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Rising Prostate-Specific Antigen after Primary Treatment of Prostate Cancer: Sequential Hormone Manipulation

Key Words
Prostate cancer · Prostate-specific antigen · Biochemical recurrence · Hormonal treatment · Androgen blockade · Antiandrogens

Abstract
Objective: To evaluate systematically the current endocrine treatment options for patients with biochemical recurrence after radical prostatectomy or radiation therapy for localized prostate cancer. ***Methods:*** Literature search of PubMed documented publications and abstracts from international meetings. Key items included timing and type of salvage hormone therapy, length of its application and handling of side effects. ***Results:*** The majority of patients with isolated prostate-specific antigen (PSA) relapse are not candidates for salvage treatment with curative intent. The PSA threshold that triggers initiation of hormonal therapy is debatable and should be based also on pretreatment risk assessment. Intermittent androgen suppression is an emerging concept to circumvent the unresolved controversy of early versus deferred endocrine therapy. Since the tumor load at time of recurrence is low, peripheral androgen blockade with an antiandrogen and a 5α-reductase inhibitor is an acceptable first choice. In case of progression, addition of a LHRH analogue would be the next step. Antiandrogen withdrawal and second-line antiandrogens are clinically of limited value. ***Conclusions:*** Biochemical-only progression after definitive treatment in curative intent is different from objective or even symptomatic relapse and allows for sequential hormonal therapy with a variety of compounds.

The biochemical failure rate after primary treatment of prostate cancer with curative intent depends on tumor-related risk factors among which high prostate-specific antigen (PSA) and Gleason score ≥7 are leading. After radical prostatectomy, a detectable PSA elevation occurs in 15–53% depending on the preselection of the patients [1, 2]. Following external beam therapy a surgical-type failure definition does not seem applicable, e.g. a PSA level >0.2 or 0.5 ng/ml. Anyhow, a PSA disease-free survival of 5 years post-radiation was only 15% (for PSA >0.2 ng/ml) versus 59% using the definition of the American Society of Therapeutic Radiology and Oncology (ASTRO) [3]. Comparable data for brachytherapy or experimental procedures are lacking.

According to the Tumor Registry of Munich in Germany, a rising PSA after radical prostatectomy or radiotherapy for apparent locally confined prostate cancer occurs in almost 15,000 patients/year [4, 5]. Some of these men had a systemic adjuvant treatment; a minority received salvage irradiation, but the majority was managed by salvage endocrine manipulation.

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Time Point of PSA Failure

Whereas metastatic prostate cancer progresses after an average of 16 months (range 3–48) despite surgical or medical castration, the situation is different in cases with isolated rising PSA [6]. Pound et al. [1] demonstrated that in 304 men with a detectable PSA after radical prostatectomy without adjuvant hormonal therapy, metastases had developed in 34% at a median of 8 years after a rising PSA. Following this point in time, the patients had a median survival time of 5 years. Diagnostic tests – computed tomography or radionucleotide bone scan – are not useful to prove the presence of lymph node or bone metastases in the early PSA-only progression, unless the PSA velocity exceeds 0.5 ng/ml per month [7, 8]. This is in keeping with a PSA doubling time <12 months, which is considered to be an auxiliary marker for prostate cancer-specific survival.

After radical prostatectomy, the distinction local or systemic recurrence may be calculated by a nomogram, e.g. with a PSA of 1 ng/ml after 1 year and a Gleason score of 8, the probability of a systemic disease is almost 80% [9]. After radiotherapy by the ASTRO definition, three consecutive PSA increases are in keeping with biochemical recurrence (sensitivity 61%, specificity 80% [10]). Following brachytherapy (seed implantation), a PSA nadir between 0.3 and 1.0 ng/ml heralds a prostate cancer relapse [11]. In general, the PSA doubling time solves the difficult issue of timing and modality of the salvage therapy.

The decision regarding the type of salvage therapy should be made individually after informing the patient of all treatment options available – even watchful waiting – in balancing the potential benefits versus adverse effects. The decision should be based on risk factors on the side of the tumor, the comorbidity, quality of life and survival. One should be aware of the anxiety and disappointment with which this clinical scenario confronts the patient [12]. An important salvage treatment is a thoroughly designed sequential androgen blockade, which was introduced by Fleshner and Trachtenberg [13].

