. They identified benign glands on surgical margins of 95 (27%) of 351 prostatectomy specimens and reported that these glands were most commonly found in the posterior–lateral region. In their study, they suggested that this may represent a significant cause for post radical prostatectomy elevation of serum PSA. Ravery [7] reported that the incision of the prostate, exposing benign glands, can be identified in 40–90% of radical prostatectomy specimens, depending on the type of surgical approach (e.g. retropubic or perineal).

Central to this approach is the ability to define and to redefine continually the prognosis of patients as the natural and treated course of their disease unfolds. Not all patients with relapsing disease have an equal risk of death due to prostate cancer and only some will develop clinical metastatic disease or symptoms of disease in their lifetimes. Do all need immediate intervention? Do all need any treatment?

## 2. How to define PSA progression?

Radical prostatectomy and radiation therapy have been the standards of treatment for clinically localized

prostate cancer for many years. Despite the fact that radical prostatectomy provides excellent cancer control, approximately 35% will experience a rising PSA level following surgery [8–13]. Although a persistent PSA value is considered a sign of residual disease, an undetectable value does not necessarily mean cure or complete eradication of the cancer. Unfortunately there seems to be a trend toward treating PSA values without pursuing the cause.

One has to differentiate between a persistent PSA value immediately following surgery, and a detectable and rising PSA value which has been undetectable initially. The first condition certainly relates to either metastatic disease at the time of surgery or residual cancer (i.e. positive margins at the surgical specimen), whereas the second condition reflects local recurrence and/or progression to metastatic disease, or the emerge of occult metastases present even at the time at initial treatment.

The PSA serum half-life is about 2.6 days. Following radical prostatectomy, PSA should fall to an undetectable level within 2 or 4 weeks, providing that all malignant and benign prostatic tissue was removed at the time of surgery. It is recommended to perform a first PSA-test 3 months after surgery [14]. Conventional PSA assays like Hybritech (Tandem-R) have detection thresholds of 0.1 ng/ml and were not designed to be accurate at lower levels. After radical prostatectomy the PSA level should be below this nadir value of 0.1 ng/ml and can then be considered as “undetectable”.

Undetectable levels immediately after surgery are not synonymous of cure since it has been proven that about 40% of these patients will progress in follow-up [15].

Although minimal PSA elevations after surgery may result from incomplete resection of benign prostatic tissue [16], any detectable and rising PSA should be considered as an indication of persistent local or distant malignant disease.

Biochemical failure can be defined as persisting detectable levels of PSA after radical prostatectomy or a PSA rise after a period of normalization.

The PSA threshold for biological failure was determined at a detectable level (Hybritech) of 0.2 ng/ml [17], since 53% of patients with this value will develop clinical recurrence over time.

A clinically relevant detectable PSA level of 0.4 ng/ml (Hybritech) was proposed by Lange and co-workers since all patients with a postoperative PSA value of 0.4 ng/ml had clinical evidence of disease recurrence within 6–49 months after surgery [18]. Similar findings were reported by Amling et al. They concluded that a

PSA cut off of 0.4 ng/ml or greater may be the most appropriate cut point to use since a significant number of patients with lower PSA do not have continued increase in it [19].

Interpretation of serum PSA after external beam radiation (EBR) is even more complicated than after radical prostatectomy, since the prostate and its tumor remain in situ. An elevation in PSA has been demonstrated in the initial treatment phase. This occurs during delivery of the first 2 Gy and can be explained by cellular damage, necrosis, inflammation and subsequent release of PSA into the circulation [20]. Thereafter a biphasic evolution is observed, an early rapid decline followed by a slower but more sustained further decrease.

The PSA serum half-life is much longer than after radical prostatectomy.

It was calculated by different institutions to be between 1.9 and 3 months [21,22]. Meek et al. [23] found a PSA serum half-life of 1.4 months thereafter.

Until recently, defining PSA recurrence after radiation therapy was widely debated [24,25]. In 1997 the American Society for Therapeutic Radiology and Oncology (ASTRO) held a consensus panel to determine guidelines for PSA recurrence after radiation therapy [26]. The panel agreed that biochemical failure is not justification per se to initiate additional treatment and not equivalent to clinical failure. However, it is an appropriate early end point for clinical trials. A reasonable definition of biochemical failure after radiation therapy is 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 three consecutive increases. PSA nadir is a strong prognostic factor but no absolute level is a valid cut off for separating successful and unsuccessful treatments. PSA nadir is similar in prognostic value to pre-treatment prognostic variables.

Using these new criteria Shipley et al. reported a multi-institutional pooled analysis of radiation therapy for clinically localized prostate cancer [27]. For 1765 men with clinical stages T1b, T1c and T2 tumors treated between 1988 and 1995 PSA recurrence-free rates at 5 and 7 years were 77.8 and 72.9%, respectively, in those with pre-treatment PSA <10 ng/ml. The 5-year PSA recurrence-free survival rates were 68, 51 and 31% for men with pre-treatment PSA 10–20, 20–30 ng/ml or greater, respectively. PSA nadir was also a strong prognostic factor. The 5-year PSA recurrence-free survival was 83, 68, 56 and 28% for PSA nadirs 0.5 or less 0.6–0.9, 1.0–1.9 and 2.0 ng/ml or greater, respectively.

An important issue after radioactive seed implantation followed by external beam radiation is the PSA

bounce. Critz et al. reported a PSA bounce in 35% (273/779) men with T1T2N0 prostate cancer treated with <sup>125</sup>Iodine radioactive prostate seed implantation followed by external beam radiation. Critz et al. concluded that the PSA bounce produces anxiety in men previously treated for prostate cancer and confounds the diagnosis of recurrence [28].

Although, definitions of PSA progression after RPE vary, no clear consensus can be found in the literature. Most recent reports (i.e. the EAU guidelines) define a PSA value of 0.2 ng/ml as a cut-off for defining PSA recurrence following RPE. It has also been shown that patients with a PSA relapse between 0.1 and 0.2 ng/ml after RPE had neither clinical nor biochemical disease progression. Following radiation therapy, however, the ASTRO recommendations define three consecutive increases of PSA as a PSA recurrence.

### 3. Diagnostic procedures

The definite diagnosis of the site of recurrence in this early phase of disease progression is problematic. The digital rectal examination (DRE) should be considered as a routine examination in follow-up in men with rising PSA, whereas DRE is not needed in patients with undetectable PSA after radical prostatectomy. Not all indurations are proof of local disease recurrence and local recurrence with a normal DRE has even been reported [16,29]. Transrectal ultrasonography (TRUS) has not been proven to be helpful in determining the site of the recurrence, but may be performed in an attempt to biopsy any abnormality palpated by DRE in the presence of a PSA elevation. However, a negative biopsy does not exclude local recurrence.

Bone scans are rarely positive (<5%) until the PSA levels increase to 40 or 45 ng/ml after radical prostatectomy [30], but are recommended together with an abdominal and pelvic CT-scan in any patient who is considered a candidate for additional salvage local therapy.

In the study by Malavaud et al. [31], no increase in urinary PSA (uPSA) was observed in patients who had undergone cystoprostatectomy, while an ample and statistically significant increase was demonstrated in the patients with prostate in situ. Furthermore, a cut-off value of 2.5 for the ratio (uPSA after massage/uPSA before massage) correctly separated 100% of the patients into these two control groups.

Such an approach was applied to radical prostatectomy patients with neither clinical nor biological (PSA < 0.1 ng/ml) evidence of disease. Urinary PSA concentrations and ratios were similar to those observed

in the cystoprostatectomy patients. In patients after radical prostatectomy in whom biopsies of the urethro-vesical anastomosis had been performed, uPSA concentrations did not allow the patients with positive and negative biopsies to be distinguished from each other, either before or after massage. By contrast, the ratio of 2.5 was statistically proven to be relevant since it allowed 100% of patients to be correctly classified. However, these encouraging preliminary results were obtained on a small series of patients and should be validated in larger series. With a similar approach, a significant PSA increase, 5 min after a 30-s vigorous massage of the prostatic bed, was recently described in only 1 of 15 patients with a suspected local recurrence [32]. Also, the PSA doubling time, proposed as a new diagnostic criterion of metastatic disease [33], showed overlapping ranges in patients with and without metastases. Other diagnostic tools have been proposed for the assessment of local recurrence. Neither digital rectal examination [34] nor transrectal ultrasonography [35] were able to differentiate scar tissue from recurrent cancer they are thus unreliable indicators of local recurrence.

#### 4. Bone scan

Traditionally, most patients with elevated post treatment PSA undergo radiographic studies, including CT and/or bone scan [36]. However, for patients with early PSA progression the yield of these studies is low. Recently Cher and Bianco studied 144 bone scans of 93 patients being evaluated for PSA recurrence after radical prostatectomy [30]. The lowest PSA associated with a positive bone scan in the absence of adjuvant hormonal therapy was 46 ng/ml. In a univariate and multivariate analysis disease stage and grade, preoperative PSA and time to recurrence did not predict whether a bone scan would be positive, and only PSA recurrence and a rapid slope of PSA increase (that is 5.0 ng/ml per month) were predictive. The authors recommended that no bone scans be used unless PSA recurrence was greater than 40 ng/ml. Considering that the majority of patients are evaluated long before PSA even gets close to 40 ng/ml, for most patients bone scans are probably not necessary. Conversely, in a smaller study of 24 post-radical prostatectomy and 20 post-radiation PSA only recurrences Johnstone et al. reported that only 5% of men with PSA recurrence following RPE had a positive bone scan [37]. Thus, concluding the routine bone scan following early PSA recurrence was not justified in all patients.

