DIRECTIONS IN DIAGNOSIS, HEALTH RELATED QUALITY OF LIFE AND THERAPY OF PROSTATE CANCER – CONTROVERSIES IN URO-ONCOLOGY

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Currently, it is recommended that prostate cancer be detected by digital rectal palpation and prostate specific antigen (PSA) elevation. TRUS coupled with ultrasound-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 active observation and alertness to start therapy when signs of rapid progression occur may therefore be an alternative to active therapy in patients with low-risk localized prostate cancer with 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 has a nonsignificant impact on overall and progression free survival. In Europe, the focus is on biochemical recurrence after 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 is the treatment of choice. These are patients that cannot be cured. Identification of intracellular androgen synthesis by prostate cancer cells has led to identification of new targets, several novel strategies, third-generation drugs, inhibitors of androgen synthesis, more potent androgen receptor antagonists. Castration-resistant prostate cancer remains dependent on androgens and signaling through androgen receptor. Substantial pain reduction, improvement in PSA response and quality of life often make chemotherapy with docetaxel for hormone refractory prostate cancer better choice than simple pain and complication treatment. The main features of each condition and its management are summarized.

Key words: **prostate cancer, treatment, surgery, castration, hormonal treatment, chemotherapy, radiotherapy, quality of life**

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INTRODUCTION

We would like to address reader's attention to the paper that defines in most cases the point of view of the European Association of Urology (EAU) (1). We tried to present an update of the most recent literature that appeared in the last few years and hope to provide the reader with a complex view of this complex field of medical science. It was done in an effort to address clinical challenges that confront the practicing urologist in the field of prostate cancer.

EPIDEMIOLOGY

According to Cooperberg *et al.* (2) and Corica and Bostwick (3), the incidence of prostate cancer increases with population age, reaching 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 newly diagnosed in Europe annually. This disease accounts for 11% of all male cancers in Europe (5) and for 9% of all cancer deaths in the European Union (6).

RISK OF PROSTATE CANCER AND ETIOLOGY

It has been observed for decades that more than one member of the same family can be affected by prostate cancer. Genetic basis and racial differences for this disease are well established, but epidemiological significance of familial factors is difficult to demonstrate (7). Some environmental factor cannot be ruled out either, insofar as many members of the same family may be exposed to the same risk factor, not recognizable in most cases. There was a higher risk with the increasing number of family members affected (8). Men with 2 or 3 first-degree relatives with prostate cancer had a 5- and 11-fold greater risk of developing the disease, respectively (9). Carter *et al*. (10) report that inherited prostate cancer should be suspected in men with the disease onset before 55 years of age or in males with 2 or more affected relatives.

CLASSIFICATION

The International Union Against Cancer (UICC) 2002 Tumor, Node, Metastases (TNM) classification is used for staging (11). There are several systems of tumor grade classification. Gleason's system is most commonly used for grading of prostate adenocarcinoma (12). Gleason 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 into account the two most extensive appearances in terms of area (primary and secondary patterns). If the 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 of 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 that is closely correlated with patient survival (13).

SCREENING AND EARLY DETECTION

The demand for a routine preventive cancer checkup is based on the oncologic 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 asymptomatic male (at risk). In addition, the principle also implies that screening currently includes a study and is initiated by a screener. Contrary to this, early detection represents individual case findings. It is initiated by the patient and/or his physician.

Reduction in mortality from prostate carcinoma varies greatly worldwide across 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. Two prospective studies have been completed: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the USA and the European Randomized Screening for Prostate Cancer (ERSPC) in Europe. The PLCO investigators found a higher incidence of prostate carcinoma in the screening group than in control group, but with the same rates of death from the disease (16). The ERSPC investigators have reported a higher incidence of prostate carcinoma in the prostate specific antigen (PSA) based screening group than in the non-screening group; however, men undergoing screening had a lower rate of death from prostate carcinoma (17).

Thus, it appears that PSA test could be recommended for prostate carcinoma screening at the present. The patient should first be informed about the potential harms and benefits of screening. Undoubtedly, there are as many prostate cancers now detected by PSA elevations without digital rectal abnormalities as there are cancers detected through positive digital rectal examination (18).

DIAGNOSIS AND STAGING

Currently, it is recommended that a cancer must be detected by digital rectal examination (DRE) and PSA elevation (19-21). Transrectal ultrasonography (TRUS) coupled with ultrasound (US)-guided biopsies might become the most appealing staging technique for early diagnosed prostate cancer. To better characterize cancers by biopsy, investigators have explored enhanced image guidance with magnetic resonance imaging (MRI); it may supplement but cannot replace systematic sampling techniques.

Thompson *et al*. (22) observed that many men may harbor prostate cancer despite low PSA values, as underscored by recent results from a US prevention study. An important question concerning clinical practice is that the free-to-total PSA ratio <20% and PSA velocity >0.75 ng/mL/year have been accepted as valid parameters that are associated with an increased risk of prostate carcinoma (23). Up to now, 12,078 men undergoing prostate biopsy were followed-up in a recent retrospective study. Threshold values of PSA

and PSA velocity were identified to improve assessment of prostate carcinoma risk in men beyond age 50 (24). Extensive studies showed the prevalence of prostate carcinoma to be 4.4% and 14.2% in men aged <50 and >50, respectively. According to these data, a PSA threshold level >2.5 ng/mL and PSA velocity threshold level >0.60 ng/mL/year seem to be appropriate for clinical practice.

The US-guided transrectal 18G core biopsy has been generally accepted and has become a standard method to obtain prostate tissue for histopathologic examination (25). According to several studies, it is possible to reach a higher cancer detection rate in an extended 21-sample biopsy compared with the standard sextant technique (26,27). In most of the studies, it was clearly shown 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 (28).

In the experience of the authors, if the first set of biopsies is negative, repeat biopsies can be recommended. The second set of biopsies exhibit a detection rate of 10%-35% (29). It is known that high-grade prostatic intraepithelial neoplasia (HGPIN) will suggest carcinoma in as many as 50%-100% of prostates. Clinical follow up and repeat biopsies are indicated (30).

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 prostate cancer (radical prostatectomy). These additional methods include watchful waiting (31), and external and/or interstitial radiation. An 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 preoperative biochemical markers and biopsies (32).

WATCHFUL WAITING AND 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. There is therefore a renewed interest in studying the natural history of this disease to better appreciate to what extent active forms of treatment may alter the outcome (33,34).