Salvage Hormone Therapy

If an isolated PSA relapse after primary therapy of prostate cancer with curative intent occurs, many patients will not be suitable candidates for a secondary local treatment. This is due to the difficulty to prove an isolated local recurrence, comorbidity or an unfavorable balance of risks and benefits of definitive local salvage attempts [14]. In choosing hormone manipulation, the timing, the absence of a trigger PSA dictating the start of a salvage endocrine treatment, the type of endocrine deprivation, the possible length of its application and the handling of side effects should be considered.

Timing

As an androgen ablation may sooner or later lead to an androgen resistance, deferring this therapy was studied. One of the causes is the growing neuroendocrine differentiation during hormonal treatment [15]. The neuroendocrine cells are rich in growth factors and do not express androgen receptors, thus allowing the prostate cancer cells to survive despite androgen ablation. It has been shown that the duration of androgen withdrawal correlates with the number of neuroendocrine cells, conversely their density is reduced via androgen administration [16]. In addition, intermittent treatment is not associated with neuroendocrine activity [17]. The subsequent randomized trials in different patient populations, i.e. locally advanced, nodal and distant metastases, suggest that early medical or surgical castration or estrogen administration improve overall and disease-free survival (table 1).

In translating the timing of androgen deprivation to the nowadays common scenario, isolated PSA recurrence after radical prostatectomy in high-risk patients (recurrence within 12 months after surgery, Gleason score ≥7 or a PSA doubling time ≤12 months), an early hormonal treatment – beginning with a PSA ≤5 ng/ml – significantly prolongs the metastases-free survival in comparison to late or omission of such treatment [21].

After external beam radiation therapy approximately 95% of the patients with a rising PSA receive a salvage hormonal therapy (most commonly LHRH-A) only. In a multivariate analysis, a shorter PSA doubling time and an earlier intervention were linked to an increased prostate cancer death [22]. This reflects a higher aggressiveness of relapsing cancer, even so T-stage, initial PSA and Gleason score were not influential. Furthermore, neoadjuvant/adjuvant hormonal therapy was used in high-risk cancers (Gleason score ≥7 or stage ≥T_3 or PSA >15).

At any rate, delaying salvage hormonal therapy is usually not accepted by the patient himself. As the trigger PSA is unknown, the patient anxiously awaits that action takes place. In the clinical setting, one could attempt to prolong the PSA doubling time by using a soy-based dietary supplement (tertiary prevention [23]), before resorting to endocrine manipulation. To shorten the time of salvage hormone therapy, intermittent an-

Table 1. Randomized trials of immediate versus deferred hormone therapy as primary treatment

Study	Population	Early therapy	Delayed therapy	Overall survival	Cause-specific survival
Medical Research Council [18]	T_{2-4} or asymptomatic N_+/M_+	Orchiectomy or LHRH-A	Orchiectomy or LHRH-A	p = 0.038	p = 0.006
EORTC 30846	N_+	Orchiectomy or LHRH-A	Orchiectomy or LHRH-A at progression	advantage 23%	not applicable
SAKK 08/88 [19]	T_{1-4} N_{0-3} M_0 asymptomatic	Orchiectomy	Orchiectomy at progression	p = 0.96	p = 0.08
Lundgren et al. [20]	T_{0-3} N_x M_0	Polyestradiol + ethinylestradiol or estramustine	Orchiectomy or LHRH-A at progression	p = 0.03	p = 0.48

EORTC = European Organization for Research and Treatment of Cancer; SAKK = Swiss Study Group for Clinical Cancer Research.

drogen suppression is another option. In another phase-3 study following an isolated PSA relapse (≥1 ng/ml) after radical prostatectomy, the patients initially received leuprorelin acetate as a 3-month depot. When the PSA dropped below 0.5, the patients were randomized to intermittent or continuous leuprorelin + cyproterone acetate (flare-up prophylaxis). The interim analysis revealed a progression-free survival of 1,233 versus 1,009 days [24]. Candidates for an intermittent endocrine therapy among patients presenting with biochemical recurrence after radical prostatectomy or irradiation must be >70 years old, have a localized tumor and a Gleason score ≤7 [25].

Trigger PSA

Epstein et al. [26] proposed a PSA threshold of ≥0.2 ng/ml after radical surgery as a sign of failure of the primary treatment. When using ultrasensitive assays, a PSA gradually rising >0.01 ng/ml indicates the recurrence of cancer expediting salvage therapy before a PSA level of 0.2 ng/ml [27]. In practice, however, a salvage hormone therapy is started at various PSA cut points: 0.2–2.5 ng/ml (62% of all cases), 2.6–5.0 ng/ml (13%), 5.1–10.0 ng/ml (11%) and >10.0 ng/ml (14%) [21].

