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Prostate Cancer

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Prostate Cancer

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Compliance rules:

- Guideline creation rules
- Conflict of interests

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1 Definition and Basic Information

Prostate cancer is by far the most frequent cancer in males [1]. More than 98% are classified as adenocarcinomas. Other rare malignancies are neuroendocrine tumors, urothelial cancer, squamous-cell carcinomas, lymphomas, etc. For a more detailed guideline we refer to the current version of the S3 Guideline on Early Recognition, Diagnosis and Therapy of the Various Stages of Prostate Cancer [2].

1.1 Epidemiology

Approx. 65,000 new cases are diagnosed in Germany each year. Cancer of the prostatic gland accounts for 26% of all cancerous diseases in males. The median age is 69 years. The incidence rate has increased continually since 1980. Age-standardized mortality has decreased by 20% in the same time interval [1].

1.2 Risk Factors

Only relatively few, widely accepted risk factors have been identified [3]. In Germany, a positive family history is registered in 16-19% of all patients [4]. Risk factors are summarized in Table 1.

Table 1: Risk Factors for the Development of Prostate Cancer

Risk Factor	Comment
Increasing age	
Ethnicity	Afro-American descent
Positive family history	• One brother with prostate cancer (RR[1] 2.9 – 3.4) • Father with prostate cancer (RR 2.1 – 2.2) • ≥ 2 afflicted first-degree relatives (RR 3.5 – 5.1) • Afflicted second-degree relatives (RR 1.7)
Hereditary syndromes	BRCA carriers
Chronic prostatitis	Sexually transmitted diseases and prostatitis (RR 1.6)

Legend:
1 RR – Relative risk

Men with Klinefelter syndrome have a significantly lower risk of developing prostate cancer, see Guideline for Klinefelter Syndrome and Cancer. It is unclear whether an early-onset testosterone substitution increases the cancer risk in these men.

2 Prevention and Early Detection

2.1 Prevention

2.1.1 Lifestyle and Nutrition

Evidence for the effective prevention of prostate cancer through lifestyle or dietary changes is weak [5]. A prospective randomized study on selenium and vitamin E did not reveal any positive effects, see Prostate Cancer Study Results. An excessive uptake of high-dosed vitamin products might increase the risk for more aggressive forms of prostate cancer.

2.1.2 Drugs

The inhibitors of 5-alpha-reductase, i.e. finasteride and dutasteride, reduce the risk for prostate cancer by 20-25%, see Prostate Cancer Study Results. Concomitantly the percentage of carcinomas displaying a high Gleason score increases [6]. A significant effect of preventive drugs on cancer-specific or overall survival has not been shown. Predominant adverse effects of 5-alpha-reductase inhibitors are erectile dysfunction, decrease in libido, and gynecomastia.

2.2 Screening

The long time course from the initial evidence of histological alterations in the prostate to the appearance of clinical symptoms gives the chance of an early recognition. Health insurance companies in Germany only cover an annual digital rectal examination (DRE) after the age of 45 years.

The current S3 Guideline recommends that all men who are at least 40 years old and who have a prospective life expectancy of more than ten years should be informed about the benefits and limitations of PSA testing [2].

2.2.1 Digital Rectal Examination (DRE)

The digital rectal examination has a high specificity in detecting prostate cancer, but a low sensitivity [2, 7]. Regular DRE does not decrease prostate cancer specific mortality.

2.2.2 PSA

The quantitative determination of the prostate–specific antigen (PSA) is a suitable parameter for the follow-up of patients with prostate cancer. For more than 20 years PSA has also been used to screen asymptomatic males. The sensitivity and specificity of this parameter depends on the definition of the threshold value. The sensitivity in detecting prostate cancer is high at a limit of 4ng/ml. Specificity decreases with increasing age.

Prospective randomized studies evaluated PSA screening versus observation, see Prostate Cancer Study Results. The results can be summarized as follows [8]:

- The rate of prostate cancer was significantly higher in the screening as compared with the observation group.
- The results relating to prostate-cancer-specific mortality are inconsistent.
- Screening has no influence on overall survival.

- Limitations of PSA screening are the high rate of false-positive results, overdiagnosis and stressful situations associated with the diagnostic procedures.

The PSA test methods have not been standardized. Results depend on the respective test system used. Calculation of the ratio of free and total PSA can increase specificity if the total PSA values are between 4 and 10 ng/ml, however, this procedure has not been validated prospectively.

The routine use of other immunological and molecular methods in serum or urine is currently not recommended outside of clinical studies. The same applies to imaging methods for screening purposes.

3 Clinical Presentation

Early symptoms do not exist. In patients with local disease the clinical symptoms do not differ from those of benign prostatic hypertrophy. Signs of the disease are:

Local symptoms (decreasing incidences)

- Urinary dysfunction
  - Prolonged voiding with weak urinary stream
  - Incontinence
  - Pollakisuria
  - Nycturia
  - Dysuria
  - Alguria
- Erectile dysfunction
- Perineal pressure
- Hematuria
- Hematospermia

General symptoms in case of advanced disease

- Unintentional weight loss
- Weakness
- Anemia
- Paraneoplastic syndromes, e.g. tendency to venous thromboembolism, see also Guideline: VTE in Cancer Patients

Other symptoms in patients with advanced disease are bone pain or pathologic fractures in case of skeletal metastases, lymphatic edemas due to extensive iliac lymph-node metastases, neurological symptoms due to cerebral metastases or spinal cord compression, coughing and dyspnea in case of pulmonary and/or pleural metastases, jaundice and hepatic insufficiency due to advanced liver metastases.

4 Diagnosis

4.1 Primary Diagnostics

The first step consists in the confirmation of the suspected diagnosis [2, 7], see Table 2. Diagnostic procedures are not recommended if the result is not relevant to therapy based on the patient's decision or severe comorbidity.

Table 2: Diagnostics in Case of Suspected Prostate Cancer

Test	Comments
Digital rectal examination (DRE)	
Quantitative PSA determination	Consider confounding urinary retention, acute prostatitis, previous manipulations of the prostatic gland (e.g. DRE, catheterism, rectoscopy / colonoscopy)
Biopsy	If the following conditions are fulfilled: • Suspicious lesion at DRE and/or • Verified PSA value ≥ 4 ng/ml or • PSA rise ≥ 0.75 ng/ml/year

Ultrasound-guided biopsy is considered standard of care. As a rule, 10 to 12 core biopsies should be taken. Prophylactic antibiotics are given either PO oder IV. Quality-assured pathohistological processing and reporting are the basis for the ensuing treatment recommendations [2].