#### 5. Computed tomography

Results of CT of abdomen and pelvis for PSA only recurrence are similar to bone scan. Johnstone et al. reported positive CT in 2 of 18 surgery (11%) and 3 of 10 radiation (30%) recurrences [37]. Mean PSA for the 5 cases was 12.4 and mean velocity was 30.6 ng/ml per year. Only 1 of 5 scans documented unique distant recurrence, 3 showed local recurrence only and 1 confirmed a bone scan and CT is limited in the setting of PSA only recurrence after surgery or radiation unless PSA is high. More importantly, these tests appear to be of no added value unless the rate of PSA increase is more than 20 ng/ml per year.

#### 6. <sup>111</sup>In capromab pentitide scan

A scintigraphic radiolabeled monoclonal antibody imaging test based on prostate specific membrane antigen called <sup>111</sup>In capromab pentitide may have clinical usefulness for PSA recurrence after radical prostatectomy [38–45]. When the test was approved by the Food and Drug Administration (FDA) sensitivity, specificity and overall accuracy were reported to be 62, 72 and 68%, respectively [38,39]. In a multicenter study Hinkle et al. reported 75% sensitivity, 86% specificity and 81% accuracy [44].

Regarding capromab pentitide scan and PSA recurrence, Levesque et al. studied 48 patients with elevated PSA (mean 28.7, median 13.8 ng/ml) after prostatectomy and found that 73% had antibody activity beyond the prostatic fossa [40]. Only 3 patients (6%) had activity only in the prostatic bed. Furthermore, 65% of patients had activity in the pelvic nodes, despite prior negative lymphadenectomy at surgery, and 23% had more distant nodal activity. Kahn et al. reported a multicenter study of 181 radical prostatectomy cases with mean PSA 7.9 ng/ml (median 2.6) evaluated with capromab pentitide scan for recurrence [41]. Scan revealed disease in 108 of 181 patients (60%), of whom 32 (29.6%) had recurrence detected only in the fossa. The majority of men in both studies had distant capromab pentitide scan activity. A concern about both studies is that PSA at the time of scans was high and the value of the test with low PSA recurrence was unknown [40,41]. Petronis et al. studied 51 patients evaluated with capromab pentitide scan, of whom 48 had radical prostatectomy and PSA recurrence [42]. Overall, 35 of 51 cases (70.6%) had a positive scan, of which only 8 (22.2%) were positive in the prostatic fossa only. Even for a PSA recurrence level of 0.1 to 1.0 ng/ml, capromab pentitide scan was

positive in 60% of cases. As noted previously, Levesque et al. [40] and Burgers et al. [46] have postulated that capromab penditide scan may be able to differentiate local from distant recurrence after radical prostatectomy, and improve selection of cases for salvage radiotherapy to the prostatic bed. In this setting Kahn et al. recently reported on 32 men who were radiated for PSA only recurrence after radical prostatectomy, with 13-month median follow-up [43]. Of 23 patients 16 (70%) with a normal capromab penditide scan outside the prostatic fossa achieved a durable complete response. PSA decreased to 0.3 ng/ml or less for at least 6 months before latest follow-up. Only 2 of 9 men (22%) with a positive scan beyond the fossa achieved a durable complete response. At the American Urologic Association Meeting in 2001, this group reported longer term (median 55 month) follow-up on their cohort. For men who had a normal capromab scan, the durable response to salvage radiation was 60%. For men who had scan positivity in the fossa only or distant to the fossa the durable response was 44 and 25%, respectively. Furthermore, administration of the capromab penditide scan test is operator dependent with nuclear medicine specialists requiring special training to read scans. Bowel and vascular structures may cause false-positive scans, and to our knowledge no histological confirmation of radical prostatectomy recurrences has been reported to date.

## 7. Role of transrectal ultrasound/biopsy

It has been the practice of some clinicians to perform transrectal ultrasound guided biopsy of the prostatic fossa or prostate gland after treatment with surgery, radiation or cryotherapy to evaluate PSA recurrence or palpable abnormality, or as a routine measure of efficacy [47–49]. In the setting of post-radiation biopsies Crook et al. have the largest PSA era experience, reporting a prospective study of 226 patients [49]. It took 2.5–3 years for biopsies to convert to negative in many patients and, therefore, for those with PSA decrease or near nadir after radiation there is little value in performing biopsy before 3-year follow-up. Even after waiting this time the value of re-biopsy has been questioned. Specifically, Svetec et al. performed ex vivo sextant biopsy on radical prostatectomy specimens of 90 patients, of whom two-thirds had received neoadjuvant hormonal therapy, which yielded a 45.6% false-negative rate [50]. Their conclusion was that the risk of a false-negative sextant biopsy was too great to rely on this means to measure the efficacy of external beam radiation, brachytherapy or cryotherapy.

Most recently ASTRO reported a consensus panel recommendation that routine prostate biopsy not be performed for evaluation of PSA recurrence after radiation unless salvage prostatectomy or other salvage procedures were being considered [51]. There is controversy about the value of transrectal ultrasound biopsy of the anastomosis for increasing PSA after radical prostatectomy. The group from the University of California San Francisco has the most reported experience with and advocate prostate bed/anastomosis biopsy [47,52]. Of 114 patients who underwent 156 transrectal ultrasound biopsies for PSA only recurrence confirmed by biopsy [52]. Two-thirds of cases had recurrences were found at the anastomotic site. Conversely, Fowler et al. concluded that routine transrectal ultrasound guided anastomotic biopsy is not indicated, and use of PSA and PSA doubling time is sufficient for clinical practice [48].

## 8. Predictors of progression

Since earlier adjuvant therapy may be beneficial in localized disease treated cases destined to have progression, many have evaluated a variety of prognostic variables in an attempt to identify those at high risk for recurrence after surgery. Pre-treatment PSA, prostatic acid phosphatase, prostatectomy or biopsy specimen Gleason sum, pathological stage, tumor volume, endorectal coil magnetic resonance imaging (MRI), DNA ploidy, race, angiogenesis and more recently molecular biomarkers, including p53, p27, bcl-2 and Ki-67, have shown significant correlation to PSA recurrence [53–70]. Most recently investigators have combined prognostic variables into models or equations used to predict the likelihood of progression. Partin et al. [57] were the first to develop a simple biostatistical model equation that categorized post-radical prostatectomy cases into three groups of low, intermediate and high risk for likelihood of serological failure. A sigmoidal transformation of PSA, prostatectomy Gleason sum and specimen confinement (margin status) were incorporated into an equation that calculated the relative risk of recurrence,  $R_w$ , as:

$$R_w = (0.061 \times \text{PSAST}) + (0.54 \times \text{postop Gleason sum}) + (1.87 \times \text{specimen confined}).$$

However, this first model was only developed for clinical stage B2 (T2b,c) cases, which are now seen less commonly. Newer models have been developed for a broader range of cases.

Moul et al. recently further validated and revised the equation at Bauer et al. [65] using data from the US

Department of Defence Center for Prostate Disease Research (CPDR) and the CAPSURE database [71]. The equation is:

$$R_r = \text{exponent}(\exp)[(0.54 \times \text{race}) + (0.05 \times \text{sigmoidal transformation of PSA [PSA(ST)])} + (0.23 \times \text{postop Gleason}) + (0.69 \times \text{pathological stage})].$$

Race was defined as 1 if the patient was black and 0 if white or other. Postoperative Gleason sum (2–10) was defined as a continuous integer value. Organ confined disease (no extraprostatic extension) was defined as 0, whereas nonorgan confined (extraprostatic extension and/or positive margins) was defined as 1. The 7-year disease-free survival rate for cases with very low, low, intermediate and high risk of recurrence was 85.4, 66, 50.6 and 21.3%, respectively. The equation calculate is available on the internet at <http://www.CPDR.org>. Bauer et al. have also developed a model to predict recurrence after radical prostatectomy using traditional clinical and pathological variables combined with molecular biomarkers (p53 and bcl-2 immunohistochemistry of radical prostatectomy specimens) [61].

These equations rely on postoperatively obtained pathological data. Recently Kattan et al. developed a nomogram to predict disease recurrence after radical prostatectomy based on pre-treatment variables of 983 PSA era treated cases [68]. Using a validation sample they showed reasonable accuracy with the area under the receiver operator characteristics curve of 79%. In 2002 the value of the Kattan nomograms were confirmed by a large international study including 6754 patients [69]. The nomogram was accurate when applied at international treatment institutions with similar patient selection and management strategies. The AUC for all institutions combined was 75%, with individual institutions AUCs ranging from 67 to 83%. D' Amico et al. published nomogram tables to predict 2-year PSA recurrence rates based on pre-treatment PSA, biopsy Gleason sum and American Joint Committee on Cancer clinical stage for 892 radical prostatectomy cases from 1 institution [70]. The advantage is that these and other nomograms can be used without a computer. Conversely, with the proliferation of computer networks equations on local area networks or the Internet are becoming widely available in clinic settings.

Roberts et al. [72] developed a multivariate proportional hazards model based on easily obtainable clinical and pathologic information: lymph node status, seminal vesicle status, surgical margin status, and Gleason score.