After radiotherapy, however, a PSA >0.2 ng/ml might be considered a failure (sensitivity 91%), but the specificity is only 9% [10]. Again, in the daily practice 20% of the physicians intervene in case of a rising PSA <10 ng/ml, 18% in case of a PSA 10–20 ng/ml, 32% in case of a PSA 20–50 ng/ml and 24% when the PSA is >50 ng/ml [22]. This reflects the problems of failure definitions after radiation [3]. 84% of the patients after brachytherapy with a PSA nadir of 0.3–1.0 ng/ml present a tumor recurrence [10].

In essence, as the trigger PSA is debatable, the decision to commence salvage hormone therapy should therefore be based also on the pretreatment risk assessment [14].

Type of Androgen Deprivation

Traditional Approaches

The elimination of the testosterone production by bilateral orchiectomy is the 'time-honored frontline' treatment to induce apoptotic regression of an androgen-dependent prostate cancer cell [28]. 94% of the metastatic cancers respond initially. Surgical castration lowers the serum testosterone level to 43 ± 32 ng/dl [29]. However, the intracellular dehydrotestosterone drops only by 75–80% due to the contribution of androgens from the adrenal glands. Kyprianou and Isaacs [30] demonstrated that there is a critical threshold of 25 ng/dl for testosterone to eliminate all post-castration remaining androgenic stimuli to the tumor cell. The National Comprehensive Cancer Network Guidelines define the castrate levels of testosterone as <20–50 ng/dl [31], but so far there is a lack of evidence as to whether the 'upper limit' post-castration ought to be <20 ng/dl as suggested by Tammela [28].

Nowadays, when treating men with a rising PSA following primary therapy with curative intent, and the option of a salvage treatment was discussed with the patient, 95% will choose a hormone therapy [22]. Among the possibilities LHRH agonists used with or without an antiandrogen are the consensus recommendations [31]. Particularly, the depot LHRH agonists appeal to the patients. It has been shown that, e.g. the 3- month depot of leuproreline virtually produced identical effects as a 1-month depot with a pronounced decline in testosterone, gonadotropin levels and PSA [32]: After the 3-month depot of leuproreline was injected subcutaneously, the testosterone fell to a median of 20 ng/dl with a safety margin of

Table 2. 5α-reductase inhibitors plus antiandrogens (peripheral androgen blockade)

Group (first author)	Patients	Medication
Fleshner [43]	22	Finasteride (1 × 5 mg), flutamide (3 × 250 mg)
Ornstein [44]	13	Finasteride (1 × 5 mg), flutamide (3 × 250 mg)
Oh [45]	20[1]	Finasteride (1 × 5 mg), flutamide (3 × 250 mg)
Kirby [46]	106	LHRH + flutamide (750) + placebo LHRH + finasteride (2 × 5 mg) + placebo Finasteride (2 × 5 mg) + flutamide (750 mg)
Barqawi [47]	71[1]	Finasteride (2 × 5 mg), flutamide (2 × 125 mg)
Tay [48]	41	Bicalutamide (1 × 150 mg), finasteride (5 mg)

[1] Patients with rising PSA.

2 months, i.e. no significant increase of testosterone and PSA [33]. Apart from this indirect mode of action, LHRH agonists inhibit the tumor directly even in androgen-independent prostate cancer [34]. This action is due to an interference with the mitogenic activity of the insulin-like growth factor (IGF-1) system.

The second type of traditional hormone treatment is the maximum androgen blockade (MAB) through which the effects of adrenally and gonadally produced androgens are eliminated. There are multiple studies comparing monotherapy demonstrating a 2.8–22% survival advantage (MAB) [35]. The majority of studies enrolled patients with metastases. Focusing on patients with a 'minimal disease', a stage close to the PSA-only situation, the progression-free survival for leuproreline + placebo was 19.1 months, but 48 months for leuproreline + flutamide [36].

There is a lack of prospective data if such a traditional approach is required in the PSA-only progression as primary hormonal manipulation. A short PSA doubling time after definitive local treatment reflecting a possible systemic disease is one possible indication, however this should be discussed with the patient [28]. Arguments against are the need to use a traditional hormonal treatment over a long time in the salvage situation with its side effects and to give up efficient secondary hormonal manipulation [37].