Deferred therapy by means of active observation (35) and alertness to start therapy when signs of rapid progression occur (36) may therefore be an alternative to active therapy in patients with low-risk localized prostate cancer and life expectancy of 10 years or less (37). Chodak *et al.* (33) and Albertsen *et al.* (34) observed 80%-90% cancer specific survival with deferred therapy after 20-year follow-up. The excellent article by Chodak *et al.* (33) describes the outcome in stage T1a patients, with cancer-specific 10-year survival rate of 90%.

Classification of Gleason score, stage and PSA level are mandatory to assess the risk of tumor progression and ultimately death from prostate cancer. Results observed in a series of patients showed that patients with a PSA <10 ng/mL, biopsy Gleason score ≤6, stage cT1c-cT2a, and life expectancy <10 years should be managed expectantly.

The established therapeutic approaches for clinically nonsignificant prostate cancer include watchful waiting and active surveillance. The optimal treatment strategy for a patient should provide long-term disease control with minimal treatment-related morbidity and maximal preservation of the quality of life.

Traditional conservative symptomatic management with palliative intention, especially in elderly patients with meaningful comorbidity, treatment options are hormone therapy, palliative transurethral resection (TUR-P), and palliative radiotherapy of bone metastases.

In a pivot trial of radical prostatectomy *versus* observation watchful waiting (WW), investigators report that some populations do not profit from radical prostatectomy, as it could be an overtreatment (38). Other investigators (SPCG-4-study) have reported reduction of mortality associated with radical prostatectomy *versus* watchful waiting (WW) (39).

All authors reporting on deferred treatment for presumed localized prostate cancer (Nx-No, Mo) stage T1a, well and moderately differentiated tumors with life expectancy of >10 years, consider that re-evaluation with PSA, TRUS and biopsies of the prostate remnant is necessary.

Furthermore, there is a considerable rate of overdiagnosing tumors which would not be life threatening

if left untreated. Therefore, treatment options such as active surveillance with curative intention of prostate cancer patients with long life expectancy have to be considered. Only in selected patients with favorable tumor characteristics may active surveillance be considered a good and relatively safe alternative option (40).

INDICATIONS FOR RADICAL PROSTATECTOMY

Objectives of radical prostatectomy

Patient selection for radical curative procedures places the urologist in a dilemma of attempting to maintain both the patient quality of life and the length of survival (41). Radical prostatectomy for treatment of prostate cancer can be performed by various techniques using the retropubic, perineal or laparoscopic approach (42-45). Current data would indicate that nerve sparing radical prostatovesiculectomy 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 when compared in a prospective randomized trial (31).

Pelvic lymphadenectomy?

The addition of pelvic lymphadenectomy should allow the clinician to assess with greater accuracy the possible presence of extended disease (46). 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 (47). According to Partin nomograms (32), patients with cT1c, PSA value <10 ng/mL and biopsy Gleason score <6 have a low risk of metastatic disease in pelvic lymph nodes, therefore additional advantage of removing lymph nodes may 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 increased. The addition of extended lymphadenectomy is necessary (46). Joniau *et al.* (49) report an incidence of 13%-27% of overstaging in patients with clinical T3 carcinoma.

Radical prostatectomy as mentioned above is indicated in patients with organ confined prostate cancer, consequently to stages of clinically localized prostate cancer. The goals are complete removal of the gland seminal vesicles and pelvic nodes, while preserving urinary continence and restoring erectile function in good general health in patients with life expectancy of 10 years.

Surgery can be performed with advantages and disadvantages, either as open radical prostatectomy (RRP), laparoscopic approach (LRP) or robotic prostatectomy (RALP) (50). RRP is associated with fewer rectal injuries and pelvic extended lymphadenectomy can easily be performed. LRP achieves a long learning curve with less high costs compared with RALP. Less blood loss, cancer control in lower-intermediate risk patients, preservation of neurovascular bundle can also be achieved using LRP/RALP (51).

Long-term cancer control has been reported in several large series with 10- to 15-year follow up. Freedom from biochemical recurrence was 66% for ORP, 80% for LRP and 72% for RALP in PT2 tumors.

Freedom from progression was 84% for ORP, 97% for LRP and 97.5% for RALP in PT2 tumors. As with other forms of treatment, the probability of recurrence after radical retropubic prostatectomy (ORP) or laparoscopic radical prostatectomy (LRP) or robotic prostatectomy (RALP) varies with the values of clinical and pathologic risk factors. There are no published data on prospective randomized studies (51-53). The average complication rate varies from 2% to 22%/ORP and from 2% to 17% LRP/RALP (54). Loss of urinary control is usually temporary, after 12 months 92% RALP and 79% ORP (55). Erectile function after 12 months achieved acceptable results after bilateral nerve sparing surgery, 93.5%/RALP and 60.6%/ORP (56).

Radical prostatectomy is an effective form of therapy for patients with clinically significant prostate cancer with an acceptable level of morbidity. Although rare, fatal complications do occur.

Experienced surgeons achieve acceptable results with ORP, LRP and RALP. The influence of different surgical techniques reveals similar pathologic and oncologic outcomes comparing RRP, LRP and RALP (57).

Results of treatment of clinical cT3 adenocarcinoma of the prostate with radical prostatectomy are satisfactory. Locally advanced disease can be treated successfully with radical prostatectomy, with a satisfactory overall survival at 5, 10 and 15 years and cancer-specific survival of 95%, 90% and 79%, respectively (48).

POSSIBLE BENEFICIAL EFFECT OF ADJUVANT HORMONAL TREATMENT

Androgen deprivation after radical prostatectomy has been controversially discussed. In the only published prospective randomized study by the Eastern Cooperative Oncology Group (ECOG trial 3886) published by Messing *et al*., patients treated with castration or GnRH therapy after radical prostatectomy with nodal involvement have a significant survival advantage. Hormonal treatment must be administered for two years (59). Detailed investigation by the Early Prostate Cancer Trialists Group shows that the progression free survival is not evident in patients with prostate cancer after standard therapy with additional 150 mg bicalutamide daily. They observed no impact on overall survival in patients with locally advanced prostatic carcinoma (60). Neoadjuvant hormonal therapy (NHT) has been used to facilitate radical prostatectomy and reduce the risk of leaving cancer behind. On the contrary, a review and meta-analysis found a nonsignificant impact on overall and progression free survival (61).

