

Directions in Diagnosis and Therapy of Prostate Cancer: Controversies in Uro-Oncology

Carlos D. M. Winkler

Clinic for Urology and Pediatric Urology AKH, Celle

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At the present time, it is recommended that the prostate cancer must be detected by digital rectal palpation (DRE) and PSA elevation. TRUS coupled with ultrasonically guided biopsies might become the most appealing staging technique for early diagnosed prostate cancer.

To promote earlier diagnosis, better PSA thresholds need to be defined, with a clear free-PSA threshold. This could be complemented by the use of nomograms and, in suspected cases, repeated biopsies, TRUS, bone scans and new imaging techniques.

Deferred therapy, by means of an active observation and alertness to start therapy when signs of rapid progression occur, may therefore be an alternative to active therapy in patients with a low risk localized prostate cancer with a life expectancy of 10 years or less.

Radical prostatectomy was more effective than watchful waiting in terms of cancer-specific survival benefit, when compared in a prospective randomized trial.

Neoadjuvant hormonal therapy (NHT) has a non-significant impact on overall, and progression free survival.

In Europe the focus is on biochemical recurrence after a curative treatment (nerve sparing radical prostatectomy and/or radiotherapy in low, intermediate and high-risk patients with 72-78 Gy.

In metastatic disease adjuvant androgen deprivation ADT Monotherapy is the treatment of choice. These are patients who cannot be cured and some data suggest that intermittent hormone therapy can lead to a better life quality than a continuous one. The substantial reduction in pain and therapy related morbidity often makes chemotherapy with Docetaxel for hormone refractive prostatic cancer a better choice to a simple pain-and-complication treatment.

The article presents the summary of the essential features of each condition as well as its management.

Key words: Prostatic neoplasms – diagnosis, surgery, therapy; Treatment outcome; Neoplasms, hormone-dependent - drug therapy; Androgen antagonist – therapeutic use; Antineoplastic agents, hormonal – therapeutic use; Drug therapy, Radiotherapy

Introduction

I would like to address reader's attention to the paper, which defines in most cases, the point of view of the European Association of Urology (EAU) (1).

I tried to update the most recent literature that has appeared during the last years and hope to present the reader with a version of this complex field of medical science.

This is done in an effort to address the clinical challenges that confront the practicing urologist in the field of prostatic cancer.

Epidemiology

According to Cooperberg et al. (2) and Corica et al. (3) the incidence of prostatic cancer increases with the age of population reaching a maximum prevalence of 33% in those aged >70 years (4). Prostate cancer is now the most commonly diagnosed malignancy in men, accounting for approximately 2.6 million of cancers diagnosed annually in Europe. This disease accounts for 11% of all male cancers in Europe (5) and represents 9% of all deaths caused by cancer in the European Union. (6).

Risk of prostate cancer, etiology

It has been observed, for many decades, that more than one member of the same family can be affected by the prostate cancer.

Genetic basis and racial differences for this disease are well established, but the demonstration that familiar factors have epidemiological significance is difficult to obtain (7). An environmental factor can never be ruled out, insofar as many members of the same family may be exposed to an identical risk factor, not recognizable to an identical risk factor, which is not recognizable in most cases.

There was a higher risk with increasing number of affected family members (8). Men with 2 or 3 first-degree relatives with prostate cancer had respectively a 5 and 11-fold increased risk of developing the disease (9).

Carter et al. (10) reported that inherited prostate cancer should be suspected in men with onset of the disease before 55 years of age or in males with 2 or more affected relatives.

Classification

The International Union Against Cancer (UICC), 2002 TNM (Tumor, Node, Metastases), classification is used for staging (11).

There are several systems of classification of the tumor grade. The most commonly used for grading the adenocarcinoma of the prostate is the Gleason's system (12).

Gleason's grading system is based on the analysis of various microscopic criteria of the tumor at low power magnification, which are divided into 5 appearances, scored from 1 to 5. As the tumor does not have a uniform appearance, this system takes account of the two most extensive appearances, in terms of the area (primary and secondary patterns). If a tumor contains smaller areas of other appearances, they are not taken into account in the final histological grade, even if one of them corresponds to a more poorly differentiated pattern. The histological grade is the sum of the two histological patterns defined or twice the score the simple pattern detected. It is therefore scored from 2 to 10. To be counted a pattern (grade) needs to occupy more than 5% of the biopsy (core or operative specimen). Gleason's system results in a histological score which is closely correlated to a patient's survival (13).