4.2 Classification and Further Diagnostics (Staging)

Classification of the extent of the primary tumor and the metastatic spread is based on TNM criteria (Table 3). Classification of prognostically relevant histological parameters is performed according to the Gleason score [9].

Table 3: Classification of Tumor Stages (clinical, TNM, UICC)

Clinical Stage	UICC Stadium	Primary Tumor	Lymph nodes	Distant Metastases	Grading
Local disease	I II	T1a T1a T1b – 2c	N0 N0 N0	M0 M0 M0	G1 G2 – 4 every G
Locally advanced	III IV	T3a T3b T4	N0 N0 N0	M0 M0 M0	every G every G every G
Metastatic disease[1]	IV	every T	N1 every N	M0 M1a-1c	every G every G

Legend:
[1] This stage is also referred to as advanced.

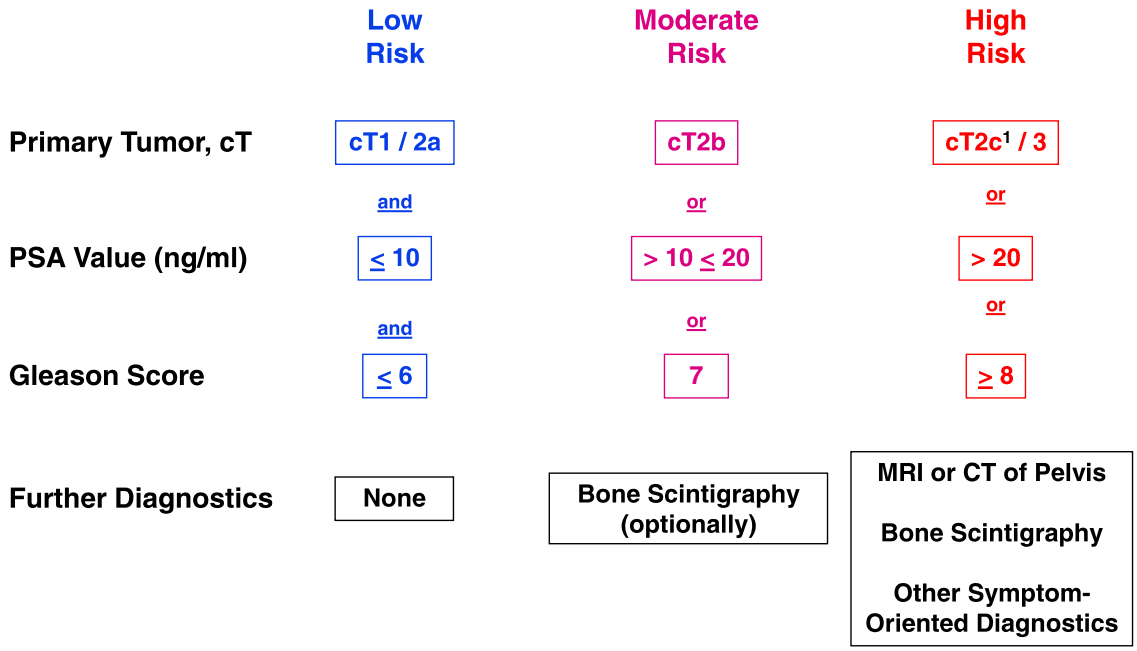
The Gleason score is a histological measure for the malignancy of the tumor tissue. It distinguishes 5 differentiation grades. Highly differentiated tissue is scored as 1, dedifferentiated tissue as 5. The Gleason score consists of two numbers:

1st number Most frequent grade of differentiation found in biopsies

2nd number Second-most frequent differentiation grade found in biopsies

An additional allocation to three risk groups is made for the locally defined carcinoma based on Gleason score, T category and PSA value, see Figure 1. This allocation also provides the basis for the recommendation of additional imaging diagnostics.

Figure 1: Risk Stratification and Further Diagnostics of Local Disease



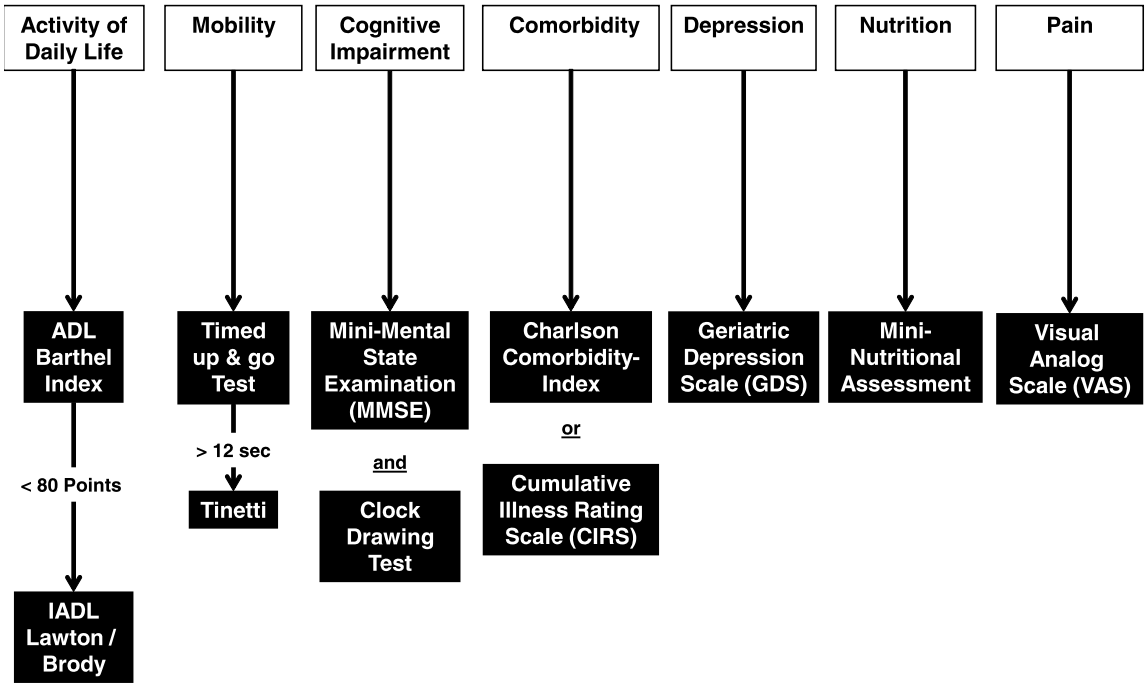
Legend:
[1] Allocation of Stage cT2c is inconsistent. It is assigned either to the intermediate or high risk group [EAU, ESMO]

Positron emission tomography (PET-CT) does not belong to the standard procedures of primary prostate cancer diagnostics.