Interestingly, this study did not find the PSA level to add significantly to the final overall model for either the modeling ( $p = 0.14$ ) or validation ( $p = 0.08$ ) groups. However, among patients classified as low risk, the PSA level did provide some additional predictive information (10-year event-free rate of 90, 84 and 67% for PSA < 4, 4 to 10 and greater than 10 ng/ml, respectively;  $p < 0.01$ ).

The results of the univariate and multivariate analyses yielded the following equation based on the multivariate Cox model coefficients:

$$R'_w = \text{lymph node involvement (0/1)} \times 1.43 + \text{surgical margin status (0/1)} \times 1.15 + \text{modified Gleason score (0 to 4)} \times 0.71 + \text{seminal vesicle involvement (0/1)} \times 0.51.$$

Men at highest risk of early recurrence were defined as having a  $R'_w$  greater than 2.84. This cut-off value was selected because it resulted in a greater than 50% rate of biochemical recurrence by 3 years.

This same equation was then applied to the validation cohort with the same  $R'_w$  cut-off. The modeling group biochemical recurrence free rate was 95, 91 and 80% in the low-risk group at 3, 5 and 10 years, respectively and 42, 35 and 18% in the high-risk group at 3, 5 and 10 years, respectively. Recently D' Amico et al. published a nomogram to predict PSA only recurrence for external beam radiation treated cases [70]. Using pre-treatment PSA, biopsy Gleason sum and American Joint Committee on Cancer clinical stage for 762 radiated cases, a probability of PSA recurrence with confidence intervals was developed. None of these patients received neoadjuvant or adjuvant hormonal therapy, and ASTRO recurrence criteria [26] were used. While this nomogram makes a contribution, many more patients are receiving variable durations of neoadjuvant and adjuvant hormonal therapy. This additional treatment will need to be accounted and adjusted for in future radiation recurrence modeling, and the current nomogram would not appear to be valid for these cases. Also, PSA nadir after radiation may be an important prognostic factor but takes time to ascertain and is affected by adjuvant/neoadjuvant hormones. Finally, it is unknown whether this nomogram will have any applicability to patients who receive brachytherapy or higher dose conformal radiation.

Nevertheless artificial neural networks (ANN) to predict biochemical failure were developed for predicting biochemical failure after radical prostatectomy [73]. Porter et al. reported using the clinical and pathological data from 196 patients who had undergone RP at one institution between 1988 and 1999 for

developing their ANN. Forty-four percent of the patients suffered from biochemical failure with an average duration of follow up of 2.5 years (range 0–11.5 years). Forty-two percent of patients had pathologic evidence of non-organ confined disease. The ANN with had a AUC of 80%, a sensitivity of 74%, a specificity of 78%, a positive predictive value of 71%, and a negative predictive value 0.81%. These results suggest that ANN models can predict PSA failure using readily available preoperative variables. Such predictive models may offer assistance to patients and physicians when deciding upon diagnostic steps and therapeutic regimens for PSA recurrence.

### 9. Treatment of biochemical recurrence

Treatment of early progression of PSA, or serological only recurrence, after radical prostatectomy and radiation is controversial. Options for surgery cases include observation, external beam radiotherapy to the prostatic bed, traditional full hormonal therapy, including orchiectomy, luteinizing hormone releasing hormone (LH-RH) agents or combined hormonal therapy, and non-traditional hormonal therapy, including intermittent hormonal therapy, antiandrogen monotherapy or medical combinations, such as an antiandrogen and 5 $\alpha$ -reductase inhibitor. For radiation cases the choices are similar except that salvage prostatectomy, cryotherapy and perhaps brachytherapy are options for carefully selected cases.

### 10. Radiation for PSA progression after radical prostatectomy

The value of adjuvant external beam radiotherapy for pathological stage C prostate cancer after radical prostatectomy has been debated for years. To our knowledge no randomised study has been reported to prove or disprove adjuvant radiotherapy in this setting, and nonrandomised case series have been conflicting. Most have only shown that radiation reduces the local recurrence rate. The Southwest Oncology Group intergroup study 8794, which randomised pathological stage C cases to radiation versus observation closed to new enrolment approximately 5 years ago but results will not be available until at least 2002 (unpublished data). In the related setting of using radiation for postoperative PSA elevation the data are even more controversial and preliminary. In stage C disease and PSA recurrence cases there is a dilemma in that it is unknown whether disease is localized in the potential field of radiation or

if there are systematic occult metastases. Furthermore, even if disease is localized, it is not clear that the dose of radiation delivered will eradicate residual/recurrent cancer.

During the last decade there has been a growing body of literature on therapeutic radiation for PSA only recurrence after surgery [25,74–88]. The majority of cases had pathological stage T3 disease after radical prostatectomy, and mean and median PSA at the initiation of radiation was generally between 1 and 2 ng/ml.

Taking the optimistic view Forman et al. studied 47 patients who received 66 Gy therapeutic irradiation to the prostate bed for PSA greater than 0 ng/ml [81]. At a median follow-up of 36 months (range 18–48) patients with initial PSA recurrence 2 ng/ml or less had an 83% disease-free survival. Conversely, if PSA was greater than 2.0 ng/ml, the disease-free survival rate was only 33%. Overall, 64% of the cohort was disease-free at 3 years. Even for men who do not achieve undetectable PSA after radical prostatectomy, although others had previously assumed metastatic disease, [75] the Wayne State group found equivalent disease-free survival compared to patients who achieved undetectable PSA [84]. They believe that the key is initiating radiation when PSA is <2 ng/ml rather than whether a postoperative undetectable value is achieved [84]. Furthermore, they strongly recommend that at least 66 Gy radiation to the prostatic bed be delivered to achieve the best outcome.

A recent study from Johns Hopkins Hospital portrays a more pessimistic view of radiation for increasing PSA after surgery [83]. Of 1699 men treated with radical prostatectomy between 1982 and 1995, 82 with elevated PSA only (57) or local recurrence (25) received salvage radiation, with a minimum follow-up of 2 years. Mean pre-radiation PSA was 2.2 ng/ml in PSA only and 4.1 in local recurrence cases. Of the 57 cases with PSA recurrence 15 (26%) had undetectable PSA (<0.2 ng/ml) 2 or more years following radiation. Overall 5-year actuarial PSA recurrence-free rate after radiation was 10%. PSA remained undetectable 2 or more years after radiation in no patient with Gleason sum 8 or greater, positive seminal vesicles or positive lymph nodes. Furthermore, only 1 of 16 men (6%) who had PSA recurrence in the first year after surgery was rendered disease-free by salvage radiation. Conversely, for patients who had delayed PSA recurrence there was a higher likelihood of responding to radiation. Specifically, for men who had PSA recurrence 5 or more years after surgery 2-year disease-free survival after radiation was 44%. Despite pre-treatment PSA not being a statistically significant variable for predicting success of radiation, patients with low initial PSA did

better. Initial mean PSA was 1.7 ng/ml for the 17 patients who had undetectable PSA 2 years after radiation compared to 3.1 for those who did not remain disease-free. Similar to the Johns Hopkins experience [83], Haab et al. [77], Egawa et al. [87] and Vicini et al. [88] have recently reported disappointing disease-free survival rates after salvage radiotherapy.

These contrasting studies illustrate a number of key concepts [77–88]. Initial PSA seems to be a key factor in dictating success. Aside from PSA level, Forman [25,81] and Garg et al. [8] believe that a radiation dose of 66–70 Gy is critical to success.

The value of salvage radiation to the prostate bed for PSA only progression after radical prostatectomy remains in question. All of the currently published studies lack long-term follow-up, and so the ultimate impact on survival is unknown. Short-term follow-up suggests that patients who undergo radiation when PSA recurrence is <2.0 ng/ml do better than those who are treated when PSA is higher. Radiation dose may also be important and preliminary data support the use of therapeutic doses of 66 Gy or higher [25,81,84]. ASTRO published a consensus panel report recommending that patients receive salvage radiotherapy before PSA > 1.5 ng/ml and at least 6400 cGy radiation dose be delivered to the prostatic bed [51].

## 11. Salvage prostatectomy for radiation failure

Although salvage radical prostatectomy for local recurrence after radiation therapy has the potential to provide long-term disease-free survival, it has not gained widespread acceptance due to associated morbidity, particularly incontinence, and high recurrence rate compared to surgery for previously untreated prostate cancer [89–98]. Before the PSA era, when cases were selected based on digital rectal examination and biopsy, morbidity was substantial with a 40–50% incidence of post-prostatectomy incontinence, universal impotence and higher risk of operative complications, such as rectal injury and reoperation [89–93]. In the current era, when cases would likely be selected based on PSA recurrence, the morbidity and outcome may be improved but no large series have been reported. More recently investigators from Wayne State University and University of Florida have reported more optimistic results of salvage prostatectomy [99,100]. Gheiler et al. evaluated 40 patients who had undergone salvage prostatectomy between 1992 and 1997, and who were selected by increasing PSA after radiation and documented recurrence on biopsy

[100]. Mean preoperative PSA was 14 ng/ml (range 1.3–43) and, when stratified by PSA less than or greater than 10 ng/ml, the 3-year disease-free survival rate was 68% versus 26%, respectively. Furthermore, in a subset of men with preoperative PSA 4.0 ng/ml or less 5 of 6 had organ confined disease and 5 (83.3%) were disease-free biochemically at 3-year follow-up. Finally, in this more modern experience 30 of 40 men (75%) had no surgical complications.