RADIATION THERAPY AND EFFECT OF ADDITIONAL HORMONAL THERAPY

External beam radiotherapy (EBRT), 3-dimensional conformal RT (3D-CRT) and intensity modulated RT (IMRT) improved 10-year PSA relapse free survival (RFS), i.e. 75.6 Gy 85% *versus* 70.2 Gy 58% (62). The European Organization for Research and Treatment of Cancer (EORTC trial 22863) reports the experiences with androgen deprivation therapy (ADT) and EBRT. The investigators demonstrated absolute survival outcomes in patients treated with combined ADT and EBRT compared with those treated with radiotherapy alone (63).

D'Amico *et al*. report that adjuvant hormonal therapy for two years is mandatory in patients undergoing irradiation in the high-risk group (64). The Radiation and Oncology Group (RTOG trial 85-31) report outcomes in patients treated with radiotherapy combined with adjuvant or delayed ADT. They observed better overall survival at 5 years (76% *vs*. 71%) and 10 years (53% *vs*. 38%) in the ADT combined with EBRT group (65). A randomized trial demonstrated improved disease free survival outcomes in patients treated with combined ADT and EBRT compared with conventional radiotherapy alone. Radiotherapy (EBRT) is an effective, noninvasive form of therapy for patients with high-risk (T3-4, Gleason score 8-10 or PSA >20 ng/mL) prostate cancer. Treatment with ADT and 74 Gy for 6 months is standard for intermediate risk patients (T2b-c or Gleason score 7 or PSA 10-20 ng/mL), and for 24-36 months ADT for high-risk patients. ADT combined with EBRT is not advised for patients with low-stage disease (T1a-2a, Gleason score <7, PSA <10 ng/mL) (66).

The Radiation Therapy Oncology Group (RTOG) 92-02 enrolled patients with high-risk prostate cancer. They observed 11% improved overall survival in patients treated for 26 months with ADT compared to 4-month ADT therapy (67). In the RTOG 86-10 study, Roach *et al*. could established that neoadjuvant concomitant and adjuvant hormonal therapy for 6 to 24-36 months in intermediate- and high-risk patients undergoing irradiation improved biochemical disease-free survival (68).

The incidence of erectile dysfunction appears to be related to vascular disruption. Treatment with erectogenic agents can result in response rates ≤70% (69).

BRACHYTHERAPY

The interest in intraprostatic implantation of radioactive material revived in the second half of the 20th century. Transperineal brachytherapy was applied in growths limited to the prostate (category stage cT1b-T2a N0, M0, Gleason score <6) in cases of histologically proven random biopsies. With good International Prostatic Symptom Score (IPSS) with an initial PSA level <10 ng/mL, <50% of biopsy cores involved with prostate cancer on a gland volume of <50 cm^3 is mandatory.

Cancer control after brachytherapy (seeds)

Freedom from biochemical recurrence rate was in the range of 75%-100% at 5 years and 66%-88% at 8-13 years (68). PSA relapse free survival rate for low-, intermediate- and high-risk patients was 82%, 70% and 48% at 7 years (69). Brachytherapy combined with EBRT is needed in the intermediate-risk patient group (70).

Complications and quality of life after low-dose brachytherapy are associated with transient urinary morbidity. Radiation induced urethritis, prostatitis, urgency, dysuria and urinary retention are the most common side effects. They gradually decline during the next 3-6 months (71).

Erectile dysfunction was observed in 30%-40% of patients requiring erectogenic agents that resulted in excellent responses (72).

The use of brachytherapy is an effective noninvasive form of therapy in patients with clinically significant

prostate cancer, with an acceptable level of morbidity. Relative contraindications include previous radiotherapy and inflammatory bowel disease. Brachytherapy is effective for selected patients with clinically confined disease.

Primary treatment options for patients with low- and high-risk factors and localized disease were brachytherapy alone or brachytherapy combined with EBRT.

Biochemical freedom from relapse after modern permanent low-dose rate brachytherapy (LDR-BT) seeds in the low-risk group at 5 years was 70%-95% and at 10 years 65%-89%. However, patients from the intermediate- and high-risk groups experienced no favorable results (73). EBRT is combined with high-dose-rate brachytherapy (HDR-BT) in the intermediate- and high-risk groups. Significant results were achieved with combined treatment (74).

Transient urinary morbidity related to radiation-induced urethritis or prostatitis accounts for the most common side effects. Erectile dysfunction was observed in 30%-40% of patients. These impairments in the quality of life have been shown to gradually improve with time.

RADIOTHERAPY AFTER PT3, PTX R1 – IMMEDIATE OR DELAYED RADIOTHERAPY AFTER RADICAL PROSTATECTOMY

The presence of positive margins after radical prostatectomy correlates with detectable postoperative elevation of PSA (75). Although the presence of 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 (76,77). Results of this modality approach (immediate postoperative radiotherapy) were presented in a randomized trial (78).

According to data presented by the Organization for Research and Treatment of Cancer (EORTC trial, 22911), clinical or biological 5-year survival was significantly improved (72.2% *vs*. 51.8%) in the immediate 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 was not seen that this treatment modality improved metastase-free survival and carcinoma specific survival in this group of patients. From these 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 in 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 prostate cancer provides histologic evidence of complete tumor removal, including margin status. The lack of histologic proof of complete tumor ablation is an inherited 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) have recently become available alternative therapeutic modalities in cases with localized prostate cancer (79).

The ideal patients for cryoablation (CSAP) are those with organ-confined prostate cancer. Prostate volume should be <40 mL, PSA serum levels <20 ng/mL and biopsy Gleason score <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 includes patients with life expectancy >10 years, therefore treatment options must be discussed with patients.

Focal therapy is an alternative technique in the treatment of prostate cancer

Considerable technological advances such as improved biopsy and imaging techniques/multiparametric (MRT) magnetic resonance imaging have improved the field of focal ablation. Several techniques (HIFU, cryoablation) have a potential for focal ablation of prostate cancer. Their use should be considered as no standard option. HIFU can be performed as primary whole gland treatment or salvage treatment (lack of long-term oncology outcome, no better than standard therapy) in patients with local recurrence after external radiation therapy (RT) or seeds (BT). Results and side effects have been acceptable but need confirmation in prospective multicenter trials (79).