4.3 Geriatric Assessment

Use of instruments for geriatric assessment is recommended for a more objective evaluation of general health condition, see Figure 2 and the Onkopedia HemOnc Database [10]. Particularly well suited are tests designed to assess autonomy, mobility and comorbidity. The indication for further tests depends on the clinical presentation and planned treatment.

Figure 2: Tests for Geriatric Assessment

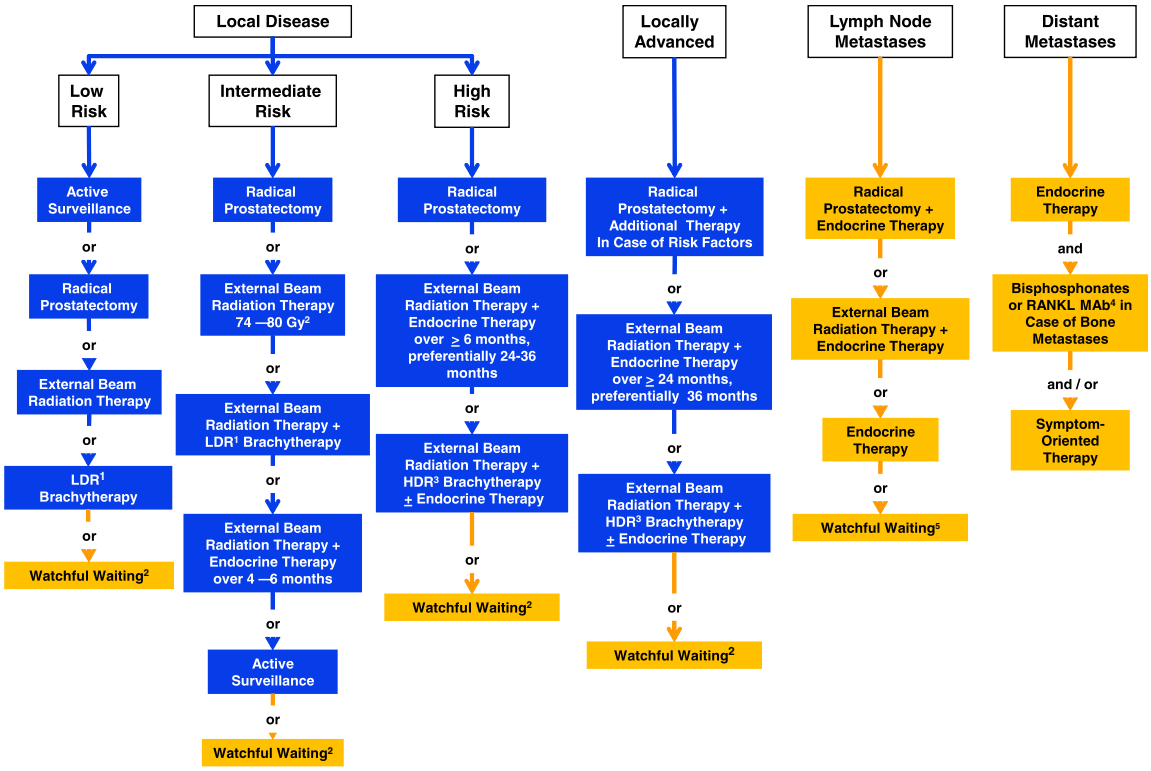


Legend:
[1]ADL – Activity of Daily Living;
[2]IADL – Instrumental Activities of Daily Living;
[3]GDS – Geriatric Depression Scale;
[4]VAS – Visual Analogue Scale

5 Therapy

Therapy recommendations are based on stage of the disease. At present, different therapeutic options are considered equivalent at all stages of prostate cancer [2, 7]. It is the task of multidisciplinary tumor boards to recommend the most appropriate treatment. Patients need access to full and comprehensive information as the basis for his autonomous decision. Figure 3 shows an algorithm for first-line therapy. Whenever possible, patients should be treated in the scope of clinical trials or registers.

Figure 3: Algorithm for First Line Therapy



Legend:

Curative therapy; *Palliative therapy;*

[1] LDR – Low Dose Rate;

[2] Gy – Gray;

[3] HDR – High Dose Rate;

[4] RANKL MAb – Antibodies directed against the RANK ligand;

[5] in asymptomatic patients

5.1 Stage-Dependent Therapy

5.1.1 Local Disease – Low Risk

Patients in the low risk group have a very high chance of cure by means of surgery or radiation, however, they also have the risk of overtreatment. Options are:

- Active Surveillance
- Radical Prostatectomy
- External Beam Radiation Therapy of the prostate gland with 74 – 80Gy
- LDR brachytherapy with ^{125}iodine in a dose of 145Gy
- Watchful Waiting – palliative therapeutic approach

Follow-up studies show prostate-cancer specific survival rates of 90 to 97 percent after ten years for these patients, irrespective of the specific therapeutic approach.

5.1.2 Local Disease – Intermediate Risk

The group of intermediate risk patients is heterogeneous. Patients in the intermediate risk group have a high chance of cure by means of surgery or radiation, however, they also have the risk of overtreatment. Options are:

- Radical Prostatectomy

- External Beam Radiation Therapy of the prostate gland
  - with 74–80Gy or
  - in combination with LDR brachytherapy or
  - in combination with endocrine Therapy over 4–6 months
- Active Surveillance, applying the extended criteria for patient selection (see chapter 5. 2. 1.)
- Watchful Waiting – palliative therapeutic approach

5.1.3 Local Disease – High Risk

An immediate initiation of curative therapy is recommended because of the high progression risk. An alternative in case of significant comorbidity consists in a palliative, symptom-oriented approach. Options are:

- Radical Prostatectomy
- External Beam Radiation Therapy of the prostate gland
  - in combination with endocrine therapy over a period of at least 6 months, preferentially 24 – 36 months, or
  - in combination with HDR Brachytherapy plus, if necessary, endocrine therapy
- Watchful Waiting – palliative therapeutic approach

5.1.4 Locally Advanced

In patients with locally advanced prostate cancer, local treatment and, if necessary, endocrine therapy are combined. Options are:

- Radical Prostatectomy
  - plus postoperative radiation in case of positive resection margins
  - salvage radiation in case of postoperative PSA value above zero
  - plus endocrine therapy, if necessary
- External Beam Radiation Therapy of the prostate gland
  - in combination with endocrine therapy over a period of 3 years or
  - in combination with HDR brachytherapy and, if necessary, endocrine therapy
- Watchful Waiting in asymptomatic patients