Garzotto and Wajsman found that neoadjuvant and adjuvant hormonal therapy with salvage prostatectomy improved outcome for a number of men [99]. In 29 patients who received salvage prostatectomy with neoadjuvant and/or adjuvant hormonal therapy between 1985 and 1993 positive margins of the salvage specimen and response to preoperative hormones were strong prognostic factors. At a mean follow-up of 5 years clinical and biochemical disease-free survival was 80% in men who had negative margins (69% of the cohort) versus 44% for those with positive margins (31%). Also, in 5 men preoperative hormones were used and failed (increasing PSA), and they only had a 20% disease specific survival at 5 years. The authors were even enthusiastic about this approach in patients with clinical T4 disease (11 in their series), finding only a 36% recurrence rate at 5-year follow-up with the addition of hormonal therapy. Despite their enthusiasm, this series was small and 21 of 29 patients continued hormones indefinitely, and so it was not clear at 5-year follow-up whether results were improved by surgery or more related to continuous hormonal therapy [101].

In general, salvage radical prostatectomy should only be considered for carefully selected patients with clinical organ confined disease before initial radiation therapy and who still have such disease [100,101]. This protocol would include men with low to intermediate Gleason sum (less or equal than 6), low pre-treatment PSA (<10 ng/ml) and low tumor stage (T1c or T2a) initially. At PSA only recurrence and consideration for salvage treatment the patient should still have a favorable Gleason sum (<6), tumor stage (<T2b) and PSA (ideally <4.0 ng/ml) [100]. Some have advocated performing seminal vesicle biopsies and eliminating from consideration anyone with a positive result [94]. Patients should also be well informed of the potential morbidity, particularly clinically significant incontinence, and carefully documented informed consent should be obtained. With more patients in the early 2000's selecting transrectal ultrasound guided perineal brachytherapy, it is reasonable to treat them by the aforementioned guidelines but it is unclear if the morbidity and outcome will be different from that seen after traditional external beam therapy.

## 12. Salvage cryotherapy for radiation failure

Cryotherapy for localized prostate cancer using transperineal cryoprobes that are placed by transrectal ultrasound guidance has been performed since 1990 [102–110]. This procedure has also been proposed as potentially less morbid alternative to salvage prostatectomy in patients with local recurrence after radiotherapy [103,105,106,108]. The group from MD Anderson reported incontinence in 28% with a commercial urethral warming device, and in 89% with an alternate homemade urethral warmer. The MD Anderson Cancer Center has had the largest published experience with percutaneous cryoprostatectomy to treat radiation recurrent, clinically localized prostate cancer [108]. A total of 150 patients with locally recurrent prostate cancer following radiation, hormonal therapy and/or systemic chemotherapy underwent salvage cryotherapy [108]. Of the men 71 had a single freeze–thaw cycle and mean follow-up of 17.3 months, and 79 had double freeze–thaw cycles and mean follow-up of 10.0 months. Overall, 45 patients (31%) had persistently undetectable PSA. Specifically, prior radiation only group men who received a double freeze–thaw treatment had a 93% negative biopsy rate 6 months after treatment and 44% biochemical failure rate (>0.2 ng/ml PSA above nadir). However, the morbidity was substantial [109]. In 143 patients the rate of postcry and 88% when 2 separate salvage cryotherapy procedures were performed. The overall rate of postcryotherapy incontinence was 43%, and 72% of incontinent men required 2 or more pads daily. The authors did not believe that postcryotherapy incontinence improved with the learning curve but also did not believe it was made worse by a potentially more effective double freeze technique. Most recently quality of life was assessed in this series of salvage cryotherapy [110]. Using a modified UCLA Prostate Cancer Index instrument, incontinence, perineal pain, tissue sloughing and American Urological Association score were associated with sub optimal urethral warming. Overall satisfaction with salvage cryotherapy was 33% and the authors did not believe that cryotherapy offered any quality of life advantage compared to salvage prostatectomy. Lee et al. used cryotherapy and adjuvant hormonal therapy to treat radiation recurrent disease [111]. They believe that using thermocouples to monitor prostate temperature lowers the risk of incontinence.

A new device was introduced by the Columbia University using a smaller probe using brachy technique. The PSA nadir was 0.1 or less, 1 or less and greater than 1 ng/ml in 81.5, 13.2 and 5.3% patients, respectively. Biochemical recurrence-free survival was 86%

at 1 year and 74% at 2 years. Reported complications included rectal pain in 39.5%, urinary tract infections in 2.6%, incontinence in 7.9%, hematuria in 7.9% and scrotal edema in 10.5% [112].

## 13. Salvage brachytherapy for radiation failure

There is little experience with salvage brachytherapy and presently it is considered experimental [113]. Wallner et al. reported their experience with 13 men who had biopsy proved palpable local recurrence following iodine implantation and then received a second implant [114]. Results were disappointing, with 2 men suffering severe rectal complications, 4 having incontinence and none remaining free of metastatic disease 6 years after re-treatment. In another study salvage brachytherapy with radioactive gold seeds appeared to be well tolerated but a mean follow-up of only 23 months was too short to assess efficacy [115].

Grado et al. recently reported the first large experience with salvage brachytherapy for men with recurrence after prior external beam radiotherapy [113]. In 49 patients (mean follow-up 64 months) with biopsy proved local recurrence treated with transperineal transrectal ultrasound guided palladium (37) or iodine (12) the 3 and 5-year actuarial biochemical disease-free survival rate was 48 and 34%, respectively. It is noteworthy that the reported morbidity was much lower than for salvage radical prostatectomy or salvage cryotherapy. Specifically, incontinence (defined as use of a pad) only occurred in 6% of patients and was only seen in association with transurethral prostatic resection (overall transurethral resection required in 7 (14%)). In addition, 2 patients had rectal ulcers and 1 required a colostomy. Salvage brachytherapy deserves further study, and more reports with longer follow-up are awaited.

## 14. Hormone therapy

The mainstay of therapy for advanced metastatic prostate cancer has been androgen deprivation with bilateral scrotal orchiectomy, estrogen therapy or androgen blockage [116–118]. Estrogens are currently rarely used because they may cause cardiovascular toxicity [119]. Combining an oral antiandrogen with testicular ablation therapy as hormonal treatment for advanced prostate cancer has been used for more than a decade [120–130].

An NCI trial found an approximate 7-month survival benefit of flutamide plus leuprolide versus placebo and

leuprolide in stage D2 prostate cancer cases. A later sub-analysis of approximately 85 patients with minimal metastatic disease and normal performance status revealed that LH-RH with flutamide provided an approximately 20-month survival benefit [122,131]. The survival benefit of LH-RH plus flutamide was compared to orchiectomy alone [124]. Patients treated with combination therapy had an approximate 15 month disease specific survival advantage [124,132]. However, most recently a large randomised trial (NCI 0105) compared orchiectomy plus flutamide to orchiectomy plus placebo and found no appreciable benefit of combination therapy [126]. The study included more than 1300 stage D2 cases and, although flutamide treated cases had a superior PSA response, there was no statistically significant survival advantage to this treatment arm. Furthermore, the potential benefit of combination therapy using flutamide in patients with “minimal” metastatic disease could not be confirmed. Most recently, a 10% survival benefit overall was found in a meta-analysis of more than 4000 patients from 9 randomised trials examining the efficacy of flutamide in combination therapy [130].

Efficacy and safety were based on a randomised study comparing bicalutamide to flutamide [125]. Bicalutamide was found to be statistically equivalent to flutamide as an antiandrogen combined with an LH-RH agent for combination therapy. A number of large studies have documented a survival benefit with orchiectomy and a recent meta-analysis also confirmed a survival benefit in patients with stage D2 prostate cancer when using nilutamide [127].

The overall value of combination hormonal therapy for advanced prostate cancer remains in debate. A total of 4 meta-analyses have been published in attempts to determine the clinical benefit of combined therapy [129–132]. Results have ranged from no significant survival benefit in the Prostate Cancer Trialists Collaborative Group study [128] to a 22% benefit reported by Caubet et al. [129] which translated into a 7-month survival benefit. Some but not all studies have found that patients with minimal metastatic disease have a more pronounced survival benefit with combined androgen blockage. It is possible that patients with PSA only recurrence could represent a similar subgroup who would have better survival with combination therapy. However, there is no randomised trial of LH-RH agonist or orchiectomy alone versus combination therapy in this particular clinical setting, and any benefit regarding this approach is purely speculative.

Recent data from the Medical Research Council (MRC) in Great Britain indicates that early hormonal

therapy delays disease progression and improves survival compared to delayed treatment for patients with nonmetastatic (M0) and traditional stage D2 (M1) disease. In the immediate hormonal therapy arm by stage groups M0, MX and M1, the death rates were 54, 57 and 76%, respectively, compared to 70, 62 and 80%, respectively, for men who received only deferred hormones. Cancer specific survival was superior ( $p = 0.02$ ) in the immediate hormonal therapy arm for all patients and most pronounced in those with M0 disease ( $p < 0.001$ ), who may be analogous to those with PSA recurrence after local therapy. If clinicians believe that M0 category in this study is similar to current era PSA only recurrences, traditional hormonal therapy would appear to be beneficial.