Cryoablation is a therapeutic option for selected patients with prostate cancer. It is indicated if there are absolute or relative contraindications for radical prostatectomy. In salvage cases for localized prostate cancer, cryoablation is therapy of choice (80). There is a lack of multicenter randomized trials.

MANAGEMENT OF ADVANCED PROSTATE CANCER – PRIMARY HORMONAL THERAPY

Monotherapy

Seidenfeld *et al*. compared monotherapy with antiandrogens *versus* medical (LHRH analogues) or surgical castration or diethylbestrol in patients with locally advanced prostate cancer. The published data show that the 2-year survival (150 mg/daily) *versus* medical or surgical castration in locally advanced prostate was better for castration patients. This study has confirmed that monotherapy is not an alternative to castration (82).

Iversen *et al*. addressed the question of monotherapy with bicalutamide (150 mg/daily) *versus* medical or surgical castration in locally advanced prostatic carcinoma patients with higher PSA levels. There was no significant difference in overall survival. The use of castration potentially contributes to decreased quality of life with more underlying disorders such as osteoporosis and cardiovascular disease (83).

COMPLETE ANDROGEN BLOCKADE (CAB)

The most commonly used treatments are bilateral orchidectomy or medical castration using a luteinizing hormone-releasing hormone (LH-RH) analogue, both of which eliminate the androgens of gonadal origin. These treatments can be used alone or in combination with an antiandrogen, which inhibits the effect of androgens by blocking the androgen receptor (combined androgen blockade, CAB). The review of the available data and cumulative meta-analysis of the leading investigators and clinical groups having studied the value of complete androgen blockade *versus* castration in the treatment of advanced prostate cancer served as a basis for extensive discussion. After 5-year follow up, response results in favor of combination therapy were published by the Prostate Cancer Trialists Collaborative Group (PCTCG) from analysis of 8275 patients. The study suggests improvement in survival and lower mortality with combination treatment (84).

The International Prostate Cancer Study Group (IPCSG) have reported late results (10 years) of a randomized study comparing medical castration *versus* CAB in advanced prostate cancer from analysis of 589 patients. Results of 10-year survival indicated that there was a small, non-significant benefit in favor of CAB flutamide plus LHRH analogue goserelin compared with goserelin alone (85). There is no general recommendation for CAB today, perhaps some patients may benefit from combination therapy (86).

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 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 (86) and after a variable period of time averaging 24 months, tumors inevitably recur with increasing serum PSA levels and are characterized by androgen independent growth. Experimental and early clinical experience with intermittent androgen suppression (IAS) suggests that the quality of life is improved and progression to androgen independence may be delayed using reversible androgen suppression and PSA as a 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 expenses.

The effects of intermittent therapy have also been tested in several phase II trials showing the efficacy of IAS in metastatic disease. Available information about IAS is still very limited. For intermittent *versus* continuous therapy, the South West Oncology Group (SWOG trial 9346) randomized 1134 men with stage D2 prostate carcinoma. After 7-month induction with ADT, PSA levels decreased to <4 ng/mL (87). Finally, PSA reduction to <0.2 ng/mL,<4 ng/mL and >4 ng/mL was identified as a significant prognostic factor with regard to survival, achieving 75 months, 44 months and 13 months, respectively, and no significant differences with regard to survival were seen between treatment groups. Hormonal therapy must be administered when PSA levels increase to 10 ng/mL (metastatic disease) and 4 ng/mL in patients with recurrent prostate cancer.

In conclusion, IAS with PSA control three times a month is at present widely offered to patients with prostate carcinoma 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)

In systemic therapy of advanced prostate cancer, a form of hormonal therapy (ADT) is a standard. In patients with symptomatic prostate cancer with positive

nodal disease and/or metastases T3-T4, PSA >25-50 ng/mL, or PSA doubling time <1 year, testosterone lowering therapy is the treatment of choice. In addition, patients with T1b-T2b are candidates for palliative therapy of symptoms. ADT is also indicated as combined or neoadjuvant (radical prostatectomy) therapy. ADT can be used in asymptomatic prostate cancer with metastases.

Furthermore, patients consent is important concerning toxicity, quality of life and prolonging free survival (89).

Moul *et al*. describe their retrospective experience with 1352 patients with biochemical recurrence after radical prostatectomy. In conclusion, immediate hormonal therapy provided benefit in patients with PSA <5 ng/mL only in cases with Gleason score 8-10 or PSA doubling time <12 months (90). Seiler *et al*. have suggested that biochemical recurrence after positive lymph nodes and radical prostatectomy may be possible. After 10-year follow up, overall survival was 75% in patients with one positive lymph node without immediate adjuvant hormonal therapy. The investigators concluded that patients with multiple positive lymph nodes required immediate adjuvant hormonal therapy. In addition, it was shown that immediate hormonal therapy administered at PSA levels >50 ng/mL or PSA doubling time <12 months was associated with increased overall survival (91). Mc Leod *et al*. could not demonstrate the advantage of adjuvant hormonal therapy with bicalutamide in patients with localized disease without radical prostatectomy, in terms of increased overall survival (85). Loblaw *et al*. report on the results of a meta-analysis of 4 randomized studies. Patients treated with immediate hormonal therapy showed decreased mortality without statistical significance (59).

Therefore, the use of delayed or immediate hormonal therapy in patients with no radical prostatectomy is not recommended today. Therapy depends on PSA value, PSA doubling time and Gleason score.

THE SIGNIFICANCE OF RISING PSA AFTER TREATMENT WITH CURATIVE INTENT

While one can take comfort in falling PSA after radical prostatectomy or irradiation of prostate cancer, rising PSA is a cause for considerable concern (92), noting that PSA levels of >0.2 ng/mL after radical prostatectomy were related directly to biochemical recurrence (recurrence of prostate cancer). The new definition of irradiation failure can be specified as a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value). Roach *et al*. (68) correlated it with recurrence in men with clinically localized prostate cancer. In conclusion, it is possible that distant dissemination may develop following 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 tumor stage, tumor grade and PSA levels pre- and post-treatment. The relapsing patients, however, were those with short PSA doubling time, advanced stage, unfavorable Gleason scale, and rapidly increasing PSA level. Most of these patients would have a metastatic disease. The PSA doubling time (>10-12 months) and slow PSA increase correlate with local recurrence.