5.1.5 Lymph-Node Metastases

Therapy is palliative in the great majority of patients with a positive lymph nodes. However, depending on the individual risk factors and the response to therapy the rate of prostate-cancer-specific survival after ten years may be up to 80 percent. Options are:

- Radical Prostatectomy plus Endocrine Therapy over a period of at least 2 years
- External Beam Radiation Therapy plus adjuvant Endocrine Therapy over a period of 3 years
- Endocrine Therapy without local first-line therapy
- Watchful Waiting in asymptomatic patients

5.1.6 Distant Metastases – Hormone-Sensitive

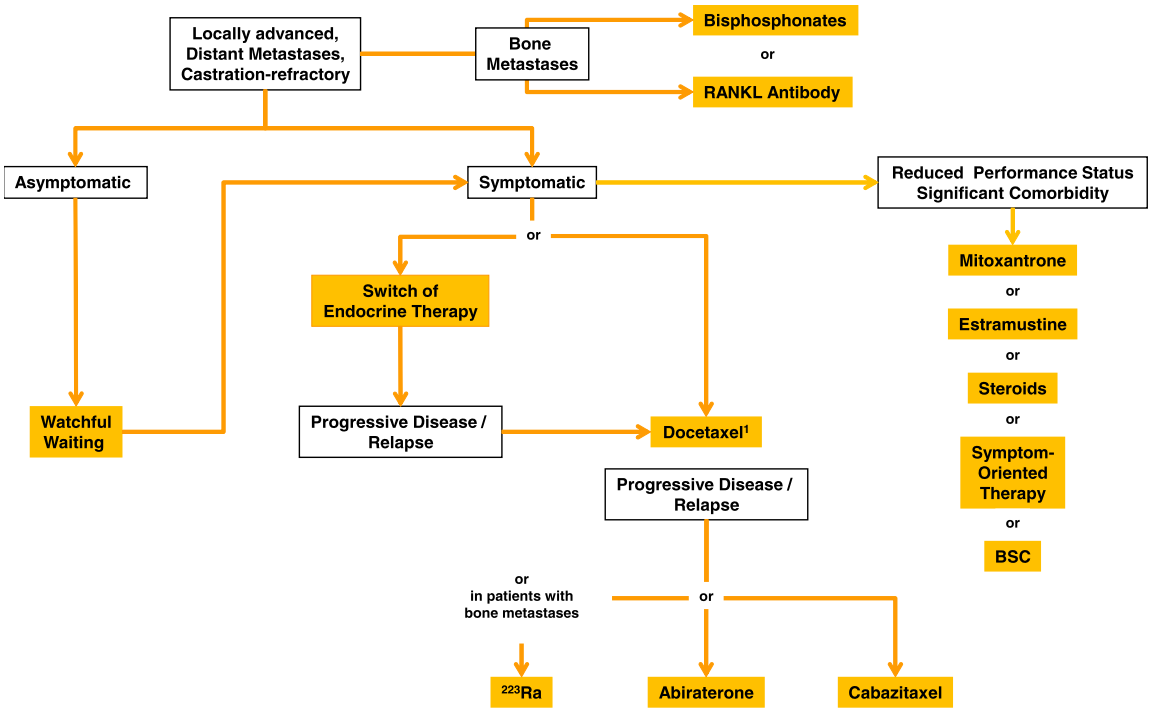
Therapy is palliative. Systemic therapy is the treatment of choice, if necessary, combined with local therapy. Options are:

- Endocrine Therapy
- Bisphosphonates or RANKL antibodies in patients with bone metastases
- Symptom–oriented, palliative therapy
- Watchful Waiting in asymptomatic patients

5.1.7 Castration-Refractory Prostate Cancer

Therapy is palliative. It depends of the general health condition, pretreatment, symptoms, specific comorbidity and the patient's choice, see Figure 4.

Figure 4: Algorithm for the Therapy of Castration-Refractory Prostate Cancer



Legend:
[1]Docetaxel: Randomized trials also included asymptomatic patients with increased PSA value in three consecutive measurements;

Options are

- Switch of Endocrine Therapy
- Chemotherapy
- Bisphosphonates or RANKL antibodies in patients with bone metastases
- Symptom–oriented therapy
- Watchful Waiting in asymptomatic patients

5.1.8 Relapse

The great majority of relapses after curative therapy is diagnosed by an increase of the PSA value. Salvage prostatectomy or salvage radiotherapy are curative approaches. Differential

therapy depends on the type of first line treatment. The following situations have to be distinguished:

Biochemical progression / local relapse after radical prostatectomy

Relapse is defined as a PSA value > 0.2ng/ml in a minimum of two consecutive measurements. Options are

- Salvage radiotherapy
- Watchful waiting in patients with
  - PSA doubling time > 10 months
  - Interval between surgery and relapse > 2 years
  - Primary Gleason score < 8

Local relapse after radiotherapy

Relapse is defined as a PSA value > 2ng/ml above the post-radiotherapeutic nadir in a minimum of two consecutive measurements. Options are

- Prostatectomy
- Endocrine therapy
- Watchful waiting: Criteria may be adapted to the local relapse after radical prostatectomy

Metastatic Disease

Therapeutic options correspond to those of first line therapy in patients with lymph-node or distant metastases.

5.2 Therapeutic Options

5.2.1 Active Surveillance

The concept was developed in order to prevent overtreatment in low risk patients – without foregoing the chance of cure. Selection criteria have been taken from the published study with the longest follow-up [11], supplemented with quantitative histological parameters, see Table 4.

Table 4: Criteria for Selection, Monitoring and Intervention of Active Surveillance Patients [2, 11]

Parameters	Inclusion Criteria - all mandatory -	Follow-Up	Intervention Criteria -one criterion mandatory -
PSA	≤ 10 ng / ml	Every 3 months over 2 years, then every 6 months	PSA DT[2] < 3 years
Gleason-score	≤ 6	Biopsy after 6 – 12 months then every 3 – 4 years	> 6
cT stage	1 - 2a		
Histology	Malignant tissue in ≤ 2 biopsies Malignant tissue / biopsy ≤ 50 %		Malignant tissue in > 2 biopsies Malignant tissue / biopsy > 50 %
Symptoms			Symptomatic progressive disease

Legend:
[1] extended initial criteria;
[2] PSA DT – PSA doubling time

Other studies applied somewhat extended inclusion criteria (PSA ≤ 15, Gleason –Score 7, cT2) plus other parameters such as prognostic scores, age, comorbidity and quality of life [7].