Non-Traditional Approaches

Primary Hormonal Manipulation. The list comprises antiandrogen (AA) monotherapy, 5α-reductase inhibitors (5-ARIs) alone or mostly in combination with non-steroidal antiandrogens (= peripheral androgen blockade).

The primary AA monotherapy gains increasing popularity. A meta-analysis of all phase-III trials of AA as single therapy for advanced prostate cancer ($T_{3,4}$ $N_{0,x}$ M_0 + T_{1-4} N_{1-3} M_{0-1}) versus medical or surgical castration came to the conclusion that survival rates may be somewhat lower if a non-steroidal AA is used [38]. As primary treatment, nilutamide is not recommended. Flutamide was studied in a number of relatively small studies, which did not show significant differences in respect to response and survival rates, but it is no standard as primary treatment [39].

In men with metastatic prostate cancer and favorable prognostic factors, flutamide and cyproterone acetate are equally effective. However, the side effects (gynecomastia, diarrhea and nausea) are more pronounced with flutamide [40]. Neither AA was tested in a phase-III trial versus castration. In contrast, bicalutamide 150 mg/day was tested in M_0 patients versus castration: there was no significant difference regarding the overall survival or time to progression [41]. The side effects favored bicalutamide, particularly regarding the sexual function domain within the quality of life, which was reduced only by 18%.

When choosing bicalutamide on the basis of these data as primary endocrine treatment for PSA-only progression, an important question is: Which secondary hormone manipulation is still effective? The 50-mg dose of bicalutamide followed by castration for hormone-naive metastatic prostate cancer produced a survival time within the range reported for initial treatment with castration [42]. Using the 150-mg dose of bicalutamide, secondary castration leads to a PSA decrease ≥20% over 3 months in 55%, even patients with objective progression responded similarly in 57% [37].

Whereas 5-ARIs as monotherapy appeared insufficiently effective, its combination with an AA is of interest (table 2). When using sequentially bicalutamide 150 mg and finasteride, 30/34 patients achieved a second PSA na-

Table 3. Molecular mechanism of antiandrogen resistance

1	Androgen receptor (AR) mutation (amplification, point mutation) changes the ligand-binding domain: flutamide (even estrogens) act as agonists
2	Ligand-independent activation of AR by oncogenes like ERBB2 or coactivator-corepressor imbalance
3	Bypass of the AR by alternative signal pathways: upregulation of the antiapoptotic genes BCL-2 or impaired expression of the AR

dir. After progression, 12/14 (86%) achieved a third PSA nadir with secondary leuproreline [48]. When finasteride + flutamide (3 × 250 mg) was administered as primary hormone treatment after secondary castration, 65% survived 5 years [45].

Secondary Hormonal Manipulation. In general, secondary hormonal manipulations have been intensively studied [49–51]. One key to the practical management is the classification of prostate cancers based on hormonal sensitivity into three classes: hormone-naive, androgen-independent (AIPC) and hormone-sensitive (castrate levels of testosterone) and hormone-independent, i.e. androgen-independent and hormone-insensitive (HRPC) [52–54]. For clinical purposes, AIPC is defined as testosterone <50 ng/dl, PSA increases by at least 5 ng/ml with two consecutive increases of 50% or one new lesion on the bone scan [55]. Despite androgen independence of prostate cancer, the androgen receptor (AR) is still activated by certain ligands: androstenedione, dehydroepiandrosterone, the growth factors TGF-β and IGF-1 as well as by alterations of the AR itself [56, 57] (table 3). Furthermore, testosterone and 5α-dihydrotestosterone occur in recurrent prostate cancer tissue at levels sufficient to stimulate the AR [58]. In the absence of AR mutations or amplification, the oncogenes ERBB2 and HRAS can cause ligand-independent AR activation [59]. At any rate, various primary molecular events which alter AR activity could cause an increase in AR mRNA, a likely final pathway for escape from standard hormone therapy [60].

Second-Line Antiandrogens. As not all antiandrogens work via the same mechanism, their sequential use may benefit prostate cancer patients [61]. When AAs are given either in a deferred or sequential version after gonadal androgen withdrawal, the extent of the disease matters. Of 209 patients progressing, 79% had pain due to metastases, only 18.6% did but 65.5% did not respond to the delayed complete androgen deprivation [62]. Similarly, in a phase-III study of the EORTC only 23% of the patients with symptomatic AIPC had a 50% PSA decline rate with deferred flutamide [63]. In contrast, Fowler et al. [64] reported with the same AA a 50% PSA decline in 80% of the patients with a localized disease versus 54% with metastases developing during the gonadal androgen deprivation.