Aside from the MRC study, Messing et al. [131] reported an Eastern Cooperative Oncology Group randomised, multicenter trial of early versus delayed hormonal therapy for advanced prostate cancer. Of the 98 men with pelvic lymph node metastases (stage D1) who underwent radical prostatectomy those who received immediate hormones had a 4.3% death rate from prostate cancer at 7-year follow-up compared to 30.8% for those observed initially ( $p < 0.01$ ). Furthermore, recurrence rates were 18.8% versus 75%, respectively, favoring immediate treatment. Whether this stage D1 disease study can be extrapolated to justify a benefit to early hormonal therapy for men with PSA only recurrence is unknown. Most recently Moul et al. reported in an AUA 2002 press release that new data presented today shows that prostate cancer patients who have had radical prostatectomy benefit significantly from early hormonal therapy. Hormonal therapy given for PSA—only recurrence prior to objective progression significantly extends progression-free survival.

The true value of traditional hormonal therapy in patients with early PSA only progression is unknown because no randomised trials with this specific category have been performed to my knowledge. Furthermore, it is unknown what constitutes a proper level of PSA to institute therapy, which is from barely detectable, such as 0.1–0.4 ng/ml, to a higher level, such as 10, 20 or even 50. In this setting patients are likely to derive long-term freedom from another PSA relapse but the survival benefit is unknown. Furthermore, the side effects of traditional hormonal therapy must not be underestimated, particularly in men who are clinically well with only increasing PSA. Today many of these men are relatively young and otherwise healthy, and the prospects of hot flashes, loss of libido, decreased muscle mass, mild anaemia and long-term concern for osteoporosis are significant.

## 15. Intermittent hormonal therapy

A topic of focus during the last few years has been the concept of intermittent hormonal therapy with the expectation that side effects such as loss of libido and impotence may be more limited. This concept has received much attention in the current era of reversible androgen deprivation with LH-RH agents and antiandrogens, early use of hormonal therapy and manifestation of potential side effects with long-term hormone therapy use [132–145]. In the specific setting of intermittent hormonal therapy for PSA only recurrence Kurek et al. reported a series of 44 patients and reviewed the literature [144]. Patients were recruited to a pilot study using leuprolide acetate (1-month depot) and cyproterone acetate when PSA after radical prostatectomy was  $>3.0$  ng/ml. Patients were then treated for 9 months with continuous hormonal therapy and all reached a PSA nadir of  $<0.5$  ng/ml. When PSA increased to  $>3.0$  ng/ml they were restarting hormonal therapy for a 9-month repeat cycle. At a mean follow-up of 48 months no patient had progression to hormone refractory disease and average duration off hormones was 26.6 months. In other series in which PSA only recurrences were treated with intermittent hormonal therapy PSA threshold at study entry was not stated and PSA at discontinuation of hormonal therapy ranged from a fixed value of 0.5–4.0 ng/ml or until nadir was achieved. The threshold to restart hormonal therapy was even more variable ranging from 3.0–40.0 ng/ml. Although animal and in vitro cell line studies suggest that intermittent hormonal therapy is beneficial, human studies with sufficient safety and efficacy are not yet available. In many cases enthusiasm for intermittent hormonal therapy has been patient driven. However, patients must be informed that the long-term efficacy of intermittent hormonal therapy is unknown, regardless of its potential benefit.

## 16. 5 $\alpha$ -Reductase inhibitors and antiandrogens

Finasteride (a 5 $\alpha$ -reductase inhibitor) and flutamide (a nonsteroidal antiandrogen), the most common agents used to date, exert effects on the prostate by blocking intraprostatic conversion of testosterone to dihydrotestosterone and blocking the cytoplasmic dihydrotestosterone receptor, respectively. Neither of these drugs has proved acceptable as monotherapy for prostate cancer. However these 2 drugs used in combination could potentially offer major advantages compared to conventional hormonal therapy [146–157].

These agents would work additively at the final intracellular pathway for androgen dependent growth of prostate tissue, including block of androgens which are produced by the adrenal gland (about 9% of total androgens in the intact male) and, therefore, which would be unaffected by testicular androgen ablation. Finasteride and flutamide do not decrease serum testosterone systemically. Serum testosterone may actually increase if flutamide blockade of the central androgen receptors stimulates an increase in luteinizing hormone through negative feedback mechanisms. Because testosterone conversion is blocked selectively in the prostate, systemic testosterone is still active when using this combination therapy. Therefore, most patients should retain pre-treatment libido, potency, muscle mass and erythropoiesis as well as psychological status. Another advantage of this combination is lower cost compared to traditional LH-RH agonist hormonal therapy.

Andriole et al. used 10 mg finasteride orally daily to treat 120 men with PSA only recurrence after radical prostatectomy [146]. Pre-treatment PSA levels were between 0.6 and 10.0 ng/ml at PSA recurrence and entry into the study. Although well tolerated, finasteride alone did not provide a durable decrease in PSA. Fleshner and Trachtenberg were the first to report the use of finasteride and flutamide combination therapy [147]. Their early studies and that of Fleshner and Fair involved patients with advanced prostate cancer and high PSA (mean 34–116 ng/ml). Similarly, Ornstein and Brufsky et al. [149,150] treated advanced cases with high PSA (mean 94–96 ng/ml). Others were the first to report a larger series of men with early progression by PSA only [151–157]. In the latest report to date 73 men previously treated with radical prostatectomy or external beam radiation who had PSA recurrence (mean 7.0 ng/ml) were treated with 10 mg finasteride and 250 mg flutamide daily [157]. Mean PSA nadir was 1.35 ng/ml and average time to reach the nadir was 6 months. Of the 73 men 45 (61.6%) achieved a nadir PSA of  $<0.2$  ng/ml. Breast tenderness, breast enlargement and nipple tenderness occurred in 71, 60 and 33% of cases, respectively. Furthermore, gastrointestinal disturbance was noted in 18% and elevated liver function tests in 9% of patients at some time during the trial. Longer follow-up of patients treated with oral combination therapy is needed and a randomised phase III trial in early progression cases is warranted. Work on antiandrogens alone for PSA only recurrence is ongoing. Data from the EPC trial using an immediate bicalutamide 150 mg monotherapy in localized or locally advanced prostate cancers showed a significantly reduced risk of disease progression [158] These

approaches will continue to expand in popularity as younger, healthier men have PSA recurrence, and do not desire the immediate and long term side effects of full hormonal therapy.

## 17. Watchful waiting

Observation or surveillance/watchful waiting are invariably used in the management of PSA recurrence. Some patients are observed for a short duration before choosing or being encouraged by the physician to opt for salvage local or systemic therapy. Others are observed for the long term, particularly those who are older, have significant co-morbidity or are deemed to have slow disease progression. Until recently there was complete uncertainty about this option because there was no natural history study of PSA recurrence cases. In mid 1999 Pound et al. published a landmark study which provided natural history data about PSA recurrence in radical prostatectomy cases [5]. Of 1997 cases of radical prostatectomy performed at Johns Hopkins Hospital between 1982 and 1987, 315 (15%) had PSA recurrence, including 304 observed until the development of documented clinical metastasis. Median actuarial time for development of metastasis was 8 years and median time from metastasis to death from prostate cancer was an additional 5. Gleason grade 8–10, PSA recurrence 2 years or less from surgery and PSA doubling time of <10 months were adverse factors that decreased metastasis-free survival. Using these prognostic factors the authors provided algorithms for prediction of metastasis-free survival [5].

Although this article provides novel natural historical data, it must be recognized that overall median follow-up of the 1997 cases was only 5.3 years. Furthermore, only 344 (17%) men have been followed for 10 years, only 103 (5%) have had metastatic disease and only 43 (2.2%) have died of prostate cancer. In addition, this experience may reflect a selection bias that may make the data not applicable to more general

patient populations. Finally, these data are only for radical prostatectomy cases and may not be relevant to those treated with external beam radiation or brachytherapy. Despite these limitations, the 8 and 13-year intervals from PSA recurrence to metastases and death, respectively, and the algorithms are useful to counsel patients regarding observation.

## 18. Conclusion

PSA progression following radical surgery and radiation therapy is a common problem facing the patient and treating urologist. Although, ideally it need to be prevented, patients experiencing biochemical failure may not necessarily experience rapid disease progression. Indeed, progression may take many years and cancer specific death even more. Certainly, adequate patient selection, based on currently available tables and nomograms may reduce biochemical failure rates. Furthermore, identification of high risk patients may allow a more “specific” treatment decision such as combination therapy, neoadjuvant or adjuvant hormone therapy.

Time to recurrence, PSA doubling time and PSA kinetics may allow a more accurate identification of recurrence site and thus, the optimal treatment strategy, such as local irradiation, hormone therapy or both. Salvage local therapy is gaining popularity with more conformable radiation protocols. However, alternative options such as cryotherapy still need to be investigated with more detail.

Overall, PSA progression is not an uncommon finding, occurring in up to 30% of patients within 7 years. Positive cancer margins, metastasis present at the time of treatment but also benign glands at surgical margins are correlated with biochemical failure. Careful patient selection may minimize biochemical failure rate and the use of artificial neural networks will enhance the later and also allow a more adequate selection of patients requiring immediate/delayed radiation or hormone therapy.