5.2.2 Surgery

Surgery is performed with curative intent in patients with local disease. Radical prostatectomy is the standard procedure. Its oncological objective is the complete removal of the prostate gland with tumor-free resection margins. Perioperative mortality is below 2% [7]. Long-term side effects consist predominantly in obstructive urinary dysfunction, incontinence, and erectile dysfunction.

5.2.2.1 Radical Prostatectomy

Surgical methods and/or approaches are:

- retropubic
- perineal
- laparoscopic (intraperitoneal or extraperitoneal)
- Robot-assisted (intraperitoneal or extraperitoneal)

Non-comparative studies show similar oncological long-term results for the different surgical techniques. The decision in favor of a certain surgical method depends largely on the experience of the respective center, the contraindications and the preferences of the patient.

Nerve-preserving surgical methods can reduce the risk of erectile dysfunction. In individual cases the application of monolateral or bilateral nerve-preserving surgical methods must be weighed against the risk of R1 resection [7].

5.2.2.2 Lymphadenectomy

Lymphadenectomy allows a more precise assessment of the stage of the disease, based on the pathohistological examination of the excised lymph nodes. Lymphadenectomy does not improve the prognosis of the patients.

If lymphadenectomy is carried out, at least 10 lymph nodes should be removed. More extensive lymphadenectomy results in higher rates of positive results. Lymphadenectomy is not recommended in low risk patients. In high risk patients the potential gain of knowledge must be weighed against the postoperative complications, i.e. lymphocele, venous thromboembolism, lymphatic edema [2].

5.2.2.3 Adjuvant Therapy after Radical Prostatectomy

The postoperative PSA reaches baseline values after successful radical prostatectomy. If this cannot be achieved, salvage radiation and, if necessary, additional endocrine therapy is recommended. Postoperative radiotherapy is recommended in patients with positive pathohistological resection margins.

Adjuvant endocrine therapy, if necessary, in combination with external beam radiation therapy may be initiated in patients with positive lymph nodes. An alternative concept is the initiation of endocrine therapy when the PSA value rises.

Adjuvant chemotherapy is not recommended.

5.2.3 Radiotherapy

Radiotherapy is performed with curative intent in patients with local disease. It is an alternative to radical prostatectomy with comparable oncological results [12]. Radiotherapy can be carried out as External Beam Radiation Therapy, as LDR brachytherapy, or as a combination of External Beam Radiation and HDR brachytherapy.

5.2.3.1 External Beam Radiation of the Prostate

The results of External Beam Radiation Therapy are dose-dependent, see Prostate Cancer Study Results. Doses ranging from 74 to 80Gy significantly improve biochemical progression-free survival as compared with doses of 64–70Gy, however, without affecting overall survival. At present, a dose of ≥ 72Gy [2] or ≥ 74Gy and < 80Gy [7] is recommended. External beam radiation therapy is based on three-dimensional radiation planning [2]. The main adverse effects of radiotherapy are due to the radiation exposure of the rectum (altered feces, rectal bleeding). Other adverse effects are erectile dysfunction and a slightly increased risk for secondary neoplasias.

Intensity-modulated radiation therapy (IMRT) might reduce the risk of adverse effects. The advantage of IMRT in the treatment of prostate cancer has not been confirmed in randomized clinical trials.

5.2.3.2 Low-Dose-Rate Brachytherapy (LDR Brachytherapy)

In Germany, low-dose-rate brachytherapy (LDR brachytherapy) uses ^{125}iodine. The implants are applied permanently via perineal route at a dose of 145Gy. Main adverse effects of brachytherapy are functional disorders of the urinary tract and erectile dysfunction. The burden of rectal radiation exposure is lower than it is in external beam radiation therapy, radiation exposure of the urethra is higher.

A peculiarity of LDR brachytherapy is a transient rise of the PSA value, the so-called PSA bounce. It occurs in up to 40% of the patients and does not have any clinical relevance.

5.2.3.3 High-Dose-Rate Brachytherapy (HDR Brachytherapy)

High-dose-rate brachytherapy (HDR brachytherapy) enables a dose-intensified, temporary radiation of the prostate gland by means of a transrectal probe using afterloading technique. It is an option for dose escalation in patients with local disease of intermediate or high risk as well as in cases of locally advanced prostate cancer, see Prostate Cancer Study Results. Results of randomized clinical trials comparing external beam radiation therapy at doses of 74–80Gy with the combination of external beam radiation therapy plus HDR brachytherapy are not available.

5.2.3.4 External Beam Radiation of the Pelvis (Lymphatic Drainage Routes)

Data pertaining to the radiation of pelvic lymph nodes are controversial and do not allow definitive recommendations. The incidence of adverse effects is increased if radiation is applied conventionally, it is significantly lower in case of intensity-modulated radiation.

5.2.3.5 External beam radiation therapy Therapy plus Endocrine Therapy

The combination of external beam radiation therapy (64–70Gy) and endocrine therapy results in a significant improvement of progression-free survival in patients with local disease of intermediate or high risk and in cases of locally advanced prostate cancer. It might also prolong overall time, see Prostate Cancer Study Results. The positive influence of endocrine therapy does not depend on whether it is applied as neoadjuvant therapy, simultaneously to radiotherapy and / or as adjuvant therapy.

Endocrine therapy for 4-6 months is recommended to patients with an intermediate risk, whereas 24-30 months are recommended to high risk patients.

It remains unclear whether an additional endocrine therapy also improves the prognosis of patients treated with the higher radiation doses (74–80Gy) administered today.

5.2.4 Watchful Waiting

According to this concept patients are only treated when the disease has become symptomatic. The intent of therapy is palliative. As yet, the results of two prospective randomized clinical trials comparing watchful waiting vs curative therapy have been published, see Prostate Cancer Study Results. The study with the longest follow-up period [13] showed a significant advantage of overall survival for radical prostatectomy, however, only in patients < 65 years. As chronological age is an inadequate parameter, which does not account for individual comorbidity, it is recommended to rather go by the patient's presumed life expectancy for orientation.

Criteria for deciding in favor of watchful waiting are:

- Low to intermediate risk
- Asymptomatic patients with high risk or locally advanced disease
- Life expectancy < 10 – 15 years
- Patient's choice

5.2.5 Other Local Therapies

Various physical methods are used for locally targeted therapy, especially in combination with minimally invasive surgery. Most popular are cryotherapy and high-intensity focused ultrasound (HIFU) therapy. Controlled comparative studies with long-term observations do not exist. These physical methods are experimental. Their application is not recommended outside clinical trials.