Screening and early detection

The demand for a routine preventive cancer checkup is based on the oncological principle that all diseases have a better chance of cure if they are detected and thus treated at an early stage (14).

Population or *mass screening* is defined as the examination of the asymptomatic male (at risk).

In addition, the principle also implies that screening currently includes a study and is initiated by a screener. Contrary to that, early detection represents individual case findings. It is initiated by the patient and/or his physician.

Reduction in mortality from prostatic carcinoma shows a wide variety worldwide all over the industrialized countries (15).

Screening for prostate cancer is based on the assumption that it is a relevant public health concern. Prospective, preferably population-based, randomized studies are still required. Finally, *two studies* are underway, the PLCO (Prostate, Lung, Colorectal and Ovary) trial in the USA and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe (16).

First results of these trial differences in cancer mortality are scheduled for 2013 and 2008 respectively.

Thus, at the present time, there is a lack of evidence to support or disregard screening programs. For prostatic carcinoma it can be said that none of the two randomized trials have been completed demonstrating that early detection results in diminished prostate cancer deaths.

Undoubtedly there are as many prostate cancers now detected by PSA elevations without digital rectal abnormalities as there are cancers detected through a positive digital rectal examination (17).

Until the last two decades this was a relatively straight forward consideration and less controversial as digital rectal examination, and PSA was the mainstay of early identification of prostate cancer (18).

Diagnosis and staging

At the present time, it is recommended that a cancer must be detected by digital rectal palpation (DRE) and PSA elevation (19, 20, 21, 22).

TRUS coupled with ultrasonically guided biopsies might become the most appealing staging technique for early diagnosed prostate cancer.

To promote earlier diagnosis, better *PSA thresholds need to be defined* (18).

Aus et al. (23) described the cumulative 7-year risk of being diagnosed with carcinoma of the prostate in a screening program based on PSA measurement. Summarizing these results, the ranges of increased PSA activity was only 34% for men with PSA levels between 3 and 6 ng/ml, 44% for those patients with PSA values between 6 and 10 ng/ml, and 71% for those patients with PSA values > 10 ng/ml.

Thompson et al. (24) observed that many men may harbor prostatic cancer despite low values of PSA has been underscored by recent results from the US prevention study.

An important question concerning clinical practice, a free-to-total PSA ratio of < 20% and PSA velocity > 0,75 ng/ml/year have been accepted as valid parameters, which are associated

with an increased risk of the prostate carcinoma (25). Up to now, 12.078 men undergoing a prostatic biopsy were followed in a recent retrospective study. Threshold values of PSA and PSA velocity were identified to improve the assessment of the prostate carcinoma risk in men beyond the age of 50 (26). Extensive studies show that the prevalence of the prostate carcinoma was 4,4% and 14,2% in men beyond 50 years and older than 50 years respectively.

According to this data, a PSA threshold level of $>2,5$ ng/ml and a PSA velocity threshold level $>0,60$ ng/ml/year seems to be appropriate for clinical practice.

The ultra sound-guided transrectal 18G core biopsy won general acceptance and has become a standard way of obtaining tissue from the prostate for histopatological examination (27). According to the experience gained from several studies it is possible to show a higher cancer detection rate in an extended 21-sample biopsy compared to the standard sextant technique (28, 29). Most of the studies clearly show that the transition zone should not be the target area for the first set of prostate biopsies. An overall accuracy of 2% cancer detection rate is to be expected (30, 31).

According to author's experience if the first set of biopsies is negative, repeated biopsies can be recommended. The second set of biopsies exhibit a detection rate of about 10-35% (32).

It is a known fact that in cases where high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) is present, as many as 50%-100% of prostates will suggest carcinoma. Clinical follow-up and repeated biopsies are indicated (33, 34).

Primary treatment of prostate cancer

Early prostate cancer management Surgery, radiation or active surveillance?