## References

- [1] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics 1999. *CA Cancer J Clin* 1999;49:8.
- [2] Stephenson RA. Population-based prostate cancer trends in the PSA era: data from the Surveillance, Epidemiology, and End Results (SEER) Program. 1998. *Monogr Urol* 1998;19:3.
- [3] Moul JW. Treatment options for prostate cancer. Part 1. Stage, grade, PSA, and changes in the 1990s. *Am J Manag Care* 1998;4:1031.
- [4] Pontes J, Chu T, Slack N. Serum prostatic antigen measurement in localized prostatic cancer: correlation with clinical course. *J Urol* 1982;128:1216.
- [5] Pound C, Partin A, Eisenberger M, Chan D, Walsh P. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591.
- [6] Djavan B, Sesterhann I, Hruby S, Marberger M. Benign prostatic glands in the surgical margin of radical retropubic prostatectomies: redefining PSA nadir. *J Urol* 2000;163:A624.
- [7] Ravery V. The significance of recurrent PSA after radical Prostatectomy: benign versus malignant sources. *Semin Urol Oncol* 1999;17:127.
- [8] Pound CR, Partin AW, Epstein JL, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: patterns

- of recurrence and cancer control. *Urol Clin North Am* 1997;24:395.
- [9] Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barret DM. Long-term (15 years) results after radical prostatectomy for clinical localized (stage T2 or lower) prostate cancer. *J Urol* 1994;152:1850.
- [10] Trapasso JG, DeKernion JB, Smith RB, Dorey F. The incidence and significance of detectable levels of serum prostate antigen after radical prostatectomy. *J Urol* 1994;152:1821.
- [11] Catalona WJ, Smith DS. 5-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. *J Urol* 1994;152:1837.
- [12] Ohori M, Goad JR, Wheeler TM, et al. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? *J Urol* 1994;152:1843.
- [13] Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28(3):555.
- [14] Villers A. PSA in a follow-up after radical prostatectomy: a review. In: Murphy G, Griffiths K, Denis L, Khoury S, Chatelain C, editors. *Proceedings from the First International Consultation on Prostate Cancer*. Cockett; 1997; AT:112.
- [15] Stein A, De Kernion JB, Smith RB, Dorey F, Patel H. Prostate specific antigen levels after radical prostatectomy in patients with organ confined and locally extensive prostate cancer. *J Urol* 1992;147:942.
- [16] Foster LS, Jajodia P, Fournier G, Shinohara K, Carroll P, Narayan P. The value of PSA and TRUS-guided biopsy in detecting prostate fossa recurrence following radical prostatectomy. *J Urol* 1993;149:1024.
- [17] Partin AW, Pound CR, Clemens JQ, Epstein JL, Walsh PC. Serum PSA after anatomic radical prostatectomy. *Urol Clin North Am* 1993;20:713.
- [18] Lange PH, Ercole CJ, Lightner DJ, et al. The value of serum prostate specific antigen determination before and after radical prostatectomy. *J Urol* 1989;141:873.
- [19] Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: What is the most appropriate cut point? *J Urol* 2001;165:1146.
- [20] Zagars CK, Poolack A. The fall and rise of PSA. Kinetics of serum PSA levels after radiation therapy for prostate cancer. *Cancer* 1993;72:832.
- [21] Kaplan ID, Cox RS, Bagshaw MA. PSA after external beam radiotherapy for prostate cancer: follow up. *J Urol* 1993;149:519.
- [22] Ritter MA, Messing EM, Shanahan TG, Potts S, Chappell RJ, Kinsella TJ. PSA as a predictor of radiotherapy response and patterns of failure in localized prostate cancer. *J Clin Oncol* 1992;10:1208.
- [23] Meek AG, Park TL, Oberman E, Wielopolski L. A prospective study of PSA levels in patients receiving radiotherapy for localized carcinoma of prostate. *Int J Radiat Oncol Biol Phys* 1990;19:733.
- [24] Waxman S, Stevens AK, Walsh RA, et al. Management of asymptomatic rising PSA after prostatectomy or radiation therapy. *Oncology (Huntingt)* 1997;11:457.
- [25] Forman JD, Velasco J. Therapeutic radiation in patients with a rising post-prostatectomy PSA level. *Oncology (Huntingt)* 1998;12:33.
- [26] American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus Statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys*, 1997; 37:1035.
- [27] Shipley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: a multiinstitutional pooled analysis. *JAMA* 1999;281:1598.
- [28] Critz FA, Williams H, Benton JB, Levinson AK, Holladay CT, Halladay D. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000;163:1085.
- [29] Pound CR, Christens-Barry OW, Gurganus RT, Partin AW, Walsh PC. Digital rectal examination and imaging studies are unnecessary in men with undetectable prostate specific antigen following radical prostatectomy. *J Urol* 1999;162:1337.
- [30] Cher ML, Bianco Jr FJ. Limited role of radionuclide bone scintigraphy in patients with PSA elevations after radical prostatectomy. *J Urol* 1998;160:1387.
- [31] Malavaud B, Salama G, Miadouge M, Vincent CH, Rischmann P, Sarramon JP, et al. Influence of digital rectal massage on urinary PSA: interest for the detection of local recurrence after radical prostatectomy. *Prostate* 1998;34(1):23.
- [32] Anscher MS. Prostate bed massage as a means to determine the source of a rising prostate specific antigen after radical prostatectomy. *Am J Clin Oncol* 1995;18:481.
- [33] Fowler JE, Pandey P, Braswell NT, Seaver L. Prostate specific antigen progression rates after radical prostatectomy or radiation therapy for localized prostate cancer. *Surgery* 1994;116:302.
- [34] Lighther DJ, Lange PH, Reddy PK, Moor L. Prostate specific antigen and local recurrence after radical prostatectomy. *J Urol* 1990;144:921.
- [35] Goldenberg LS, Carter M, Dashetsky S, Cooperberg PL. Sonographic characteristics of the urethrovesical anastomosis in the early post radical prostatectomy patient. *J Urol* 1992;147:1307.
- [36] Terris MK, Klonecke AS, McDougall IR, et al. Utilization of bone scans in conjunction with prostate-specific antigen levels in the surveillance for recurrence of adenocarcinoma after radical prostatectomy. *J Nucl Med* 1991;32:1713.
- [37] Johnstone PA, Tarman GJ, Riffenburgh R, et al. Yield of imaging and scintigraphy assessing biochemical failure in prostate cancer patients. *Urol Oncol* 1997;3:108.
- [38] Kahn D, Williams R, Seldin DW, et al. Radioimmunoscintigraphy with <sup>111</sup>In labelled CYT-356 for the detection of occult prostate cancer recurrence. *J Urol* 1994;152:1490.
- [39] Kahn D, Haseman M, Libertino J, et al. Indium-111 capromab pendetide (ProstaScint) imaging of patients with rising PSA post-prostatectomy. *J Urol* 1997;157(Suppl 204):A795.
- [40] Levesque PE, Nieh PT, Zinman LN, et al. Radiolabeled monoclonal antibody indium 111-labeled CYT-356 localizes extraprostatic recurrent carcinoma after prostatectomy. *Urology* 1998;51:978.
- [41] Kahn D, Williams RD, Manyak MJ, et al. <sup>111</sup>In-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy. *J Urol* 1998;159:2041.
- [42] Petronis JD, Regan F, Lin K. Indium-111 capromab pendetide (ProstaScint) imaging to detect recurrent and metastatic prostate cancer. *Clin Nucl Med* 1998;23:672.
- [43] Kahn D, Williams RD, Haseman MK. Radioimmunoscintigraphy with In-111 labeled capromab pendetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. *J Clin Oncol* 1998;16:284.
- [44] Hinkle GH, Burgers JK, Neal CE, et al. Multicenter radioimmunoscintigraphic evaluation of patients with prostate carcinoma using indium-111 capromab pendetide. *Cancer* 1998;83:739.
- [45] Elgamal AA, Troychak MJ, Murphy GP. ProstaScint scan may enhance identification of prostate cancer recurrence after prostatectomy, radiation, or hormonal therapy: analysis of 136 Scans of 100 patients. *Prostate* 1998;37:261.
- [46] Burgers JK, Hinkle GH, Haseman MK. Monoclonal antibody imaging of recurrent and metastatic prostate cancer. *Semin Urol* 1995;13:103.
- [47] Foster LS, Jajodia P, Fournier Jr G, et al. The value of prostate specific antigen and transrectal ultrasound guided biopsy in detecting prostatic fossa recurrences following radical prostatectomy. *J Urol* 1993;149:1024.