Changing antagonistic and agonistic properties of AAs permit their sequential administration. When patients progress while being treated with a bicalutamide-based MAB, the sequential use of flutamide (375 mg/day) leads in 25/55 (45%) to PSA declines and in 12/55 (22%) of >50% lasting 1–13 months (median 6 months) [65]. Responders were preferentially patients with late biochemical progression (table 4). Bicalutamide was systematically studied in patients with AIPC [67]. Overall, 12/51 (24%) patients experienced a PSA decline >50% after 200 mg bicalutamide daily. When given sequentially to flutamide withdrawal responders, 42% had a PSA decline >50% as opposed to 35% of flutamide withdrawal non-responders. In contrast, with secondary bicalutamide (200 mg/day) after gonadal androgen deprivation alone, the response rate came down to 15%. With 150 mg bicalutamide daily in a sequential version replacing flutamide in the MAB, the results were in the same range [68, 69]. Even 50 mg/day bicalutamide given at the time of progression after gonadal androgen deprivation was followed by >50% PSA declines in 14/28 and 10/32 men respectively [70, 71].

The third AA studied after failure of primary hormone therapy was nilutamide (150–300 mg/day). The >50% PSA declines were 29, 40 and 50%, respectively [72–74]. Responses were better in patients on gonadal androgen deprivation than after MAB as well as after an antiandrogen withdrawal (AAWD) response. Nilutamide was still effective as a fifth-line hormone therapy. In experimenting with a variety of secondary hormone treatments, Kojima et al. [75] demonstrated that responders had a reasonable survival and were likely to experience remission even after a third-line application.

AAWD is standard after a rising PSA in patients on MAB [49]. It was observed first by Kelly and Scher [76] after flutamide withdrawal resulting in a PSA response in 25% of the patients. In the meantime, such a withdrawal effect was documented with the other AAs, DES and megestrol acetate. In two prospective studies, however, only 13% versus 15% of the patients experienced a PSA decline and 2% an objective tumor response [77, 78]. It is

Table 4. Androgen-independent progression (= PSA rise twice above nadir): prognostic groups [66]

Risk	Prognostic variable	Carcinoma-specific survival time (median), months
Low	PSADT >6 months	89.1 (CI 69–109)
Intermediate	PSADT <6 months PSA re-rise >7 months PSA nadir under hormone therapy ≤0.5	38.4 (CI 27–50)
High	PSADT >6 months PSA re-rise <7 months or >7 months plus: PSA nadir >0.5	14.0 (CI 8–20)

PSADT = PSA doubling time; CI = confidence interval.

of note that a second AAWD with a PSA decline >50% (8% of the patients) can occur [75]. In general, however, the clinical utility of AAWD is limited.

Adrenal Androgen Inhibitors. Ketoconazole or aminoglutethimide are not commonly used in Europe. When a total of 263 patients with relapsing prostate cancer were treated with a second-line ketoconazole, an objective remission could be seen in 32.3% lasting 1–12 months [79]. Although single institution phase-II trials demonstrated >50% PSA declines in 55% (median response lasting 8.5 months) with ketoconazole (400 mg 3 times/day) + hydrocortisone + AAWD [80], the latter results could not be confirmed in a recent phase-III trial (Cancer and Leukemia Group B 9583): 260 patients received AAWD followed by ketoconazole at the time of PSA progression or AAWD with ketoconazole simultaneously. A PSA response occurred in 30% versus 13% ($p < 0.001$) in favor of the combination. 14% of the patients allocated to AAWD + ketoconazole achieved objective responses which led to a survival of 41 versus 13 months in the sequential arm [78]. The efficacy of this adrenalytic agent when combined with AAWD points to the AR as the key to their mode of action. To what extent the hydrocortisone given in combination plays a role is a matter of speculation. In a phase-III trial, hydrocortisone + placebo with 230 patients in the latter arm 16% experienced a >50% PSA response [81].