Different urologists have their own special methods for dealing with presumed localized prostatic cancer. These additional methods include watchful waiting (35), immediate endocrine therapy, and external and/or interstitial radiation. The important thing is the absence of metastases. When they are absent, any treatment that completely removes or destroys the primary growth will result in cure, and when metastases are present, none is likely to do so. When making such decisions, many physicians rely on nomograms based on pre-operative biochemical markers and biopsies (36).

Watchful waiting (active surveillance)

The efficacy of different types of treatment for localized prostate cancer has come under question. While radical prostatectomy and radiotherapy have been associated with low progression rates and high survival figures, it is well known that in many patients the cause of death is not prostate cancer. Therefore, there is a renewed interest in studying the

natural history of this disease to better appreciate the extent, to which active forms of treatment may alter the outcome (37, 38).

Deferred therapy, by means of active observation (39) and alertness to start therapy when signs of rapid progression occur (40), may therefore be an alternative to active therapy in patients with low risk localized prostate cancer with a life expectancy of 10 years or less (41).

Chodak et al. (37) and Albertsen et al. (38) observed an 80-90% cancer specific survival with a deferred therapy treatment after a follow-up of 20 years.

The excellent article of Chodak et al. (37) described the outcome for stage T1a patients, with cancer-specific 10-year survival rates of 90%.

Classification of the Gleason score, stage and PSA level on the risk of tumour progression and ultimately death from prostate cancer are mandatory.

Klotz et al. (42) observed in a series that patients with a PSA <10 ng/ml, biopsy Gleason score ≤ 6 , stage cT1c-cT2a, live expectancy <10 years should be managed expectantly. All authors reporting on deferred treatment for presumed localized prostate cancer (Nx-No, Mo) stage T1a - well -and moderate differentiated tumours, with a life expectancy of >10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is necessary.

Indications for radical prostatectomy

Objectives of RPE

The selection of patients for radical curative procedures put the urologist in a dilemma about attempting to maintain both, the quality of life and the duration of survival of the patient (43, 44).

Radical prostatectomy for the treatment of prostate cancer can be performed by various techniques using a retropubic, perineal or laparoscopic approach (45, 46, 47, 48, 49, 50).

Current data would indicate that nerve sparing radical prostatectomy is the most effective way of dealing with adenocarcinoma of the prostate, which is organ-confined within the anatomic margins of the prostate gland. The experience with radical prostatectomy was more effective than watchful waiting in terms of cancer-specific survival benefit (35), when compared in a prospective randomized trial.

Pelvic lymphadenectomy?

The addition of pelvic lymphadenectomy should allow the clinician to assess with greater accuracy the possible presence of extended disease (51).

Besides being a staging procedure, extended pelvic lymph node dissection might be curative, or at least beneficial in a group of patients with limited lymph node metastases (52, 53, 54).

According to Partin nomograms (36) patients with cT1c, PSA value < 10 ng/ml and biopsy Gleason score < 6 have a *low risk* of metastatic disease in the pelvic lymph nodes, therefore additional advantage of removing lymph nodes might not be necessary.

In patients with *intermediate risk* (cT2a, PSA value 10-20 ng/ml, biopsy Gleason score =7), or *high risk* (>cT2b, PSA>20 ng/ml, biopsy Gleason score>8), the presence of pelvic nodal metastases is elevated. The addition of an extended lymphadenectomy is necessary (51). Joniau et al. (55) reported an incidence of 13-27% of overstaging in patients with clinical T3 carcinoma.

Treatment results of clinical cT3 adenocarcinoma of the prostate with radical prostatectomy: These results have been satisfactory. Locally advanced disease can be treated successfully with radical prostatectomy with a satisfactory overall survival at 5,10 and 15 years and a cancer-specific survival of 95%, 90% and 79%, respectively (55, 56, 57, 58, 59).

Possible beneficial effect of adjuvant hormonal treatment: Neoadjuvant hormonal therapy (NHT) has been used to facilitate radical prostatectomy, and reduce the risk of leaving cancer behind (60).

To the contrary, a Cochrane review and meta-analysis observed a non-significant impact on overall, and progression free survival (61).

Androgen deprivation after radical prostatectomy has been controversially discussed (62, 63).

In the only published prospective randomized study by Messing et al. (64) early adjuvant therapy after radical prostatectomy with nodal involvement provide a significant survival advantage.