- [48] Fowler Jr JE, Brooks J, Pandey P, et al. Variable histology of anastomotic biopsies with detectable prostate specific antigen after radical prostatectomy. *J Urol* 1995;153:1011.
- [49] Crook JM, Perry GA, Robertson S, et al. Routine prostate biopsies following radiotherapy for prostate cancer: results for 226 patients. *Urology* 1995;45:624.
- [50] Svetec D, McCabe K, Peretsman S, et al. Prostate rebiopsy is a poor surrogate of treatment efficacy in localized prostate cancer. *J Urol* 1998;159:1606.
- [51] Cox JD, Gallagher MJ, Hammond EH, et al. Consensus Statements on radiation therapy of prostate cancer: Guide-lines for prostate rebiopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *J Clin Oncol* 1999;17:1155.
- [52] Connolly JA, Shinohara K, Presti Jr JC, et al. Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. *Urology* 1996;47:225.
- [53] Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical prostatectomy. *Cancer* 1993;71:3582.
- [54] Norberg M, Holberg L, Wheeler T, et al. Five year follow-up after radical prostatectomy for localized prostate cancer: a study of the impact of different tumor variables on progression. *Scand J Urol Nephrol* 1994;28:391.
- [55] Ravery V, Boccon-Gibod LA, Meulemans A, et al. Predictive value of pathological features for progression after radical prostatectomy. *Eur Urol* 1994;26:197.
- [56] D'Amico AV, Whittington R, Malkowicz SB, et al. A multivariate analysis of clinical and pathological factors that predict for prostate specific antigen failure after radical prostatectomy for prostate cancer. *J Urol* 1995;154:131.
- [57] Partin AW, Piantadosi S, Marshall FF. Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology* 1995;45:831.
- [58] Lerner SE, Blute ML, Bergstralh EJ, et al. Analysis of risk factors for progression in patients with pathologically confirmed prostate cancers after radical retropubic prostatectomy. *J Urol* 1996;156:137.
- [59] Bauer JJ, Sesterhenn IA, Mostofi FK, et al. Elevated levels of apoptosis regulator proteins p53 and bcl-2 are independent prognostic biomarkers in surgically treated clinically localized prostate cancer patients. *J Urol* 1996;156:1511.
- [60] Bettencourt MC, Bauer JJ, Sesterhenn IA, et al. Ki-67 expression is a prognostic marker of recurrence after radical prostatectomy. *J Urol* 1996;156:1064.
- [61] Bauer JJ, Connelly RR, Sesterhenn IA, et al. Biostatistical modeling using traditional variables and genetic biomarkers for predicting the risk of prostate carcinoma recurrence after radical prostatectomy. *Cancer* 1997;79:952.
- [62] Isaacs JT. Molecular markers for prostate cancer metastasis. Developing diagnostic methods for predicting the aggressiveness of prostate cancer. *Am J Pathol* 1997;150:1511.
- [63] Bostwick DG. Practical clinical application of predictive factors in prostate cancer. A review with an emphasis on quantitative methods in tissue specimens. *Anal Quant Cytol Histol* 1998;20:323.
- [64] Moul JW, Connelly RR, Perahia B, et al. The contemporary value of pretreatment prostatic acid phosphatase to predict pathological stage and recurrence in radical prostatectomy cases. *J Urol* 1998;159:935.
- [65] Bauer JJ, Connelly RR, Sesterhenn IA, et al. Biostatistical modeling using traditional preoperative and pathological prognostic variables in the selection of men at high risk for disease recurrence after radical prostatectomy for prostate cancer. *J Urol* 1998;159:929.
- [66] Bettencourt MC, Bauer JJ, Sesterhenn IA, et al. CD34 r5' immunohistochemical assessment of angiogenesis as a prognostic marker for prostate cancer recurrence after radical prostatectomy. *J Urol* 1998;160:459.
- [67] Cordon-Cardo C, Koff A, Drobnjak M, et al. Distinct altered patterns of p27<sup>Kip1</sup> gene expression in benign prostatic hyperplasia and prostatic carcinoma. *J Natl Cancer Inst* 1998;90:1284.
- [68] Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998;90:766.
- [69] Graefen M, Karakiewicz PI, Cagiannos I, et al. International Validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2002;20:3206.
- [70] D'Amico AV, Whittington R, Malkowicz SB, et al. Pre-treatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999;17:168.
- [71] Moul JW, Connelly RR, Lubeck DP, Bauer JJ, Sun L, Falnders SC, et al. Predicting risk of prostate specific antigen recurrence after radical prostatectomy with the center for prostate disease research and cancer of the prostate strategic urologic research endeavor database. *J Urol* 2001;166:1322–7.
- [72] Roberts WW, Bergstralh EJ, Blute ML, Slezak JM, Carducci M, Han M, et al. Contemporary identification of patients at high risk of early prostate cancer recurrence after radical retropubic prostatectomy. *Urology* 2001;57(6):1033–7.
- [73] Porter CP, O'Donnell C, Crawford ED, et al. Artificial neural network model to predict biochemical failure following radical prostatectomy. *Mol Urol* 2002;5(4):159.
- [74] Kaplan ID, Bagshaw MA. Serum prostate-specific-antigen after post-prostatectomy radiotherapy. *Urology* 1992;39:401.
- [75] McCarthy JF, Catalona WJ, Hudson MA. Effect of radiation therapy on detectable serum prostate specific antigen levels following radical prostatectomy: early versus delayed treatment. *J Urol* 1994;151:1575.
- [76] Wu JJ, King SC, Montana GS, et al. The efficacy post prostatectomy radiotherapy in patients with an isolate elevation of serum prostate-specific antigen. *Int J Radiat Oncol Biol Phys* 1995;32:317.
- [77] Haab F, Meulemans A, Boccon Gibod L, et al. Effect of radiation therapy after radical prostatectomy on serum prostate-specific antigen measured by an ultrasensitive assay. *Urology* 1995;45:1022.
- [78] Schild SC, 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;156:1725.
- [79] Medini E, Medini I, Reddy PK, et al. Delayed/salvage radiation therapy in patients with elevated prostate specific antigen levels after radical prostatectomy. A long term follow-up. *Cancer* 1996;78:1254.
- [80] Coetzee LJ, Hars V, Paulson DF. Postoperative prostate-specific antigen as a prognostic indicator in patients with margin-positive prostate cancer, undergoing adjuvant radiotherapy after radical prostatectomy. *Urology* 1996;47:232.
- [81] Forman JD, Meetze K, Fontes E, et al. Therapeutic irradiation for patients with an elevated post-prostatectomy prostate specific antigen level. *J Urol* 1997;158:1436.
- [82] Morris MM, Dallow KC, Zeitman AL, et al. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;38:731.
- [83] Cadeddu JA, Partin AW, DeWeese TL, et al. Long-term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. *J Urol* 1998;159:173.
- [84] Garg MK, Tekyi-Mensah S, Bolton S, et al. Impact of post prostatectomy prostate-specific antigen nadir on out-comes following salvage radiotherapy. *Urology* 1998;51:998.
- [85] Raymond JF, Vuong M, Russell KJ. Neutron beam radiotherapy for recurrent prostate cancer following radical prostatectomy. *Int J Radiat Oncol Biol Phys* 1998;41:93.
- [86] Valicenti RK, Cornelia LG, Ismail M, et al. Pathologic seminal vesicle invasion after radical prostatectomy for patients with