On the other hand, these patients may have benefited from more vigorous initial treatment such as possibly with radical prostatectomy, irradiation, or perhaps androgen deprivation as an adjunct to irradiation. Bone scintigraphy and computed tomography may be helpful and sensitive methods to detect a recurrence if 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 lymph nodes in the future. Thus, more studies are needed to investigate or evaluate these options before they can be recommended for routine use in clinical practice (93).

TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

An escape phenomenon occurs after an average of 24-36 months under androgen suppression therapy by surgical castration, LHRH, and steroidal or non-steroidal antiandrogens (94). The majority of patients with metastatic prostate cancer show PSA rising as a sign of androgen-independent but still androgen-sensitive tumor progression.

Castration-resistant prostate cancer (CRPC) is defined by the European Association of Urology (EAU) as follows: testosterone levels (<50 ng/dL or <1.7 nmol/L); three consecutive PSA rising values within 3 weeks, with 2 PSA levels >50% over nadir; antiandrogen withdrawal 4 weeks for flutamide, 6 weeks for bicalutamide; patients show PSA rising despite ADT; metastatic cancer: >2 bone metastases or other location (1).

At the present, our knowledge about treatment of castration-resistant prostate cancer has changed. The antineoplastic approaches include second line hormonal treatment (corticosteroids, inhibitors of the CYP17 enzyme, giving freedom from PSA recurrence for 4-8 months (89).

Ketoconazole, a nonspecific inhibitor of androgen synthesis, showed clinical activity, however, high doses are needed but are associated with significant side effects (neurotoxicity, gastrointestinal intolerance and liver toxicity). In addition, it is recommended to give concomitant hydrocortisone to restore other steroid hormones.

The identification of intracellular androgen synthesis by prostate cancer cells has led to identification of new targets. Several novel strategies such as inhibitor of androgen synthesis (abiraterone) have shown that the disease continues to progress also in the hormone refractory stage. CRPC remains dependent on androgens and signaling through the androgen receptor (95).

A randomized study has shown the usefulness of abiraterone plus prednisone compared to prednisone alone. The benefits have been reported with 4.6 months in significant overall survival, with mild or moderate side effects with secondary mineralocorticoid excess, i.e. fluid retention, hypokalemia and hypertension. It is considered a new standard of care (96,97).

In conclusion, the European Association of Medical Oncology ESMO has recommended the first- and second line hormonal therapy approach for patients with castration-resistant prostate cancer.

CHEMOTHERAPY

In practice, these patients suffer from a castration-resistant symptomatic and metastatic prostate cancer. In the case of localized or disseminated symptomatic metastases, chemotherapy remains the best treatment option (99). Tannock *et al*. report their experience in the first trial (TAX327 study) in patients with metastatic hormone-resistant prostate cancer treated with mitoxantrone and prednisone *versus* docetaxel plus prednisone. They compared docetaxel 75 mg/m^2 3-weekly or 30 mg/m^2 weekly with prednisone 10 mg daily *versus* standard arm of mitoxantrone 12 mg/m^2 3-weekly with prednisone 10 mg daily. The most effective treatment was the 3-weekly regimen, which produced significant 24% improvement in overall patient survival. They demonstrated median survival improvement of 2.4 months in comparison with the control arm (18.9 months *vs*. 17.4 months docetaxel *vs*. 16.5 months mitoxantrone). There also were significant improvements in pain (35% *vs*. 22%), PSA response (45 *vs*. 32%) and quality of life. The toxicity rates were mostly hematologic in most cases (99). Petrylak *et al*. published the second study from the South West Oncology Group trial 99-16; they randomized 770 patients to 3-weekly docetaxel (60 mg/m^2) in combination with estramustine (280 mg daily 1-5) 3-weekly, compared with mitoxantrone and prednisone. A similar result to that seen with TAX327 was observed, with 23% improvement in survival. The median survival improvement was about 2 months (18 months docetaxel *vs*. 16 months mitoxantrone; p=0.008) and 28% reduction in the risk of death (100). These two reported docetaxel based studies must be accepted as the standard of care in patients with CRPC who might be considered for chemotherapy. With a 3-weekly regimen based on docetaxel, there was a statistically significant improvement in the patient quality of life and prolongation of survival by 2 months.

PALLIATIVE THERAPEUTIC OPTIONS – RADIOTHERAPY, CORTISONE, ANALGESICS AND ANTIVOMITING DRUGS

The action of radiotherapy, which is a local treatment, is limited in the case of disseminated lesions and when the origin of pain is difficult to determine. Patients treated by this method are generally in the terminal stage of the disease. Analgesia has been achieved in a large number of cases but it is difficult to evaluate its duration, as these patients often die soon after irradiation, probably because of their already severely impaired status.

Very good results have been published in the literature with bisphosphonates to prevent skeletal complications (101).

We are left with nonspecific analgesia, which has progressed considerably over recent years. The treatment of a patient with advanced disseminated metastases involves simultaneous administration of high doses of morphine and high doses of nonsteroidal, then steroidal anti-inflammatory agents. Zoledronic acid diminished osteoclastic activity in most of the patients. As a result of these advances, pain can be controlled in the majority of patients.

The treatment of patients with symptomatic bone metastases should involve a multimodal and interdisciplinary approach

Bone metastases and skeletal related events (SRE) are frequent complications in terminal stage. Special atten-

tion should be paid to clinical signs of hypercalcemia, chronic pain, and pathologic bone fractures. Treatment approaches currently include oncologic and medical therapy, pain therapy and radiation therapy (102).

In 70%-90% of patients, pain can be relieved by adherence to the WHO cancer pain recommendations (WHO I, non-opioid analgesics; WHO II and WHO III, opioid analgesics) (103). Other treatment options are inhibitors of the Receptor Activator of Nuclear Factor (RANKL) system.

One study showed good outcome comparing time to first SRE, denosumab *vs.* zoledronate 27.7 *vs*.19.4 months (8 month benefit for the former) (104). Additional pain relief with radiotherapy (EBRT), radium 323 or strontium are other alternatives to be considered.

CONCLUSIONS

As an international community, urologists are not only struggling with the dilemma of helping the patient 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 bias of their colleagues. In the area of prostate cancer, there are many clinical situations that have more than one treatment option. The essential features of each condition and its management are summarized.