Despite this report of spectacular results, this approach might be flawed for several reasons. Firstly, large tumours seem to consist of a high percentage of macroscopic lymph node involvement, and 70% of the patients have evidence of surgical margin-positive disease or seminal vesicle involvement. Secondly, there is no evidence that microscopic lymph node involvement perse will have a positive impact on a disease outcome.

The detailed investigations of the Early Prostate Cancer Trial show that the progression free survival is not evident in patients with prostate cancer after standard therapy with additionally 150 mg bicalutamid daily. To the contrary, they observed a favourable impact on overall survival in patients with locally advanced prostatic carcinoma (62).

Radiation therapy (DxT) The effect of dose escalation and additional hormonal therapy

With the use of *dose escalation* radiation therapy it has become possible to deliver a better outcome in patients with prostatic cancer.

Kupelian et al. (65) utilize external radiation in patients with *low risk* prostate cancer with a dose of >72Gy or< 72Gy. After irradiation, biochemical disease-free survival is statistically significantly better 69% vs 63% in patients with increased external irradiation.

Improvement of prognosis of patients with *intermediate risk* cT1c-T3 could be achieved by higher doses ranging from 76 to 81 Gy. Zelefsky et al. (66) observed a significant improvement in 5-year survival without biochemical relapse. These clinicians usually apply a dose of 78Gy. Combination with adjuvant hormonal treatment for 6 months after receiving external radiation of 72Gy improved the results.

Pollak et al. (67) published results of a randomized radiotherapy dose-escalation trial comparing 70Gy with 78Gy. From these data it is evident that in cases with *high risk* prostate cancer radiotherapy dose- escalation improves 5 year biochemical disease-free survival (68,69,70). In fact their data demonstrate that patients receiving an adjuvant androgen deprivation (ADT) and external irradiation have improved biochemical disease-free survival. It even cannot be excluded that a proportion of these patients have a relapse outside the pelvis. Bolla et al. (71,72) could establish that neoadjuvant and adjuvant hormonal therapy for two years is mandatory for patients undergoing irradiation in the *high-risk* group (73, 74, 75, 76, 77, 78).

Transperineal brachytherapy

The interest in intraprostatic implantation of radioactive material revived in the second half of the last century when urologists made it evident that hormone therapy was not the ideal approach in nonmetastasized prostatic cancer (79).

Ash et al. (80) published transperineal brachytherapy in growths limited to the prostate (category stage cT1b-T2aNo, Mo, a Gleason score ≤6, in enough cases of histologically proven number of random biopsies.

A good International Prostatic Symptom Score (IPSS) with an initial PSA level of ≤10 ng/ml, ≤50% of biopsy cores involved with prostatic cancer on a gland volume of ≤50cm³ is mandatory.

Machtens et al. (81) reported in a paper recurrence-free survival data of patients treated with permanent seed implants. After 5 and 10 years they range from 71% to 93% and from 65% to 85% respectively.

Up to the present time there is no benefit from combining neoadjuvant or adjuvant deprivation to low-dose rate (LDR) brachytherapy.

Nevertheless, a number of complications have been reported following brachytherapy, such as urinary retention (1.5-22%), post-implant TURP (about 8.7%) and incontinence (0-19%) as acute urinary symptoms.

In addition to the acute manifestations chronic urinary morbidity might occur in about 20% of patients associated with symptoms before to therapy.

Radiation therapy pT3, pTxR1

Immediate or delayed radiotherapy after radical prostatectomy?

The presence of positive margins after radical prostatectomy correlates with detectable post-operative elevation of PSA. Although the presence of an elevated PSA following radical prostatectomy, denotes residual disease, one has to reconcile the fact that only 7-10% of patients following radical prostatectomy will develop clinical local recurrence (82).

A significant difference between two groups of patients (positive vs. negative margins) was found according to preoperative and postoperative Gleason score as well as according to T-staging (83).

The results of this modality approach (immediate postoperative radiotherapy) are presented in three randomized trials (84).

In the data presented (EORTC study, 22911) clinical or biological 5-years survival has been significantly improved (72.2% vs. 51.8%) in the *immediately adjuvant radiotherapy group* (60 Gy) to radiotherapy delayed until local recurrence (70 Gy) in patients after radical retropubic prostatectomy.