Estramustin Phosphate (EMP). In a recent phase-III trial in 34 patients (stage D2, PSA 6.5–540.8 ng/ml) with AIPC following gonadal androgen deprivation, 560 mg/day EMP was administered orally. 24% achieved >50% PSA declines with a median duration of 8 months (range 2.2–18.8). The PSA responders had a cancer-specific survival rate of 83% after 2 years versus 44% in the non-responders [82]. EMP was studied in a phase-III trial (SWOG 9916) in patients with HRPC: docetaxel + EMP led to a >50% PSA decline in 50% of the patients [83]. Following adrenal suppression, EMP (3 × 140 mg/day p.o.) + vinblastine (5 mg/m^2/week) achieved a PSA response rate of 63.1% (median PSA decrease 71.2%), median survival 6 months, but even 16.9 (3.8–40.5) months following the beginning of the adrenal suppression [84].

Table 5. Secondary hormone manipulation: options

Antiandrogens	deferred – sequential – withdrawal
LHRH agonists	deferred – combined
Adrenalytic agents	deferred – combined (with AAWD)
Estrogens	deferred – combined (with LHRH-A)
Somatostatins	deferred – combined (with corticosteroids)

AAWD = Antiandrogen withdrawal.

Estrogens. Although the AIPC cells express estrogen receptor-β, DES and diethylstilbestrol diphosphate detour the receptor and exert a direct cytotoxic effect leading to a cell cycle arrest and apoptosis. Interestingly, AIPC cells are more susceptible than androgen-sensitive cells [85, 86]. Unfortunately, in a phase-III trial the efficacy of 3 mg DES plus the anticoagulant warfarin in AIPC was only 24% as determined by >50% PSA declines, which is low when balanced against the thromboembolic complications [87, 88].

More optimistic was a small phase-II study including 21 men with rising PSA following gonadal androgen deprivation. Using 1 mg DES 9/21 (43%, range 22–69%) had a PSA response, preferably patients who had only one previous hormone exposure [89].

Other Compounds Used Second Line. The activity of gestagens, the steroidal AA cyproterone acetate or liarozole is low, limiting their clinical utility [51].

Somatostatin Analogues. In the early 1990s, octreotide was tested in 34 men with symptomatic prostate cancer metastases demonstrating pain relief without serious side effects [90–93]. With the same compound (0.3 mg s.c./day), Vainas et al. [94] treated 8 patients with D3 prostate cancer for 1 year, 2 had an objective plus subjective and 2 a subjective response, only. Lanreotide + dexamethasone were tested in 4 HRPC patients with a response duration of 3 months [95]. In a second report from the same authors, 8/11 patients with AIPC, AAWD and bone metastases achieved >50% PSA declines plus a 13-month (median) improvement of bone pain [96]. In addition to ongoing LHRH-A, dexamethasone + 30 mg lanreotide was administered intramuscularly every 14 days. The median progression-free survival was 7 months (95% CI 4–10). The mechanism of action is obviously related to a reduction of IGF-1 ('survival factor'), however, glucocorticoids can also downregulate the IGF-1. Whether prostatic GnRH receptors are suppressed by lanreotide as has been demonstrated for LHRH receptors in prostate cancer from LHRH-A exposed patients has to be studied further [97].

In essence, there is a bewildering array of secondary or sequential hormone manipulations (table 5). Their administration has to be balanced against the side effects which are usually modest [reviewed by 51]. Ketoconazole, however, has various unpleasant side effects: 33% nausea plus vomiting, and dry skin, nail dystrophy and desiccation of the mucosa occurs in some patients [79]. Besides the well-known cardiovascular toxicity of DES, one should consider the fact that patients with biochemical progression as the only sign of a local treatment failure will be exposed to androgen deprivation for up to 10 years. A significant loss of bone density will be the consequence [98].

Conclusion

The majority of patients with rising PSA following primary therapy with curative intent get an androgen deprivation as initial treatment. As the tumor load at the time of recurrence is low, peripheral androgen blockade is an acceptable first choice. At this distressing moment for the patient, it is usually difficult to postpone the inception of systemic treatment until the PSA has risen to 10 ng/ml or above. A systemic therapy which does not interfere with the testosterone level is – at this point of time – preferred by most patients to an immediate gonadal androgen deprivation. As to whether immediate AA application alone is superior has not been studied yet. Which is the most efficient secondary hormone manipulation remains to be determined. A short PSA doubling time (table 4) makes the addition of a LHRH-A to the AA (MAB) a logical advice. If the primary hormone manipulation consisted of an AA plus a 5-ARI, the latter can presumably be discontinued. The third-line hormone manipulation is the AAWD. Thereafter the available options are up to the treating urologist (table 5). At any rate, biochemical-only progression is different from objective or even symptomatic relapse which allowed a sequential hormone manipulation.

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