5.2.6 Endocrine Therapy

Prostate cancer cells express androgen receptors. The synthesis of testosterone and its derivatives, receptor binding, and the expression of androgen receptors are targets of an effective pharmacological therapy. Endocrine therapy is highly effective in patients with prostate cancer. It is applied as first-line therapy in patients with metastatic disease, and increasingly in the adjuvant situation subsequent to radiotherapy in curative intent [14] .

5.2.6.1 Orchiectomy

In 1940 und 1941 Niehans and Huggins first published their observations on the hormone dependence of prostate cancer and the effects of orchiectomy. Surgical castration thereupon became the standard treatment of patients suffering from an advanced stage of the disease. Bilateral orchiectomy became established as the oldest method. It eliminates the synthesis of testosterone. The method is inexpensive. Specific disadvantages of orchiectomy are the mental stress and the irreversibility of androgen suppression.

5.2.6.2 GnRH Agonists (Analogues)

GnRH agonists lower testosterone concentrations to castration level within a period of 3–4 weeks. This effect is reversible once administration of the drugs is terminated. Their application proceeds subcutaneously. The adverse effects are the same as those elicited by other forms of androgen suppression. The first application of GnRH analogies induces a short-term rise of the testosterone level and an increase of the PSA value, along with the risk of an initial exacerbation of clinical symptoms (flare phenomenon). This effect can be attenuated by the concomitant administration of antiandrogens in the first weeks of therapy. GnRH agonists are, for example, leuprorelin, goserelin, triptorelin, buserelin and histrelin. GnRH agonists are first-choice drugs in endocrine therapy.

5.2.6.3 GnRH Antagonists (Blockers)

Antagonists of the gonadotropin releasing hormone (GnRH) bind competitively to the receptor in the pituitary gland. The blockade of LH (luteinizing hormone) and FSH (follicle stimulating hormone) release decreases the testosterone concentration to castration level within 1-3 days. Abarelix and degarelix belong to this pharmacological group. The adverse effects are the same as those elicited by other forms of androgen suppression. There is a risk of serious systemic allergic reactions in case of abarelix. Results of long-term observations in randomized clinical trials are not yet available.

5.2.6.4 Antiandrogens: Bicalutamide / Flutamide

The non-steroidal antiandrogens bicalutamide and flutamide are competitive inhibitors of the androgen receptors. They are effective in the therapy of the locally advanced and metastatic prostate cancer. In comparison with LHRH agonists, the long-term effects on progression-free and overall survival have been inconsistent, with a tendency toward unfavorable results using the non-steroidal androgens. The advantage of this substance group lies in the somewhat less cumbering adverse effects on performance status and libido, as compared with LHRH agonists. Hepatotoxicity is a specific adverse effect.

5.2.6.5 Inhibitors of Cytochrome P450 c17 (CYP17)

Cytochrome P450 is a central enzyme in testosterone synthesis. Unspecific (ketoconazole, aminoglutethimide) and specific inhibitors (abiraterone) block the physiological androgen synthesis in the testes and adrenal glands, but also the autonomous production by the cancer cells. Abiraterone was first tested in patients with castration-refractory prostate cancer who progressed under or after palliative chemotherapy with docetaxel. It led to a significant prolongation of overall survival time, see Prostate Cancer Study Results [15]. Specific adverse effects result from the mineralocorticoid action i.e. edemas, hypertension and hypokalemia.

5.2.6.6 New Androgen Receptor (AR) – Antagonists

One of the pathophysiological mechanisms of castration-refractory prostate cancer is the reactivation of the androgen receptor (AR) in tumor cells, despite maximal androgen blockade. Highly selective and specific AR antagonists provide new therapeutic options. A recently published phase-III-study on Enzalutamide (MDV3100) showed a significant improvement in overall survival, see Prostate Cancer Study Results.

5.2.6.7 Cyproterone Acetate

Cyproterone acetate is steroidal antiandrogen. It blocks both the androgen receptors and the release of GnRH. Cyproterone has been used for over 40 years in the therapy of the metastasized prostate cancer. Still there are only few data based on long-term trials. Progression-free survival is somewhat shorter compared to LHRH agonists, in combination it prevents the flare phenomenon. Hepatotoxicity is a specific adverse effect.

5.2.6.8 Maximal Androgen Blockade

The combination of androgen suppression (androgen deprivation) and antiandrogens is referred to as maximal (or complete or total) androgen blockade. Several clinical studies compared the maximal androgen blockade with androgen suppression (orchiectomy or LHRH agonists) in patients with locally defined and/or locally advanced prostate cancer. The results are inconsistent, see Prostate Cancer Study Results. Metaanalyses revealed a slight, however, not statistically significant advantage of the combination therapy. It is associated with a higher rate of adverse effects [16].

5.2.6.9 Intermittent Therapy

The concept of intermittent therapy was introduced to reduce the effects of long-term androgen suppression, and it was tested especially in the scope of phase-II studies. A recently presented, large phase-III study showed a significant advantage in overall survival for the continuous therapy in patients with minimal tumor burden, and no significant difference in patients with extensive disease. Patients under intermittent therapy had less adverse effects and a better quality of life, see Prostate Cancer Study Results.

5.2.6.10 Antiandrogen Deprival

Cessation of a long-term antiandrogen therapy results in 15–30% of the patients in a decline of the PSA value. This effect may last over several months, however, it is usually only of short duration. The clinical remission rates are under 5%, see Prostate Cancer Study Results.

5.2.6.11 Management of Adverse Effects of Androgen Suppression

The adverse effects of long-term androgen suppression may be considerable and must be weighed against the oncological benefits of this therapy in the individual case. Frequent side effects are hot flushes (55 – 80 %), gynecomastia and chest pain, loss of libido, erectile dysfunction, reduced physical fitness, fatigue, metabolic alterations including an increase of body fat and a decrease of glucose tolerance, osteoporosis and anemia. Patients with preexisting cardiac risk factors (coronary heart disease, status post myocardial infarction) may have a

higher mortality under antiandrogen therapy. Recommendations for the specific management of symptomatic adverse effects of androgen suppression are summarized in Table 5.