The radiation effect is limited. It has not been seen that this treatment modality improves metastases-free survival and carcinoma specific survival in this group of patients.

The question that arises is should all patients with positive surgical margins be treated with immediate adjuvant radiation therapy in an attempt to prevent recurrence? From this data it is evident that immediate radiation therapy should be the treatment of choice in cases with multifocal positive surgical margins and a Gleason score >7, or patients with a PSA level ≥ 0.1 ng/ml one month after radical prostatectomy.

Alternative therapeutic options

Radical prostatectomy has remained the reference standard treatment for localized prostate cancer. Surgery of the prostate cancer provides histological evidence of complete tumor removal, including margin status. The lack of histo-

logical proof of complete tumor ablation is an inherent disadvantage of all ablative technologies.

However, with cryoablation, the ability to achieve real-time ultrasound imaging of the iceball appears to overcome this challenge.

Besides external beam radiation and/or brachytherapy cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) has recently become available alternative therapeutic modalities in cases with localized prostate cancer (85).

The ideal patients for cryoablation (CSAP) are those with organ-confined prostate cancer. Prostate volume should be <40 ml. PSA serum levels should be <20 ng/ml and the biopsy Gleason score should be <7. Long-term follow-up of 10 and 15 years is the final step needed to definitively determine the role of cryosurgical ablation in the treatment of localized prostate cancer. In general the treatment population included patients with a life expectancy >10 years, therefore treatment options must be discussed with the patients.

Management of advanced prostate cancer

Hormonal therapy, controversies of palliative hormonal treatment

Most authors agree that medical castration is probably better achieved today by the depot administration of long-acting LHRH analogues. Randomized trials have shown that these drugs are as effective as orchidectomy or 3 mg diethylstilbestrol (DES) daily. The physiological surge of testosterone induced by the initial LHRH analogues administration can be countered by the administration of an antiandrogen given for 1 week prior to LHRH agonist and continued during the first month of therapy.

The most direct technique for lowering plasma androgen levels is bilateral orchidectomy, removing the primary source of testosterone in male patients for a life time. Medical castration was achieved by the oral administration of (DES) daily. A number of studies confirmed its efficacy for cancer control but revealed significant cardiovascular toxicity and associated mortality (86, 87, 88).

In the meantime *at least two prospective randomized trials* addressed the question of monotherapy with Bicalutamid (150 mg/daily) vs. medical or surgical castration including 1435 patients with locally advanced Mo or widespread disease M1 prostatic carcinoma are available (89).

Some essential data of this study are briefly summarized herein. With respect to the M1-category patients, an improvement in overall survival with castration is present, although the difference in median survival between the two groups was only 6 weeks. These authors concluded that non-steroidal antiandrogens in contrary to steroidal antiandrogens could be a therapy alternative and may be recommended. A survival

benefit only for patients with higher PSA level ≥ 400 ng/ml has been observed (90). No significant difference in overall survival occurred in the Mo- category.

Complete androgen blockade (CAB)

The clinical introduction of anti-androgens as second line hormonal treatment after failure of the initial castration further confirmed additional patient responses ranging from 6 to 15% (91).

The idea to move this clinical response up front by combining both therapies was first experimented by Bracci utilizing cyproterone acetate (CPA) and by Labrie utilizing flutamide at the time of initial treatment (92, 93).

The review of the available data, and the cumulative meta-analysis of the leading investigators and clinical groups who had studies on the value of complete androgen blockade vs. monotherapy in the treatment of advanced prostate cancer served as a basis for an extensive discussion (94).

After a follow-up of 5 years the response results in favour of the combination were published by Seidenfeld and Iversen (86, 89). The study suggests an improvement less than (<5%) in survival with the combination treatment.