- prostate carcinoma: effect of early adjuvant radiation therapy on biochemical control. *Cancer* 1998;82:1909.
- [87] Egawa S, Matsumoto K, Suyama K, et al. Limited suppression of prostate-specific antigen after salvage radiotherapy for its isolated elevation after radical prostatectomy. *Urology* 1999;53:148.
- [88] Vicini FA, Ziaja EL, Kestin LL, et al. Treatment outcome with adjuvant and salvage irradiation after radical prostatectomy for prostate cancer. *Urology* 1999;54:111.
- [89] Carson CC, Zincke H, Utz DC, et al. Radical prostatectomy after radiotherapy for prostatic cancer. *J Urol* 1980;124:237.
- [90] Thompson IM, Rounder JB, Spence CR, et al. Salvage radical prostatectomy for adenocarcinoma of the prostate. *Cancer* 1988;61:1464.
- [91] Neerhut GJ, Wheeler T, Cantini M, et al. Salvage radical prostatectomy for radiorecurrent adenocarcinoma of the prostate. *J Urol* 1988;140:544.
- [92] Link P, Freiha FS. Radical prostatectomy after definitive radiation therapy for prostate cancer. *Urology* 1991;37:189.
- [93] Moul JW, Paulson DF. The role of radical surgery in the management of radiation recurrent and large volume prostate cancer. *Cancer* 1991;68:1265.
- [94] Ahlering TE, Lieskovsky G, Skinner DG. Salvage surgery plus androgen deprivation for radioresistant prostatic adenocarcinoma. *J Urol* 1992;147:900.
- [95] Pontes JE, Montie JE, Klein EJ, et al. Salvage surgery for radiation failure in prostate cancer. *Cancer* 1993;71:976.
- [96] Stein A, Smith RB, deKernion JB. Salvage radical prostatectomy after failure of curative radiotherapy for adenocarcinoma of prostate. *Urology* 1992;40:197.
- [97] Lemer SE, Blute ML, Zincke H. Critical evaluation of salvage surgery for radio-recurrent/resistant prostate cancer. *J Urol* 1995;154:1103.
- [98] Rogers E, Ohori M, Kassabian VS, et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol* 1995;153:104.
- [99] Garzotto M, Wajzman Z. Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: results at 5-year follow up. *J Urol* 1998;159:950.
- [100] Gheiler EL, Tefilli MV, Tiguert R, et al. Predictors for maximal outcome in patients undergoing salvage surgery for radio-recurrent prostate cancer. *Urology* 1998;51:789.
- [101] Moul JW. Editorial comment. *J Urol* 1998;159:954.
- [102] Onik GM, Cohen JK, Reyes GD, et al. Transrectal ultrasound-guided percutaneous radical cryosurgical ablation of the prostate. *Cancer* 1993;72:1291.
- [103] Coogan CL, McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. *J Urol* 1995;154:1813.
- [104] Wieder J, Schmidt JD, Casola G, et al. Transrectal ultrasound-guided transperineal cryoablation in the treatment of prostate carcinoma: preliminary results. *J Urol* 1995;154:435.
- [105] Bales GT, Williams MJ, Sinner M, et al. Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy. *Urology* 1995;46:676.
- [106] Miller Jr RJ, Cohen JK, Shuman B, et al. Percutaneous, transperineal cryosurgery of the prostate as salvage therapy for post-radiation recurrence of adenocarcinoma. *Cancer* 1996;77:1510.
- [107] Shinohara K, Connolly JA, Presti Jr JC, et al. Cryosurgical treatment of localized prostate cancer (stages T1 to T4): preliminary results. *J Urol* 1996;156:115.
- [108] Pisters LL, von Eschenbach AC, Scott SM, et al. The efficacy and complications of salvage cryotherapy of the prostate. *J Urol* 1997;157:921.
- [109] Cespedes RD, Pisters LL, von Eschenbach AC, McGuire EJ. Long-term follow up of incontinence and obstruction after salvage cryosurgical ablation of the prostate: results in 143 patients. *J Urol* 1997;157:237.
- [110] Perrotte P, Litwin MS, McGuire EJ, et al. Quality of life after salvage cryotherapy: the impact of treatment parameters. *J Urol* 1999;162:398.
- [111] Lee F, Bahn DK, McHugh TA, et al. Cryosurgery of prostate cancer. Use of adjuvant hormonal therapy and temperature monitoring a one year follow-up. *Anticancer Res* 1997;17:1511.
- [112] Ghafar MA, Johnson CW, De la Taille A, Benson MC, Bagiella E, Fatal M, et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy. The Columbia experience. *J Urol* 2001;166:1333.
- [113] Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. *Urology* 1999;53:2.
- [114] Wallner KE, Nori D, Morse MJ, et al. 125 iodine reimplantation for locally progressive prostatic carcinoma. *J Urol* 1990;144:704.
- [115] Loening SA, Turner JW. Use of percutaneous transperineal 198Au seeds to treat recurrent prostate adenocarcinoma after failure of definitive radiotherapy. *Prostate* 1993;23:283.
- [116] Moul JW. Contemporary hormonal management of advanced prostate cancer. *Oncology (Huntingt)* 1998;12:499.
- [117] Moul JW. A better definition of advanced prostate cancer for today's patients. *Contemp Urol* 1997;9:15.
- [118] Ziada AM, Crawford ED. Advanced prostate cancer. *Prostate Cancer Prostate Dis* 1999;2:21.
- [119] Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. *J Urol* 1995;154:1991.
- [120] Labrie F, Dupont A, Belanger A, et al. Combination therapy with flutamide and castration (LHRH agonist or orchiectomy) in advanced prostate cancer: a marked improvement in response and survival. *J Steroid Biochem* 1985;23:833.
- [121] Janknegt RA, Abbou CC, Bartoletti R, et al. Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993;149:77.
- [122] Eisenberger MA, Crawford ED, Wolf M, et al. Prognostic factors in stage D2 prostate cancer, important implications for future trials: results of a cooperative intergroup study (INT 0.0036). *Semin Oncol* 1994;21:613.
- [123] Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostate cancer. *N Engl J Med* 1989;321:419.
- [124] Denis LJ, Carneiro de Moura JL, Bono A, et al. Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC Trial (30853). *Urology* 1993;42:119.
- [125] Schellhammer PF, Sharifi R, Block NL, et al. Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized multicenter trial. *Urology* 1997;50:330.
- [126] Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998;339:1036.
- [127] Bertagna C, De Gery A, Huchner M, et al. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostate cancer. A meta-analysis of seven randomized, double-blind trials (1056 patients). *Br J Urol* 1994;73:396.
- [128] Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomized trials with 3283 deaths in 5710 patients. *Lancet* 1995;346:265.
- [129] Caubet JF, Tosteson TD, Dong EW, et al. Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using non-steroidal antiandrogens. *Urology* 1997;49:71.
- [130] Bennett CL, Tosteson TD, Schnitt B, et al. Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: a meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide. *Prostate Cancer Prostate Dis* 1999;2:4.

- [131] Messing E, Manola J, Wilding G, et al. Immediate hormonal therapy vs. observation for node positive prostate cancer following radical prostatectomy and pelvic lymphadenectomy: a randomized Phase III Eastern Cooperative Oncology Group Inter Group trial. *J Urol* 1999;161(Suppl):175 (A673).
- [132] McLeod DG, Crawford ED, DeAntoni EP. Combined androgen blockade: the gold standard for metastatic prostate cancer. *Eur Urol* 1997;32(Suppl):70.
- [133] Denis LJ, Keuppens F, Smith PH, et al. Maximal androgen blockade: final analysis of EORTC Phase III Trial 30853. *Eur Urol* 1998;33:144.
- [134] The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br. J. Urol.* 1997;79:235.
- [135] Schroder FH. Endocrine treatment of prostate cancer—recent developments, early vs. delayed endocrine treatment and side-effects. *BJU Int* 1999;83:16.
- [136] Klotz LH, W H, Morse MJ, et al. Intermittent endocrine therapy for advanced prostate cancer. *Cancer* 1986;58:2546.
- [137] Goldberg SL, Bruchovsky N, Gleave ME, et al. Intermittent androgen suppression in the treatment of prostate cancer: a preliminary report. *Urology* 1995;45:839.
- [138] Higano CS, Ellis W, Russell K, et al. Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. *Urology* 1996;48:800.
- [139] Tunn UW. Intermittent endocrine therapy of prostate cancer. *Eur Urol* 1996;30(Suppl):22.
- [140] Oliver RT, Williams G, Paris AM, et al. Intermittent androgen deprivation after PSA-complete response as a strategy to reduce induction of hormone-resistant prostate cancer. *Urology* 1997;49:79.
- [141] Grossfeld GD, Small EJ, Carroll PR. Intermittent androgen deprivation for clinically localized prostate cancer: initial experience. *Urology* 1998;51:137.
- [142] Horwich A, Huddart RA, Gadd J, et al. A pilot study of intermittent androgen deprivation in advanced prostate cancer. *Br J Urol* 1998;81:96.
- [143] Gleave M, Bruchovsky N, Goldenberg SL, et al. Intermittent androgen suppression for prostate cancer: rationale and clinical experience. *Eur Urol* 1998;34(Suppl):37.
- [144] Kurek R, Rennerberg H, Luebben G, et al. Intermittent complete androgen blockade in PSA relapse after radical prostatectomy and incidental prostate cancer. *Eur Urol* 1999;35(Suppl):27.
- [145] Gleave M, Goldenberg SL, Bruchovsky N, et al. Review: Intermittent androgen suppression for prostate cancer: rationale and clinical experience. *Prostate Cancer Prostate Dis* 1998;1:289.
- [146] Andriole G, Lieber M, Smith J, et al. Treatment with finasteride following radical prostatectomy for prostate cancer. *Urology* 1995;45:491.
- [147] Fleshner NE, Trachtenberg J. Combination finasteride and flutamide in advanced carcinoma of prostate: effective therapy with minimal side effects. *J Urol* 1995;154:1642.
- [148] Fleshner NE, Fair WR. Anti-androgenic effects of combination finasteride plus flutamide in patients with prostatic carcinoma. *Br J Urol* 1996;78:907.
- [149] Ornstein DK, Rao GS, Johnson B, et al. Combined finasteride flutamide therapy in men with advanced prostate cancer. *Urology* 1996;48:901.
- [150] Brufsky A, Fontaine-Rothe P, Berlane K, et al. Finasteride and flutamide as potency-sparing androgen-ablative therapy for advanced adenocarcinoma of the prostate. *Urology* 1997;49:913.
- [151] Sandhu SS, Matveev VB, Kaisary A. Finasteride plus flutamide for prostatic carcinoma. *Br J Urol* 1997;80:60.
- [152] Harding P, Moul JW, McLeod DG. Combination flutamide and finasteride in PSA-only recurrence after prior local prostate cancer therapy. *J Urol* 1998;159(Suppl):130 (A491).
- [153] Brooks JR, Berman C, Nguyen H, et al. Effect of castration, DES, flutamide, and the 5 alpha-reductase inhibitor, MK-906, on the growth of the Dunning rat prostatic carcinoma, R-3327. *Prostate* 1991;18:215.
- [154] Schroder FH. Antiandrogens as monotherapy for prostate cancer. *Eur Urol* 1998;34(Suppl):12.
- [155] Fleshner NE, Trachtenberg J. Sequential androgen blockade: a biological study in the inhibition of prostatic growth. *J Urol* 1992;148:1928.
- [156] Fleshner NE, Trachtenberg J. Treatment of advanced prostate cancer with the combination of finasteride plus flutamide: early results. *Eur Urol* 1993;24(Suppl):106.
- [157] Lisle T, Mackenzie S, Ziada A, et al. Androgen deprivation therapy using finasteride and low dose flutamide to treat PSA failure following therapy for clinically localized adenocarcinoma of the prostate (CaP). *J Urol* 1999;161(Suppl 4):299 (A1151).
- [158] Wirth M, Tyrrell C, Wallace M, Delaere KP, Sanchez-Chapado M, Ramon J, et al. Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001;58(2):146.