Table 5: Management of Adverse Effects of Long-Term Androgen Suppression

Adverse Effects	Risk factors	Therapy Recommendation
Anemia	• Renal insuffiency • Other hematological diseases, e.g. MDS • Metastatic bone marrow involvement	Symptom-oriented • Transfusions • Optionally erythropoietin[1] • Optionally intravenous iron
Erectile dysfunction	• Preexisting erectile dysfunction	Phosphodiesterase-5-inhibitors • Sildenafil • Tadalafil • Vardenafil
Gynecomastia		• Prophylactic radiation[1] • Tamoxifen[1, 2] • Mastectomy
Hot flushes		• Optionally cyproterone acetate • Optionally antidepressants (venlafaxine) • Optionally clonidine
Cardiovascular diseases	• Coronary heart disease • Myocardial infarction • Severe cardiac insufficiency	• Physical activity • Weight reduction, if possible • Diet change, if possible • Stop smoking
Loss of libido		No specific therapy
Metabolic syndrome	• Diabetes mellitus • Lipid metabolic disorder • Obesity	• Physical activity • Weight reduction, if possible • Diet change, if possible
Osteoporosis	• Low physical activity • Absent exposure to sunlight • Vitamin D deficiency	• Physical activity • Calcium 1,000mg + vitamin D 400 I.U. • Zoledronate[1] • Denosumab[1]

Legend:
[1] see Prostate Cancer Study Results;
[2] Off-label use

5.2.7 Chemotherapy

Chemotherapy is indicated in hormone-refractory prostate cancer, see Figure 3. A decline of the PSA values by at least 50 percent can be achieved with various substances in up to 50% of the patients. The objective remission rates of measurable tumor manifestations lie below 20 percent, see Prostate Cancer Study Results.

In the randomized studies chemotherapy was applied together with low-dosed steroids (prednisolone or prednisone 5mg 2x/day or 10mg 1x/day). They are now the standard of care when systemic therapy is applied, see Prostate Cancer System Therapy.

5.2.7.1 First-Line Therapy

Standard therapy consists of the administration of docetaxel with prednisone or prednisolone every three weeks [17]. Treatment is recommended in symptomatic patients. The rise of PSA

values, confirmed in two consecutive measurements with an interval of at least one week, may also lead to the initiation of chemotherapy. Primary objective is the relief of cancer-related symptoms. Further objectives are prolongation of progression-free survival, delay of cancer-related symptoms, and prolongation of overall survival.

5.2.7.2 Second-Line Therapy after Docetaxel

Recently the second-line options have been distinctly extended, asking for criteria in differential therapy, see Figure 3. Options are

- Abiraterone
- Cabazitaxel
- ^{223}Ra
- Other chemotherapy: docetaxel retreatment, estramustine, mitoxantrone
- Best supportive care including symptom-oriented therapy and steroids

Abiraterone, cabazitaxel and ^{223}Ra each lead to a significant prolongation of median overall survival by 2.4 to 3.9 months. Results of direct comparisons among these new substances are not available.

Sequential therapy is recommendable to the majority of patients with docetaxel-refractory disease. This may start abiraterone due to its more favorable profile of adverse effects. In case of contraindications or relevant comorbidity (see Chapter 5.2.6.5.), abiraterone refractoriness, relapse, or limiting adverse effects, treatment with cabazitaxel is recommended. For relevant comorbidity and contraindications in cabazitaxel therapy see Chapter 5.2.7.7. In patients with bone metastases only and no reduction of bone marrow reserve, ^{223}Ra can be given prior to abiraterone, but also prior to cabazitaxel.

5.2.7.3 Treatment Duration

Treatment duration depends on response and tolerability. Therapy with docetaxel, cabazitaxel or mitoxantrone was each conducted with a maximum of 10 cycles in the pivotal studies.

Patients with a decrease in the PSA value by at least 50 percent under docetaxel therapy have a significantly longer survival time as compared with patients displaying either a slight response or none at all (20.8 versus 11.4 months).

The benefit of chemotherapy for patients in a reduced general health condition, i.e. ECOG > 2, has not been demonstrated.

5.2.7.4 Docetaxel

Docetaxel belongs to the taxanes. In a randomized clinical study on first-line therapy the three-weekly administration of docetaxel led to prolongation of overall survival time by 2.9 months compared to mitoxantrone, see Prostate Cancer Study Results. The remission rate was 12%, the PSA value dropped in 45% of the patients. Quality of life was significantly improved. Serious adverse effects (grade 3/4), which were reported in more than 20% of the patients in the pivotal studies, were: alopecia (65%), fatigue (53%), nausea/vomiting (42%), neutropenia (32%), diarrhea (32%), sensory neuropathy (30%), onychodystrophy (30%). The rate of treatment-associated mortality was at 0.3%.

An alternative is the weekly application of docetaxel. It is of equal effectivity in lowering the PSA value, however, it does not significantly prolong overall survival compared to mitoxantrone. The adverse effects are similar to those of three-weekly administrations, however, the risk of grade 3/4 neutropenia is very low (2%).

In analogy to the pivotal studies treatment is recommended for up to 10 cycles. Continuation of therapy beyond progression is not recommended. Docetaxel retreatment is possible in relapse after termination of first-line therapy, unless limiting adverse effects have appeared. It can induce a second decline of the PSA value in up to 50 percent of the patients. The time interval between first-line therapy and retreatment should be at least 3 months.

5.2.7.5 Mitoxantrone

Mitoxantrone belongs to the group of anthracyclines and anthracenes. In a randomized clinical trial on first-line therapy, mitoxantrone induced a significant improvement of the disease-related symptoms, prolongation of relapse-free survival by 1.4 months as compared to the control group, but not to a prolongation of overall survival, see Prostate Cancer Study Results. In more recent studies, the median survival times were significantly shorter with mitoxantrone as compared to docetaxel administered in first-line or cabazitaxel administered in second-line therapy. Serious adverse effects (grade 3/4), which appeared in more than 20% of the patients in the randomized first-line therapy randomized trials, were: nausea/vomiting (38%), fatigue (35%) and a reduced left-ventricular ejection fraction (22%). The rates of therapy-associated fatalities in first-line and second-line therapy were at 0-0.3 % and 2%, respectively.

5.2.7.6 Estramustine

Estramustine is a product that combines nitrogen mustard and estradiol. It has hormonal and cytostatic effects. Administered as monotherapy, estramustine lowers the PSA value in up to 30% of the patients, without exerting a significant influence on progression-free or total survival. Stressful adverse effects are the consequence of the hormone therapy, entailing an increased propensity for venous thromboembolism, cardiovascular complications, peripheral edemas, gynecomastia, as well as nausea and vomiting. In combination chemotherapy estramustine enhances the response rates and in the metaanalysis also prolongs the time to PSA progression and overall survival, see Prostate Cancer Study Results. Estramustine is administered orally.