REFERENCES

1. Heidenreich A, Bastian PJ, Bellmunt J *et al*. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014; 65:467-79.

2. Cooperberg MR, Lubeck DP, Metha SS, Carroll PR; CaPSURE. Time trends for prostate cancer: implications for outcomes (data from CaPSURE). J Urol 2003; 170: 21-5.

3. Corica FA, Bostwick DG. Clinically unsuspected and undetected (clinical stage TO) prostate cancer diagnosed on random needle biopsy. Urology 1999; 53: 557-62.

4. Klippel KF, Jurincic CD. Prostatakarzinom. In: Krause W, Rothauge C-F, editors. Andrologie: Krankheiten der Prostata. Stuttgart: Ferdinand Enke Verlag; 1991; p. 207-20. (in German)

5. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002; 38: 99-166.

6. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075-107.

7. Farkas A, Marcella S, Rhoads GG. Ethnic and racial differences in prostate cancer incidence and mortality. Ethn Dis 2000;10: 69-75.

8. Galić J. Epidemiologija, čimbenici rizika i rano otkrivanje karcinoma prostate. Med Vjesn 2009;41(1-2): 37-46. (in Croatian)

9. Gronberg H, Damber L, Damber JE. Familial prostate cancer in Sweden: a nationwide register cohort study. Cancer 1996; 77: 138-43.

10. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992; 89: 3367-71.

11. Sobin LH, Wittekind C, editors.TNM Classification of Malignant Tumours, 6th edn. New York: Wiley-Liss; 2002.

12. Gleason DF. Histologic grading of prostate cancer: a perspective. Human Pathol 1992; 23: 273-9.

13. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111: 58-64.

14. Luboldt H-J, Rübben H. Früherkennung des Prostatakarzinoms. Dtsch Arztbl 2004; 101: A1736-38. (in German)

15. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the "PSA-ERA". Int J Cancer 2001; 92(6): 893-8.

16. Andriole GL,Crawford ED, Grubb RL *et al*. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104: 125-32.

17. Schröder FH, Hugosson J, Roobol MJ *et al*. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366: 981-90.

18. Grosman H, Grinspon D, Lopez M, Bellora O, Scorticati C, Mazza O. Free prostate specific antigen index (free PSA)/ total prostate specific antigen (total PSA) accurate cutoff. Rev Arg Urol 2004; 69(4): 235-40.

19. Mihaljević I, Mudri D, Glavaš-Obrovac Lj, Tucak A. Tumorski markeri karcinoma prostate. Med Vjesn 2009; 41(1-2): 21-8. (in Croatian)

20. Romics I. Technique of ultrasound guided prostate biopsy. Med Vjesn 2004; 36(1-4): 43-6.

21. Galić J, Knežević M, Tucak A, Mrčela M. Prikaz i usporedba rezultata dobivenih nakon transperinealne i transrektalne biopsije prostate s uzimanjem 12 bioptičkih uzoraka. Med Vjesn 2004; 36(1-4): 61-7. (in Croatian)

22. Thompson IM, Pauler DK, Goodman PJ *et al*. Prevalence of prostate cancer among men with a prostate-specific antigen level 4.0 ng *per* milliliter. N Engl J Med 2004; 350: 2239-46.

23. Catalona WJ, Smith DS, Wolfert RL *et al*. Evaluation of percentage of free serum prostate-specific antigen to improve specifity of prostate cancer screening. JAMA 1995; 274: 1214-20.

24. Sun L, Moul JW, Hotaling JM *et al*. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int 2007; 99: 753-7.

25. Veltman J, Goosen T, Laguna P, Wijkstra H, de la Rosette J. New technical improvements for TRUS in the diagnosis of prostate cancer. Eur Urol 2002; Suppl 1: 8-14.

26. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic *versus* directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989; 142(1): 71-5.

27. Guichard G, Larre S, Gallina A *et al*. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol 2007; 52: 430-5.

28. Morote J, Lopez M, Encabo G, de Torres I. Value of routine transition zone biopsies in patients undergoing ultrasound-guided sextant biopsies for the first time. Eur Urol 1999; 35: 294-7.

29. Djavan B, Ravery V, Zlotta A *et al*. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol 2001; 166: 1679-83.

30. Haggman MJ, Macoska JA, Wojno KJ, Oesterling JE. The relationship between prostatic intraepithelial neoplasia and prostate cancer: critical issues. J Urol 1997; 158(1): 12-22.

31. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin tables) for the new millennium. Urology 2001; 58(6): 843-8.

32. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, Chisholm GD, Moskovitz B, Livne PM, Warner J. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994; 330: 242-8.

33. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998; 280: 975-80.

34. Ochiai A, Troncoso P, Chen M, Lloreta J, Babaian R. The relationship between tumor volume and the number of positive cores in men undergoing multisite extended biopsy: implication for expectant management. J Urol 2005; 174: 2164-8.

35. Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 2006; 176: 1392-7.

36. Griffin C, Yu X, Loeb S, Desireddi V, Han M, Graif T, Catalona W. Pathological features after radical prostatectomy in potential candidates for active monitoring. J Urol 2007; 178: 860-3.

37. Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005; 23: 8165-9.

38. Wilt TJ, Brawer MK, Jones KM *et al*. Radical prostatectomy *versus* observation for localized prostate cancer. N Engl J Med 2012; 367: 203-13.

39. Bill-Axelson A, Holmberg L, Garmo H *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014; 370: 932-42.

40. Fröhner M, Wirth M. Organ-und Funktionserhalt beim Prostatakarzinom. Urologe 2014; 53: 1295-301. (in German)

41. Walsh PC. The discovery of the cavernous nerves and development of nerve sparing radical retropubic prostatectomy. J Urol 2007; 177: 1632-5.

42. Grdović C. Usporedba otvorenih i laparoskopskih radikalnih prostatektomija učinjenih na Odjelu za urologiju Opće bolnice Zadar. Med Vjesn 2009; 41(1-2): 79-81. (in Croatian)

43. Vodopija N, Župančić M, Koršić L, Kramer F, Parać I, Krstanoski Z. Laparoskopska radikalna prostatektomija: rezultati kod 140 operiranih bolesnika. Med Vjesn 2004; 36(1-4): 79-84. (in Croatian)

44. Kröpfl D, Zebić N, Roggenbuck U, Burmester L, Mandt D. Radikalna prostatektomija – iskustva stečena liječenjem 801 bolesnika u razdoblju od 1993. do 2003. godine. Med Vjesn 2004; 36(1-49: 69-77. (in Croatian)

45. Winkler C, Bitar A, Klippel K-F. Anterograde retropubic radical prostatectomy (RRP) in 1480 patients. Results of a follow-up study of 300 patients, learning curve and outcome in a retrospective evaluation. Med Vjesn 2004; 36(1-4): 49-53.