Intermittent androgen suppression (IAS)

No other treatment exists that equals or surpasses androgen ablation in controlling the growth of prostate cancer. Approximately 80% of prostate cancer patients achieve symptomatic and objective responses following androgen suppression, and serum prostate specific antigen (PSA) levels decrease in almost all patients. However, for reasons that remain unknown, the cell death process induced by androgen ablation by whatever means fails to eliminate the entire malignant cell population (95) and after a variable period of time averaging 24 months, tumours inevitably recur with increasing serum PSA levels and are characterized by androgen independent growth. Experimental and early clinical experience with intermittent androgen suppression (IAS), suggest that quality of life (QOL) is improved and progression to androgen independence may be delayed using reversible androgen suppression and PSA as the trigger point. IAS may offer a "way out" of the *immediate versus delayed treatment controversy*, by balancing the benefits of immediate androgen ablation with reduced treatment-related side effects and expense. The effects of intermittent therapy have also been tested in several phase II trials showing the feasibility of intermittent androgen suppression (IAS) in metastatic disease.

Available information about IAS is still very limited. For intermittent vs. continuous therapy the SWOG trial 9346 randomized, 1134 men with stage D2 prostate carcinoma. After 7 months induction with ADT with PSA levels decrease <4ng/ml (96). Finally it is clear that a PSA reduction to <0.2 ng/ml, <4ng/ml and >4 ng/ml was identified as a significant prognostic factor with regard to survival, achieving 13

months, 44 months and 75 months, respectively, and no significant differences with regard to survival were seen between treatment groups. In conclusion, IAS is a relevant option for patients with prostate carcinoma

In conclusion, IAB is at present widely offered to patients with CaP in various clinical settings. However, many aspects need to be clarified, such as timing, duration and type of treatment.

Delayed or immediate hormonal therapy (ADT)?

An extensive overview of hormonal treatment, and the timing to introduce therapy in patients with advanced prostatic carcinoma is controversial, in particular whether androgen blockade for locally advanced disease and asymptomatic metastatic disease delivered immediately at diagnosis favourably influences survival and QOL compared to delayed ADT while signs and symptoms of clinical progression remain controversial.

There are three studies currently available for reviewing the issue of early vs. deferred treatment. No prospective randomized trials are available.

There is only one retrospective study using biochemical tests and standardized follow-up schedules, including 1352 patients after radical prostatectomy with a rising PSA levels after therapy (97).

According to the analysis, immediate androgen ablation conducted in the post-PSA era in patients with advanced prostate cancer who received immediate (MO) vs. deferred ADT (M1) are presented. In both patients groups there is no significant advantage in overall and carcinoma-specific survival. Immediate androgen therapy provides a benefit in patients with a Gleason- score >7 or a PSA doubling time <12 months.

The significance of rising PSA after a treatment with curative intent

While one can take comfort in a falling PSA after radical prostatectomy or irradiation of prostatic cancer, a rising PSA is cause for considerable concern (98); noted that PSA levels of >0.2 ng/ml after radical prostatectomy were related directly to a biochemical recurrence (recurrence of prostate cancer). The new definition of radiation failure can be defined as a rise of 2 ng/ml above the post-treatment PSA-nadir (lowest value). Roach et al (78) correlated it with a recurrence in men with clinically localized prostate cancer.

In conclusion, it is possible that distant dissemination may develop secondly to local failure. The existence or re-growth of local residual disease in localized prostatic carcinoma promotes and enhances spread of metastatic disease.

The probability of distant metastases is related to the stage of the tumor, the grade of the tumor and the PSA level pre and

post treatment. Relapsing patients however were those with short PSA doubling time, advanced stage unfavorable Gleason scale and rapidly increasing PSA level. For the most part these patients would have a metastatic disease. The PSA doubling time (>10-12 month) and slowly PSA increase correlate with a local recurrence.

On the other hand these patients might have benefited from more vigorous initial treatment such as is possible with a radical prostatectomy, radiation or perhaps androgen deprivation as an adjunct to irradiation.

Both bone scintigraphy and CT may be helpful and remains a sensitive method to detect a recurrence if the serum PSA level is >20 ng/ml, particularly when PSA velocity is >2 ng/ml/year.

Additionally endorectal MRI may be helpful for detecting a recurrence if PSA level is >2 ng/ml.

Finally new antibody radiolabelled scintigraphy and PET techniques may provide more accurate information for detecting recurrent or metastatic disease of the lymph nodes in the future. Thus more studies are needed to investigate or evaluate those techniques, before they can be recommended for routine use in clinical practice (99).