5.2.7.7 Cabazitaxel

Cabazitaxel belongs to the taxanes. Cabazitaxel was tested as second-line therapy after docetaxel in a randomized clinical trial versus mitoxantrone in patients who were in a good or somewhat reduced general health condition (ECOG≤2), see Prostate Cancer Study Results [18]. The remission rate (RECIST) and the PSA response rate were at 14.4 % and 39.2%, respectively. The median survival time was extended by 2.4 months. Serious adverse effects (grade 3/4), which occurred in more than 5% of the patients in the pivotal study, were: neutropenia (82%), anemia (11%) and diarrhea (6%). Therapy-associated mortality was at 5%, most frequently due to infectious complications in neutropenia and to cardiac complications.

5.2.7.8 Other Substances

At least a 50% decline of PSA values is also achievable under chemotherapy with 5-fluorouracil (20%), platinum derivates (25%), Vinca alkaloids (10%) or anthracyclines (50%). Data indicat-

ing a significant improvement of clinical symptoms or a prolongation of overall survival are not available.

5.2.8 Immunotherapy

Recent studies demonstrate the efficacy of therapeutic approaches which stimulate the autologous immune system in advanced-stage prostate cancer patients. Immunotherapy for prostate cancer is not approved in Germany, Austria and Switzerland.

5.2.8.1 Sipuleucel-T

This vaccine relies on the *ex-vivo* activation of autologous leukocytes obtained by leukapheresis with the recombinant fusion protein PAP-GMCSF (prostatic acid phosphatase and granulocyte macrophage colony-stimulating factor), see Prostate Cancer Study Results. Retransfusion of the activated leukocytes is performed three times in intervals of 2 weeks. The survival time of asymptomatic patients with metastatic castration-refractory prostate cancer was prolonged by 4.1 months. Sipuleucel-T did not have any influence on progression-free survival. Predominant adverse effects grade 3/4 consisted were chills (1.2%) and headache (0.3%).

5.2.8.2 PROSTVAC-VF

PROSTVAC-VF consists of two recombinant viral vectors containing PSA transgenes and the three co-stimulatory molecules B7.1, ICAM and LFA-3. The subcutaneous application of the product together with GM-CSF is performed seven times in intervals of 2 to 4 weeks. In a small study randomized study on oligosymptomatic patients with metastatic castration-refractory prostate cancer, the overall survival was significantly prolonged. PROSTVAC-VF did not exert any influence on progression-free survival. Results of larger clinical studies are still awaited.

5.2.9 Bone Metastases

Local and systemic treatment is available for patients with bone metastases [2, 7, 19]. Radiation is the treatment of choice in case of severe local pain or risk of fractures. Surgery is an additional option in patients with pathological fractures or unstable vertebral body fractures. Direct decompressive surgery followed by postoperative radiotherapie is recommended in patients with spinal cord compression caused by metastatic cancer. Systemic measures consist of causal therapy and administration of bisphosphonates or the RANKL antibody denosumab.

Denosumab has a higher efficacy than zoledronate. The difference is statistically significant, but low when expressed in absolute figures, see Prostate Cancer Study Results. The administration of denosumab is recommended in patients with impaired renal function. If bisphosphonates are effective and well tolerated, switch of treatment is not recommended.

Specific side effect of treatment with bone-modifying substances are osteonecrosis of the jaw (ONJ). The incidences after bisphosphonates and the RANKL antibody are comparable.

5.2.9.1 Bisphosphonates

Positive studies exist with respect to zoledronate and clodronate. Therapy with zoledronate resulted in a significant risk reduction for osseous complications in patients with castration-refractory prostate cancers. In patients with metastatic, hormone-sensitive prostate cancer therapy with clodronate was also associated with a significant prolongation of overall survival time, however, without exerting a significant effect on the rate of skeletal-related events, see

Prostate Cancer Study Results. Bisphosphonates are also recommended in cancer-induced hypercalcemia.

5.2.9.2 RANKL Antibodies

Denosumab is a human monoclonal antibody that binds to the RANK ligand, thus preventing the activation of RANK and inhibiting osteoclast activation. Denosumab was found to be at least equivalent to zoledronate in a large multicenter clinical trial on patients with castration-refractory prostate cancer. The main adverse effects were hypocalcemia and osteonecrosis of the jaw. Denosumab can also be administered in patients with impaired renal function.

5.2.9.3 Radionuclides

Alpha emitters are effective in patients with painful bone metastases. Most recently, prolongation of median overall survival was also shown for patients with castration-refractory prostate cancer and bone metastases, see Prostate Cancer Study Results. The median survival time of patients treated with ^{223}Ra was 2.8 months longer than that of the control group. In Germany, Austria and Switzerland ^{153}Sa has been the most widely used radionuclide.

5.2.10 Further, Palliative Therapy Options

Palliative care is an integrative, multidisciplinary approach. It includes physical, psychological, spiritual and social problems. The need and the possibilities of palliative therapy should be discussed in time with all persons involved. Further measures particularly suited for the palliative treatment of patients with advanced prostate cancer are:

5.2.10.1 Steroids

The administration of steroids can alleviate relevant symptoms such as pain, loss of appetite, fatigue and decreasing physical capacity [7]. In 20-50% of the patients it causes a decrease of the PSA value. Applicable are dexamethasone, prednisone, and prednisolone.

6 Rehabilitation

Surgery, radiation, and systemic treatment of patients with prostate cancer might lead to defects of various degrees which are secondary to therapy and might require targeted somatic and psychosocial rehabilitative measures. One particularly stressful disorder, which can be successfully treated, is urinary incontinence.

Rehabilitation goals subsequent to radical prostatectomy and/or external beam radiation therapy are: reduction of post-therapeutic voidance disorders of the urinary bladder and the bowels, reduction of functional disorders concerning urinary stress incontinence and erectile dysfunction, restoration of physical and mental fitness, reduction of worries and anxieties as well as information and counseling .Die Patients should be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures and further claims which ensue from social legislature. As far as the rehabilitation hospital is concerned, the preferences of the patient should be taken into consideration (Article 9 of German Social Code IX). Notwithstanding, a recommendation for an institution specializing in oncology should be given in order to assure an optimal rehabilitation success.

7 Follow-up

Objectives of follow-up are early diagnosis of relapse with the chance of cure and prolonged survival, detection of adverse effects after therapy, and secondary prophylaxis. Since salvage therapy is a successful option in prostate cancer patients with local relapse, structured follow-up is recommended after first-line therapy with curative intent, see Table 6. The prognostic impact of the follow-up concept has not been evaluated in prospective clinical studies.

Table 6: Follow-up in Patients after First-Line Therapy with Curative Intent

Analysis	Months 3	6	9	12	15	18	21	24	30	36	42	48	60	72	...
Case History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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12 Links

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