46. Heidenreich A, Ohlmann CH, Polyakov G. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007; 52: 29-37.

47. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281(17): 1591-7.

48. Aus G, Nordenskjold K, Robinson D, Rosell J, Varenhorst E. Prognostic factors and survival in node-positive (N1) prostate cancer – a prospective study based on data from a Swedish population-based cohort. Eur Urol 2003; 43(6): 627-31.

49. Joniau S, Hsu C-Y, Lerut E *et al*. A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. Eur Urol 2007; 51: 388-96.

50. Thüroff JW. Laparoskopische *vs*. Robotische Operationen in der Urologie. Urologe 2012; 51:615-6. (in German)

51. Thomas C, Neisius A, Roos FC, Thüroff JW. Robotisch assistierte radikale Prostatektomie. Urologe 2015; 54: 178-82. (in German)

52. Han M, Partin AW, Pound CR *et al*. 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: 555-65.

53. Rassweiler J, Schulze M, Teber D *et al*. Laparoscopic radical prostatectomy with the Heilbronn technique: oncological results in the first 500 patients. J Urol 2005; 173: 761-4.

54. Diaz M, Peabody JO, Kapoor V *et al*. Oncologic outcomes at 10 years following robotic radical prostatectomy. Eur Urol 2015; 67: 1168-76.

55. Saar M, Ohlmann CH, Janssen M *et al*. Die radikale Prostatektomie. Intra-und postoperative Komplikationen erkennen und behandeln.Urologe 2014; 53: 976-83. (in German)

56. Ficarra V, Novara G, Rosen RC *et al*. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012; 62: 405-17.

57. Coelho RF, Rocco B, Patel MB *et al*. Retropubic, laparoscopic and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010; 24: 2003-15.

58. Busch J, Gonzalgo M, Leva N *et al*. Propensity Score Vergleich der verschiedenen radikalen Operationstechniken beim high risk Prostatakarzinom. Akt Urol 2015; 46: 45-8. (in German)

59. Messing EM, Manola J, Yao J *et al*. Eastern Cooperative Oncology Group study EST 3886: Immediate *versus* deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006; 7: 472-9.

60. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Casodex Early Prostate Cancer Trialists Group. Bicalutamide 150 mg plus standard care *vs*. standard care alone for early prostate cancer. BJU Int 2006; 97: 247-54.

61. Bonney WW, Schned AR, Timberlake DS. Neoadjuvant androgen ablation for localized prostatic cancer: pathology methods, surgical end points and meta-analysis of randomized trials. J Urol 1998; 160: 1754-60.

62. Symon Z, Griffith KA, McLaughlin PW *et al*. Dose escalation for localized prostate cancer: substantial benefit observed with 3D conformal therapy. Int J Radiat Oncol Biol Phys 2003; 57: 384-90.

63. Bolla M, Collette L, Blank L *et al*. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 2002; 360: 103-6.

64. D'Amico AV *et al*. Six-month androgen suppression plus radiation therapy *vs*. radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004; 292(7): 821-7.

65. Pipelich MV, Winter K, Lawton CA, Krisch RE, Wolkow HB, Movsas B *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005; 61: 1285-90.

66. Bolla M, van Tienhoven G, Warde P *et al*. External irradiation without long-term androgen suppression for prostate cancer with high metastatic risk: 10 year results of an EORTC randomized study. Lancet Oncol 2010; 11: 1066-73.

67. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD *et al*. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008; 26: 2497-504.

68. Roach M, Bae K, Speight J, Wolkow HB, Rubin P, Lee RJ *et al*. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008; 26: 585-68.

69. Incrocci L, Hop WC, Slob AK. Efficacy of sildenafil in an open label study as a continuation of a double-blind study in the treatment of erectile dysfunction after radiotherapy for prostate cancer. Urology 2003; 62: 116-20.

70. Zelefsky MJ, Kuban DA, Levy LB *et al*. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with permanent brachytherapy. Proceedings of the 47th Annual American Society for Therapeutic Radiology and Oncology Meeting. Int J Radiat Oncol Biol Phys 2005; 63: 33.

71. Davis BJ, Pisansky TM, Wilson TM *et al*. The radial distance of extraprostatic extension of prostate carcinoma: implications for prostate brachytherapy. Cancer 1999; 85: 2630-7.

72. Zelefsky MJ, Yamada Y, Marion C *et al*. Improved conformality and decreased toxicity with intraoperative computer-optimized transperineal ultrasound-guided prostate brachytherapy. Int J Radiat Oncol Biol Phys 2003; 55: 956-63.

73. Merrick GS, Butler WM, Galbreath RW *et al*. Erectile function after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2002; 52: 893-902.

74. Burri RJ, Ho AY, Forsythe K *et al*. Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010; 77: 1315-21.

75. Hoskin PJ, Rojas AM, Bownes PJ *et al*. Randomized trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localized prostate cancer. Radiother Oncol 2012; 103: 217-22.

76. Bedalov G, Bartolin Ž, Zeljko Z, Puškar D, Savić I, Radović N, Persec Z, Jurenec F. Radikalna prostatektomija i pozitivni kirurški rubovi. Med Vjesn 2005; 37(1-4): 95-7. (in Croatian)

77. Bottke D, Wiegel T. Adjuvant radiotherapy after radical prostatectomy: indications, results and outcome. Urol Int 2007; 78: 193-7.

78. Porres D, Pfister D, Brehmer B, Heidenreich A. Organbegrenztes Prostatakarzinom mit positivem Resektionsrand. Urologe 2012; 51: 1246-52. (in German)

79. Bolla M, van Poppel H, Collete L *et al*. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). Lancet 2005; 366: 572-8.

80. Baumunk D, Scostak M. Therapie des lokalisierten Prostatakarzinoms mit hochintensivem fokussiertem Ultraschall. Urologe 2015; 54: 183-90. (in German)

81. Witzsch UKF, Becht E. Kryoablation des Prostatakarzinoms. Urologe 2015; 54: 191-201. (in German)

82. Seidenfeld J, Samson DJ, Hasselblad V *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med 2000; 132: 566-77.

83. Iversen P, Tyrell CJ, Kaisary AV *et al*. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology 1998; 51: 389-96.