Treatment of hormone-resistant prostatic cancer

Although the majority of patients (70%) with prostatic cancer respond objectively and/or subjectively to hormone treatment, an escape phenomenon occurs after an average of 2 to 3 years (52).

Hormone-resistant stage T3 or M+ prostatic cancer is defined by the fact that the disease continues to progress despite a well conducted hormone treatment.

Non-compliance with the treatment regimen (often seen in elderly men) should be ruled out, by the observation of castrate level serum testosterone, as the main reason for treatment failure.

This escape results from selection of preexisting or de novo appearance of hormone resistant clones.

What is the definition of progression?

Classically, definition of failure of the primary treatment and progression was based on clinical criteria. Now that PSA has been shown to be a good marker of tumour progression, we have to consider that the primary treatment has failed as soon as PSA starts to rise again. These biological changes precede clinical progression by several months.

At the present state of our knowledge, the precise definition of recurrent or relapsed prostate carcinoma remains controversial. The current literature is reviewed, regarding hormone-resistant carcinoma. Androgen-independent, but hor-

none-sensitive prostate carcinoma, has to be differentiated from true HRPC from the outset. In practice the first group still responds to secondary hormonal manipulations, such as antiandrogen withdrawal, oestrogens and corticosteroids, the second group is resistant to all hormonal measures (100).

Second line hormonal treatment

When should a second line hormonal treatment be considered?

An alternative treatment must be considered when the level of PSA starts rising, when new spots appear on follow-up bone scan and of course when the patient becomes symptomatic again. The longer we wait the less effective will be the second line hormone therapy.

When a cancer is resistant to a primary hormonal treatment, can it still respond to another hormonal treatment? At present there are multiple therapeutic options for second line endocrine management available.

We already know that our capacity to prolong survival is limited and this means that our choice for second line therapy should aim more at improving the quality (QOL) than the duration of survival, taking into consideration the patients specific expectations and wishes.

Which endocrine therapy to choose is determined by factors which are depending on the patient, the tumour and the first line therapy and is given by a therapeutic algorithm (101).

When a metastatic prostate cancer is resistant to LHRH analogues, subcapsular orchiectomy, CAB or anti-androgen monotherapy (mean duration of response 36 months) it can still respond to another hormonal treatment.

When the patient relapses the addition of anti-androgens, LHRH-analogues or addition of LHRH-analogues in monotherapy, a response can be obtained in some cases (mean duration of response 4-6 months) in the presence of resistance to standard hormonal therapy.

Are there any other hormonal modalities?

Antiandrogen withdrawal responses have also been reported after treatment with bicalutamide and flutamide (102, 103) with a median duration of response of approximately 4 months. *Alternative treatments other than hormones?* The benefits of a secondary hormonal manipulation such as adrenal testosterone inhibitors low-dose DES, steroids or non-hormonal therapy such as chemotherapy seems to result in declining PSA in a group of patients.

Treatment options after true hormonal treatment failure are chemotherapy. Cytotoxic therapy

The efficacy of Docetaxel in the treatment of patients with (HRPC) was evaluated.

Painful metastases treatment

The substantial reduction in pain and therapy related morbidity frequently makes chemotherapy for hormonal refractory prostate cancer a better alternative to simple pain and complication treatment (104).

A significant improvement in median survival of approximately two months could be demonstrated for Docetaxel with Prednisolone as compared with mitoxantrone plus prednisone in the management of hormone-resistant prostate cancer (HRPC) in two prospective randomized clinical Phase III trials. The influence of Docetaxel achieves a significant improvement in pain and quality of life (QOL) in this trial. The results of the treatment outlined above demonstrate a PSA decline in 45% compared to 32% in the mitoxantrone group (105, 106).

The following conclusions can be drawn from these publications: Docetaxel had a beneficial effect in the treatment of true (HRPC) and becomes treatment of choice in refractory carcinoma of advanced stage.

Role of chemotherapy

The beginning of the treatment with chemotherapy of patients with advanced refractory prostate cancer is not well defined.

In practice, these patients suffer from their bone metastases. We shall not discuss painless metastases with PSA relapse which do not require any particular treatment apart from that of the primary tumor. However, spine and hips disseminated asymptomatic metastases must be watched and treated for possible pathological fractures. In the case of a localized or disseminated symptomatic metastasis, the best treatment remains chemotherapy.

Palliative therapeutic options (radiotherapy, cortisone, analgetics and antivomiting drugs)

If the patient does not like chemotherapy, classical palliative treatment must be prescribed. The action of radiotherapy, which is a local treatment, is limited in the case of disseminated lesions and when the origin of the pain is difficult to determine.

Patients treated by this method are generally at the terminal stage of the disease. Analgesia has been achieved in a large number of cases but it is difficult to evaluate the duration as these patients often die soon after this irradiation probably, because of their already severely impaired status.

Very good results have been published in the literature with bisphosphonates in order to prevent skeletal complications (107, 108).

We are left with non-specific analgesia, which has progressed considerably over recent years. The treatment of a patient with advanced disseminated metastases involves the simulta-

neous administration of high doses of morphine and high doses of non-steroidal, then steroidal anti-inflammatory agents.

Zoledronic acid, is an excellent analgesic for multiple bone pain. As a result of these advances, pain can be controlled in the majority of patients.

Conclusions

As an international community, urologists are not only struggling with the dilemma of helping a patient to decide on an optimal treatment plan, but they also have to deal with the uniqueness of their patient population, the availability of technology, and the practice biases of their colleagues.

In the area of prostate cancer, there are many clinical situations which have more than one treatment option. Rather, the essential features of each condition and its management are summarized.

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UPUTE VEZANE UZ DIJAGNOZU I TERAPIJU KARCINOMA PROSTATE: KONTROVERZE U UROONKOLOGIJI

Carlos D. M. Winkler

Klinika za urologiju i pedijatrijsku urologiju AKH, Celle

SAŽETAK

U današnje se vrijeme preporuča otkrivanje karcinoma prostate digitalnom rektalnom palpacijom (DRE) i PSA elevacijom. TRUS bi zajedno s ultrazvučno vođenim biopsijama mogla postati najkorisnija tehnika za rano otkrivanje karcinoma prostate. Kako bi se dijagnoza postavila što prije, moraju se definirati bolje granice PSA s jasnim slobodnim graničnim vrijednostima PSA. To može biti upotpunjeno upotrebom nomograma i u spornim slučajevima ponovljenim biopsijama, TRUS postupkom, skeniranjem kostiju i novim tehnikama oslikavanja.

Odgadanje liječenja uz aktivno promatranje i spremnost na početak terapije, kada se pojave znakovi progresije, mogu biti alternativa aktivnoj terapiji u pacijenata s lokaliziranim karcinomom prostate niskoga rizika uz očekivani životni vijek od 10 godina ili manje.

Radikalna je prostatektomija, kada se uspoređi u očekivanoj randomiziranoj studiji, bila učinkovitija od čekanja uz promatranje u smislu preživljenja specifičnoga za rak.

Neoadjuvantna hormonalna terapija (NHT) nema značajniji utjecaj na ukupno preživljenje bez napredovanja bolesti. U Europi naglasak je na biokemijskom povratu bolesti nakon liječenja (Radikalna prostatektomija uz poštedu živaca i/ili radioterapija kod niskorizičnih, srednjerizičnih i visokorizičnih pacijenata s 72-78 Gy).

Kod bolesti koja je metastazirala izabire se adjuvantna deprivacija androgena ADT monoterapija kao metoda liječenja. To su pacijenti koji se ne mogu izliječiti i neki podaci ukazuju da intermitentna hormonalna terapija može dovesti do bolje kvalitete života od konstantne. Kemoterapija s Docetaxelom za liječenje hormonskoga karcinoma prostate često je bolji izbor od jednostavnoga liječenja boli i komplikacija, zbog značajnijega smanjenja smrtnosti uzrokovane boli i liječenjem. Sažete su osnovne karakteristike svakog stanja i upravljanja njime.

Ključne riječi: Tumori prostate – dijagnoza, operacija, liječenje; Ishod liječenja; Tumori, hormonski ovisni - terapija lijekovima; Androgeni antagonisti – terapijska upotreba; Protutumorski lijekovi, hormonski – terapijska upotreba; Terapija lijekovima; Radioterapija