84. Prostate Cancer Trialists Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet 2000; 355: 1491-8.

85. Tyrrell CJ, Altwein JE, Klippel F, Jurincic-Winkler C *et al*.: for the International Prostate Cancer Study Group. Comparison of an LH-RH analogue (goeserelin acetate, Zoladex) with combined androgen blockade in advanced prostate cancer: final survival results of an international multicentre randomized trial. Eur Urol 2000; 37: 205-11.

86. Loblaw DA, Virgo KS, Nam R *et al*. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007; 25: 1596-605.

87. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. Cancer Res 1990; 50: 2275-82.

88. Hussain M, Tangen CM, Higano C *et al*. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer – data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006; 24: 3984-90.

89. Mottet N, Bellmunt J, Bolla M *et al*. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing and castration-resistant prostate cancer. Eur Urol 2011; 59: 572-83.

90. Moul JW, Wu H, Sun L *et al*. Early *versus* delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004; 171: 1141-7.

91. Seiler R, Studer UE, Tschan K *et al*. Removal of limited nodal disease in patients undergoing radical prostatectomy: long-term results confirm a chance for cure. J Urol 2014; 191: 1280-5.

92. Cookson MS, Aus G, Burnett AL *et al*. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for localized prostate cancer update panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007; 177: 540-5.

93. Salminen E, Hogg A, Binns D, Frydenberg M, Hicks R. Investigations with FDG-PET scanning in prostate cancer show limited value for clinical practice. Acta Oncol 2002; 41(5): 425-9.

94. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281(17): 1591-7.

95. Merseburger AS, Kuczyk MA, Wolff JM. Pathophysiologie und Androgendeprivationstherapie des kastrationsresistenten Prostatakarzinoms. Urologe 2013; 52: 219-25. (in German)

96. Fizazi K, De Bono J, Haqq M *et al*. Final overall survival(s) analysis of COU-AA-301, a phase 3 study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) pretreated with docetaxel. Eur J Cancer 2011; 47(Suppl):2.

97. Solarić M, Šobat H, Kaučić H *et al*. Sistemska terapija raka prostate. Med Vjesn 2009; 41(1-2): 59-67. (in Croatian)

98. ESMO. Prostate cancer: ESMO Clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2007; 18(Suppl): 36-7.

99. Tannock IF, de Wit R, Berry WR *et al*. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-12.

100. Petrylak DP, Tangen CM, Hussain MH *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 361: 1513-20.

101. Saad F, Gleason DM, Murray R *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002; 94: 1458-68.

102. Rolfes N, Lümmen G. Behandlung von symptomatischen Knochenmetastasen bei urologischen Tumoren. Urologe 2014; 53: 832-9. (in German)

103. Zimmer A, Greul F, Meißner W. Schmerztherapie in der Urologie. Urologe 2013; 52: 585-97. (in German)

104. Lipton A, Fizazi K, Stopeck A *et al*. Superiority of denosumab to zoledronic acid, for prevention of skeletal-related events: a combined analysis of pivotal randomized phase 3 trials. Eur J Cancer 2012; 48: 3082-92.

SAŽETAK

SMJERNICE ZA DIJAGNOZU, ZDRAVSTVENIM STANJEM UVJETOVANU KVALITETU ŽIVOTA I TERAPIJU KARCINOMA PROSTATE – PROTURJEČJA UROLOŠKE ONKOLOGIJE

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Za rano otkrivanje karcinoma prostate danas se preporuča provesti digitorektalnu palpaciju te pratiti povišenje vrijednosti antigena specifičnog za prostatu (PSA). Transrektalna ultrasonografija (TRUS) zajedno s ultrazvučno vođenim biopsijama mogla bi postati najprihvatljivija tehnika utvrđivanja stadija za rano otkrivene karcinome prostate. Kako bi se postigla ranija dijagnoza potrebno je bolje definirati granične vrijednosti za PSA s jasno iskazanom graničnom vrijednosti za slobodni PSA. Tome bi se moglo pridodati i korištenje nomograma te u suspektnim slučajevima ponovljenih biopsija, TRUS-a, koštanih skeniranja i novih slikovnih tehnika u dijagnostici. Terapija s odgodom u kojoj se koriste metode aktivne opservacije i spremnosti na započinjanje terapije čim se pojave znaci brze progresije bolesti mogla bi stoga biti alternativa aktivnoj terapiji u bolesnika s lokaliziranim karcinomom prostate niskoga rizika, očekivanoga životnog vijeka deset godina ili manje. Prospektivna nasumična istraživanja pokazala su da je radikalna prostatektomija učinkovitija nego praćenje i čekanje u pogledu doprinosa preživljavanju kod bolesnika oboljelih od karcinoma. Neoadjuvantna hormonska terapija nema značajan utjecaj na cjelokupno preživljenje, kao ni na preživljenje bez progresije bolesti. U Europi je fokus postavljen na biokemijski relaps bolesti nakon kurativnoga liječenja (poštedna radikalna prostatektomija i/ili radioterapija kod bolesnika niskoga, umjerenoga i visokog rizika sa 72-78 Gy). Adjuvantna androgena deprivacija je terapija izbora kod metastatskoga oblika bolesti, kod bolesnika koje nije moguće izliječiti. Identifikacija unutarstanične androgene sinteze koju provode stanice karcinoma prostate dovela je do identifikacije novih ciljeva te do nekoliko novih strategija i lijekova treće generacije: inhibitora androgene sinteze, potentnijih antagonista androgenih receptora. Karcinom prostate rezistentan na kastraciju ostaje ovisan o androgenima i signalizaciji putem androgenih receptora. Kemoterapija docetakselom u liječenju refraktornog karcinoma prostate postiže značajnije smanjenje boli, bolji odgovor PSA i bolju kvalitetu života u usporedbi s jednostavnim postupcima liječenja boli i komplikacija. Ovaj rad daje pregled ključnih obilježja pojedinih bolesti te načina njihovog liječenja.

Ključne riječi: **karcinom prostate, liječenje, operacijski postupak, kastracija, hormonska terapija, kemoterapija, radioterapija, kvaliteta života**